

**Access to NCD medicines: emergent
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and key structural factors**





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Foreword

Noncommunicable diseases (NCDs) were responsible for an estimated 40 million (74%) of all deaths globally in 2019, with the majority of these deaths occurring in low- and middle-income countries.¹ The ongoing COVID-19 pandemic poses further challenges for creating and maintaining healthy environments, and people living with NCDs are at increased risk of severe illness and death due to COVID-19.

COVID-19 has also revealed the lack of adequate investments in Primary Health Care (PHC) and Universal Health Coverage (UHC), leading to 50-60% disruption for all major NCD and mental health services in more than 70% of countries. Insufficient global action on NCDs, combined with the COVID-19 pandemic, is increasing the possibility that Sustainable Development Goal (SDG) targets 3.4 and 3.8 will not be met. While present and future climatic changes, humanitarian emergencies, and the resultant economic effects will likely exacerbate the incidence of some NCDs.²

The pandemic has highlighted the need to strengthen health systems, particularly PHC, including health information systems, health infrastructure, and health workforce to aid in improving access to NCD medicines.³ Achieving objectives and targets of the World Health Organization (WHO) NCD-Global Action Plan and SDG targets in a post-COVID-19 world requires a concerted response and the integration of the NCD agenda into existing global and national efforts to rebuild resilient health systems, with whole-of-government approaches and by engaging stakeholders; in order to Build Back Better.⁴

Medicines and health products have a complex pathway to reach the patient. Improving access to medicines and health products for the diagnosis, management, and treatment of NCDs is multi-faceted and part of a broader challenge of ensuring access to health care. The Roadmap for access to medicines, vaccines, and health products (2019–2023)⁵ was developed to demonstrate the work required across the value chain including research and development, selection processes, regulatory pathways, treatment guidance, procurement and supply chain, fair pricing, monitoring availability, and ensuring safe and appropriate use, among others.⁶

The response needs to be comprehensive and based on implementing the World Health Organization's (WHO) core technical guidance on expanding access to medicines and health products for NCDs and mental health conditions, while investing in the prevention and management of NCDs through stronger patient-centred PHC-focused health systems towards achieving UHC, and the health-related SDGs.⁷ WHO is looking forward to working with countries to expand access to medicines and health products for NCDs and mental health conditions, and to ensure that the human, social, and financial burden of NCDs does not reverse the development successes of previous years.

Dr. Ren Minghui, (Assistant Director-General, WHO Universal Health Coverage/Communicable and Noncommunicable Diseases Division) and Dr. Mariângela Simão (Assistant Director-General, WHO Access to Medicines and Health Products Division)

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Abbreviations

ACE	angiotensin-converting enzyme (inhibitors)
ANVISA	Agência Nacional de Vigilância Sanitária
API	active pharmaceutical ingredient
ARB	angiotensin II receptor blocker
ART	antiretroviral therapy
C-TAP	COVID-19 Technology Access Pool
CARRS	Centre for Cardio-metabolic Risk Reduction in South Asia
CCMDD	Central Chronic Medicines Dispensing and Distribution
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVAX	COVID-19 Vaccines Global Access
COVID-19	coronavirus disease
CVD	cardiovascular disease
DGFT	Directorate General of Foreign Trade (India)
EMA	European Medicines Agency
EML	WHO Model List of Essential Medicines
FPP	finished pharmaceutical product
GDP	gross domestic product
GMP	good manufacturing practice
GPS	global positioning system
HAI	Health Action International
HEPA	high-efficiency particulate absorbing
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHR	International Health Regulations
INN	international nonproprietary name
KSM	key starting material
LDC	least developed countries
mAb	monoclonal antibody
MCB	master cell bank
MMD	multi-month dispensing
MNS	mental, neurological and substance use

MPP	Medicines Patent Pool
MRP	material requirements planning
NCD	noncommunicable disease
NEML	national essential medicines list
NMRA	national medicines regulatory authority
OAT	opioid agonist maintenance treatment
OECD	Organisation for Economic Co-operation and Development
PDL	population doubling level
PEPFAR	United States President's Emergency Plan for AIDS Relief
PPE	personal protective equipment
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews
SEZ	special economic zone
SKU	stock-keeping unit
SMD	small-molecule drug
SME	small and medium enterprises
SNS	Strategic National Stockpile United States
SRA	stringent regulatory authority
TRIPS	WTO Agreement on Trade-Related Aspects of Intellectual Property Rights
UAV	unmanned aerial vehicle
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
US\$	United States dollars
USAID	United States Agency for International Development
USFDA	United States Food and Drug Administration
WCB	working cell bank
WCO	World Customs Organization
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization



Glossary

Active pharmaceutical ingredient (API):

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Bulk product: Any pharmaceutical product that has completed all processing stages up to, but not including, final packaging.

Cell bank: A collection of appropriate containers whose contents are of uniform composition and stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Complex emergency: A disaster complicated by civil violence, government instability, macroeconomic collapse, population migration, elusive political solutions, etc., in which any emergency response has to be conducted in a difficult political and security environment, potentially involving a multisectoral, international response that goes beyond the mandate or capacity of any single agency.

Excipient: A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

Finished pharmaceutical product (FPP):

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

Formulated bulk: An intermediate in the medicine product manufacturing process, consisting of the final formulation of antigens, adjuvants and excipients at the concentration to be filled into primary containers.

Good manufacturing practice (GMP): That part of quality assurance that ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Impurity: Any component present in the drug substance or medicine product that is not the desired product, a product-related substance or excipient including buffer components. It may be related to either the process or the product.

Intermediate: This can be a material produced during steps of the processing of an active pharmaceutical ingredient (API) that undergoes further molecular change or purification before it becomes an API. Intermediates may be isolated, or may be a material produced during steps in the manufacture of a vaccine that undergoes further processing before it becomes the final product.

Key starting material (KSM): Any material used at the beginning of the manufacturing process, as described in a marketing authorization or product licence. Generally, the term refers to a substance of defined chemical properties and structure that contributes an important and/or significant structural element (or elements) to the active substance (for example in the case of vaccines, synthetic peptides, synthetic glycans and starting materials for adjuvants). The starting material for an antigen (drug

substance) obtained from a biological source is considered to consist of: (a) cells; (b) microorganisms; (c) plants, plant parts, macroscopic fungi or algae; or (d) animal tissues, organs or body fluid from which the antigen (drug substance) is derived

Licence holder: An individual or a corporate entity possessing a marketing authorization for a pharmaceutical product.

Marketing authorization: Also referred to as a product licence or registration certificate. A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a medical product in the respective country after evaluation of safety, efficacy and quality. In terms of quality, it establishes inter alia the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients. It also includes details of the packaging, labelling, storage conditions, shelf life and approved conditions of use. It may also be referred to as product licence or licence in this and other documents.

Master cell bank (MCB): A quantity of well characterized cells of animal or other origin, derived from a cell seed at a specific population doubling level (PDL) or passage level, dispensed into multiple containers and stored under defined conditions. The MCB is prepared from a single homogeneously mixed pool of cells. In some cases, such as genetically engineered cells, the MCB may be prepared from a selected cell clone established under defined conditions. However, the MCB may not be clonal. The MCB is used to derive a working cell bank (WCB).

MedMon: WHO Essential medicines and health products price and availability monitoring mobile application (WHO EMP MedMon app) is a tool to rapidly collect and analyse data on the price and availability of medicines in health facilities and procurement centres. Based on elements of the well respected World Health Organization/Health Action International (WHO/HAI) method for measuring medicine prices, availability, affordability and price components, the WHO EMP MedMon app allows users to routinely monitor the prices and availability of medicines in a sustainable, cost-effective and timely manner, regardless of user access to internet or cellular data. The tool is designed to avoid duplication of efforts and potential manual entry errors that can occur when data are collected on paper and then transferred to an electronic format.

Monoclonal antibodies (mAbs): Homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

Packaging material: Any material, including printed material, used in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary, according to whether they are intended to be in direct contact with the product.

Pharmaceutical alternatives: Products are pharmaceutical alternative(s) if they contain the same active pharmaceutical moiety or moieties but differ in dosage form (e.g. tablets versus capsules), strength and/or chemical form (e.g. different salts or different



esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

Pharmaceutical dosage form: The physical form in which a medicine is presented; the name of a dosage form combines its physical form and the intended route of administration, for example, a tablet (to be swallowed) or oral suspension (liquid suspension of solid particles intended for oral intake and swallowing).

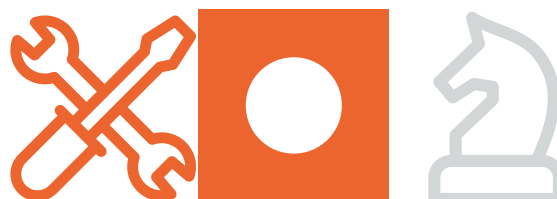
Prequalification: Standardized prequalification procedure of WHO to assess, in principle, whether candidate products: (i) meet WHO technical guidance on quality, safety and efficacy, including compliance with WHO recommended standards for good clinical practice, good manufacturing practices, good laboratory practices and good distribution practices; (ii) adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines; and (iii) meet relevant operational packaging and presentation specifications, for the purpose of providing guidance to interested United Nations agencies and WHO Member States in their procurement decisions. United Nations agencies and WHO Member States using information resulting from WHO prequalification should perform additional steps of qualification prior to purchasing such products, including ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, pre-shipment quality control and other related aspects, including the registration status of the products to be procured.

Resilience: The ability of a system, community or society exposed to hazards to resist, absorb, accommodate, adapt to, transform and recover from the effects of a hazard in a timely and efficient manner, including through the preservation and restoration of its essential basic structures and functions through risk management (as defined by the United Nations General Assembly in 2016).

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

Stringent regulatory authority (SRA): A regulatory authority that is: (i) a member of the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the United States Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan, also represented by the Pharmaceuticals and Medical Devices Agency; (ii) an ICH observer, being the European Free Trade Association, as represented by Swissmedic and Health Canada (before 23 October 2015); or (iii) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

Working cell bank (WCB): A quantity of well characterized cells of animal or other origin, derived from an MCB at a specific PDL or passage level, dispensed into multiple containers and stored under defined conditions. The WCB is prepared from a single homogeneously mixed pool of cells (often, this is the MCB). One or more of the WCB containers is used for each production culture.



Executive summary

The coronavirus disease (COVID-19) pandemic exacerbated pre-existing inequalities in the treatment and care of non-communicable diseases (NCD). This report examines the effect of the COVID-19 pandemic on access to NCD medicines, and the policies and strategies implemented by countries and health systems to anticipate and mitigate stresses across NCD medicine supply chains. The full range of upstream and downstream impacts are investigated, including: manufacturing; procurement, importation and last mile delivery; patient-level effects through affordability and availability; and the effects on NCD medicine availability by category of disease. The report culminates in recommended actions and interventions for key stakeholders in the NCD pharmaceutical supply chain, including governments, regulatory authorities, manufacturers and the private sector; as well as directions for future research for improving access and supply chain access resilience.

Methods

The study used a convergent, parallel, mixed-methods design to assess the full range of upstream and downstream impacts of the COVID-19 pandemic on access to NCD medicines. A scoping review of published academic literature, a desk review of grey literature and interviews were conducted to explore the causes of interruptions across the supply chain, as well as the ways in which health authorities used both established and innovative approaches to maintain supply continuity in challenging contexts. Quantitative analyses of data on active pharmaceutical ingredient (API) traded were conducted to determine the effects on global markets. WHO Country Capacity Surveys were used to assess changes in the availability of NCD medicines during the pandemic, by both WHO region and World Bank income group (2020 -2021)⁸. Government-reported shortages data from Australia, Brazil, South Africa and the United



WHO Laboratory Officer Debashish Paul meets with laboratory personnel at the IEDCR Field Laboratory in Cox's Bazar Medical College. © WHO / Blink Media – Fabeha Monir

8. 2020 -2021 World Bank income groups classification (low-, lower-middle-, upper-middle-, and high-income countries)

States of America were used to examine upstream causes of supply interruptions, delays in shipping and/or changes in demand.

Findings

Manufacturing:

The COVID-19 pandemic was the first global event to send a shockwave through all parts of the global pharmaceutical manufacturing supply chain almost simultaneously. Shortages and delays in the sourcing of manufacturing input materials; curfews, quarantines and stay-at-home measures and resultant staffing disruptions; and the occasional delay of quality assurance inspections for regulatory or marketing approval were identified as factors influencing the disruptions in NCD pharmaceutical manufacturing. Concurrent risk mitigation measures such as compensating or shifting operations in response to the reduced capacity or limited manufacturing inputs were only partially successful in anticipating new trade and operational challenges, with evident disruptions in import-dependent APIs and associated price increases for some APIs including for budesonide, gliclazide, lisinopril and salbutamol. Similarly, reports from national shortages databases reveal an increased rate of shortages related to manufacturing and API supply in countries sampled (Brazil, South Africa and the United States).

Procurement, importation and last mile delivery:

Few wholesalers or manufacturers anticipated the scale of freight disruptions and effects of cascading losses of transport capacity and export bans. The scale of export bans is not systematically reported, but the World Trade Organization (WTO) estimated that, as of April 2020, 20 countries and customs territories had introduced export restrictions on medicines (4). While many countries created priority paths or exceptions to protect the transport of essential goods such as medicines, definitions of essential goods varied between countries and interviewees reported significant challenges in the practical use of these exceptions.

The sharp contraction in global shipping capacity led to difficult decisions for all actors. Interviewees estimated that freight costs had increased by 2–6 times pre-pandemic costs in 2020. Intranational and intraregional freight costs increased, although to a lesser extent, with interviewees reporting an increase of around one fifth relative to pre-pandemic levels. The volume, availability and predictability of air cargo routes were severely disrupted, with routes dependent on connecting flights and those with lower profit margins for carriers particularly affected. Maritime transport was also disrupted as a result of port closures, crew-change restrictions, changes in documentation requirements, physical examinations of vessels and crew members and quarantines. Countries already disadvantaged in global medicine markets, including low-income countries with fewer resources, landlocked countries dependent on air cargo and ports in other jurisdictions, and countries subject to international trade sanctions were disproportionately affected. The contraction of the commercial airline industry in April 2020 particularly affected the shipment of medicine formulations with small volumes, such as paediatric formulations and medicines for rare diseases. Temperature-sensitive medicines and health products were also affected by unexpected delays in transport. The literature on last mile delivery highlighted challenges in integrating NCD health services as well as the social determinants of accessing health services: the experiences of patients visiting HIV/hypertension clinics in Uganda and



breast cancer patients trying to afford and reach services in Mumbai demonstrate the interrelated challenges patients face when emergencies disrupt transportation (2-3).

As part of mitigation measures, some procurement agencies implemented demand controls to stabilize their supply chains, while some larger private sector firms were able to store surplus manufacturing materials. Downstream risk mitigation strategies focused on smoothing demand, improving visibility, optimizing distribution, increasing safety stocks and identifying potential shortages as early as possible. Last mile delivery responses included expansion of multi-month prescribing, innovative delivery methods and prioritization of at-risk patients and clinically essential medicines.

Availability and affordability of NCD medicines:

The primary challenge identified in assessing the impact of the COVID-19 pandemic on shortages and stockouts of NCD medicines and resources is the limited data availability across the pharmaceutical value chain. Three data sources were used to triangulate the effects of COVID-19 on affordability and availability: 1) national level surveys, 2) selected national shortages data and 3) literature review of drivers of affordability and access.

The WHO NCD Department expanded the Country Capacity Surveys to gather information from countries on the impact of the pandemic on NCD-related resources and services. Survey findings showed an increase in the unavailability of medicines from 15% in 2020 to 21% in 2021 (4). The 2021 survey also demonstrated the persistence of inequities, with the greatest disparities between high- and low-income countries observed in the availability of beta-blockers, insulin, statins and steroid inhalers.

A number of countries maintain monitoring and reporting mechanisms for medicines shortages. The actors managing these mechanisms vary from country to country and include national medicines regulatory agencies (NMRAs), pharmacist associations, procurement programmes and hospital and pharmacy networks. National shortages databases in Australia, Brazil, South Africa and the United States were analysed (these

countries were selected because data are publicly available and include the specific causes of shortage events). The number of reported shortages increased during the COVID-19 pandemic from 2019 baseline levels in all countries. The primary drivers of these increases were manufacturing in Australia, commercial changes and viability in Brazil and demand increases in South Africa and the United States.

Although some medicines became unaffordable because of increases in supplier costs, the more significant drivers were losses in employment and income. The increase in poverty from 2019 to 2020 is the largest on record since the World Bank started tracking poverty globally with a consistent method (5). The loss of employment and income associated with COVID-19 exacerbated the already significant access challenges resulting from high prices, especially for poor and uninsured people, as well as for those who need medicines that are still under patent. The economic shock of the early weeks of the pandemic also reduced revenues for some manufacturers and wholesalers. Health financing was disrupted in some cases, with funds reallocated for emergency use. For health budgets where co-payments are a significant source of financing, revenue decreased unexpectedly as many people self-isolated and elective care was postponed. Interviewees reported that the rules and norms around payment contracts also changed in some cases, with some manufacturers newly requiring full upfront payment.

Access to NCD medicines by disease category:

The analysis was extended to include NCD medicines access and availability, based on NCD disease-specific categories. This included how the pandemic affected access to specific medicines for cardiovascular disease (CVD), diabetes, cancer, chronic respiratory disease, pain, palliative care and mental health, drawing on information from the published academic literature, WHO Country Capacity Surveys and national shortages databases. In general, the findings corresponded with the broader NCD pharmaceutical value chain challenges identified.



The UN Solidarity Flight lands at the Maya Maya International Airport in Brazzaville with COVID-19 medical supplies - including protective personal equipment, thermometers and respirators - transported by the UN Solidarity Flight on April 18 2020. © WHO

Conclusion and pathways to improve NCD medicine access during the COVID-19 pandemic and beyond

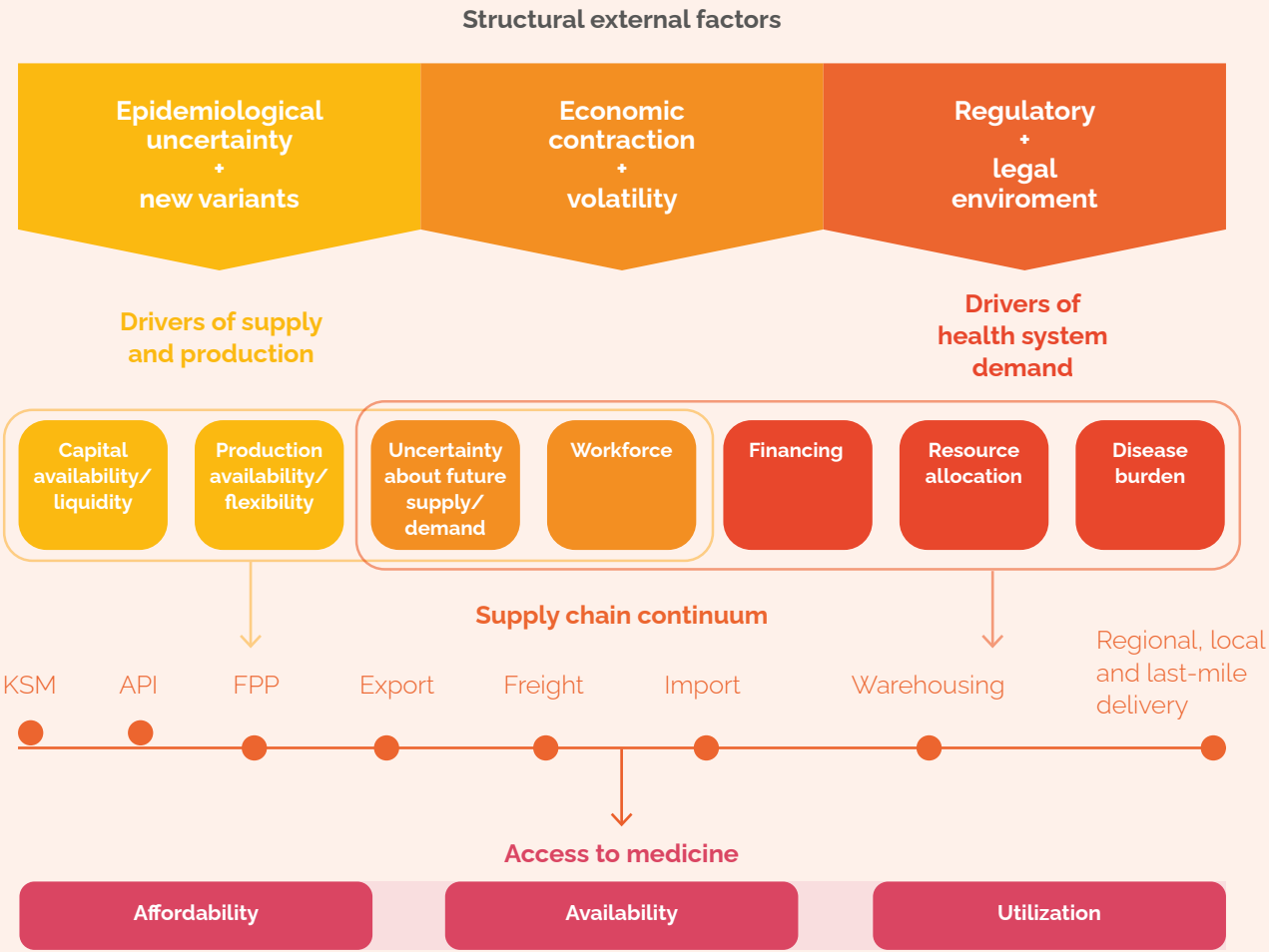
NCD mortality continues to rise and is projected to reach more than 100 million deaths annually by 2025 (6). NCD treatment and care requires continuous coordination across every level of the health system. Integrated people-centred service delivery approaches anchored in strengthened primary health care and broader health systems are required for sustainable improvement towards achieving the Universal Health Coverage, the WHO Global NCD Action Plan and the health-related Sustainable Development Goal targets. As the world is reeling from the effects of the COVID-19 pandemic, there is a need to reflect on successes and failures in the global supply chain for NCD medicines.

Limited data availability was identified as a significant barrier to assessing interruptions to global manufacturing capacity, particularly in the context of pandemics and other health emergencies. Robust, systematically collected data on medicines markets are

essential to building early warning and mitigation systems for shortages. WHO-supported development of reporting standards and data indicators for NCD health product shortages could improve comparability and upstream visibility of global production and supply. Measures to promote monitoring and transparency across the NCD supply chain could include governments collaborating with manufacturers to conduct molecule and product-specific risk assessments, as well as report annual manufacturing volumes to assess supply capacity.

A successful response requires long-term planning and cross-sectoral, integrated approaches. While significant strides have been made in adapting country strategies and policies to respond to challenges in NCD medicines and management requirements during the pandemic, challenges remain. Many of the actions needed to strengthen the resilience of medicine supply chains in the context of pandemics and emergencies overlap with those needed to create health systems that are responsive, equitable and accountable, including strengthening governance and financing mechanisms.

Fig. 1.1. Conceptual model of the impact of the COVID-19 pandemic on access to NCD medicines



API: active pharmaceutical ingredient; FPP: finished pharmaceutical product; KSM: key starting material.

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WHO country office staff member, Polipos Kaloulou Bantsimba, works with partners at the Maya International Airport in Brazzaville to coordinate the storage and delivery of essential COVID-19 medical supplies transported by the UN Solidarity Flight on April 18 2020. © WHO / Gregor Donaldson

1. INTRODUCTION

The interplay between noncommunicable disease (NCD) epidemics and the coronavirus disease (COVID-19) pandemic has exacerbated pre-existing inequalities in NCD treatment and care. People with NCDs are more vulnerable to severe illness and death as a result of contracting COVID-19. At the same time, screening, diagnosis, treatment, palliative care and rehabilitation have been disrupted by the ongoing pandemic. NCDs were responsible for more than 15 million premature deaths (between the ages of 30 and 69 years) in 2019, of which 85% were in low- and middle-income countries [\(2\)](#).

People with NCDs need uninterrupted, reliable access to quality-assured and affordable medicines and health products. Although earthquakes, hurricanes and supply contamination have shut down key manufacturing sites in the past, the COVID-19 pandemic has been the first sustained shock event to affect all parts of the global pharmaceutical manufacturing supply chain almost simultaneously. Supply chains for NCD medicines are globally dispersed and highly complex. Breakdowns of supply chains for medicines can happen at the local, regional or global level and affect the manufacture and movement of medicines at any point from active pharmaceutical ingredient manufacturing through to, last mile delivery and dispensing. Despite the substantial political will and efforts to ensure continuity in supply chains for essential goods such as medicines, supply chain disruptions have led to higher costs and lower availability for many products and routes. These disruptions have disproportionately affected the health systems of less wealthy countries and those living with NCDs.

The COVID-19 pandemic directly and indirectly affected each stage of the pharmaceutical value chain, with effects seen across regions, products and market segments. Fig. 1.1 is a conceptual model of the impacts of COVID-19 on NCD

medicine production, supply chains, demand and access. The conceptual model was developed through a review of pre-COVID-19 literature and input from World Health Organization (WHO) NCD, medicine, shortages and supply chain specialists.

One of the key challenges in assessing the effect of the COVID-19 pandemic on access to NCD treatments is the lack of baseline data, as well as interruptions in data collection during the pandemic. Upstream, data on medicines export volumes, prices, sources and interruptions have historically not been systematically collected at the global level, and in only a handful of cases at local and regional levels. Where shortage information is available at the national level, it is generally only collected based on local mandates or on a voluntary basis from manufacturers and/or supply chain actors experiencing shortages. There have been recent initiatives towards global reporting of shortages (World Health Assembly (WHA) resolution 69.25 Addressing the global shortage of medicines and vaccines), and in 2019 WHO launched a shortages portal to consolidate available information and provide a reporting mechanism for countries [\(3\)](#). Downstream, WHO collects data to measure medicine prices, affordability and availability through the MedMon tool.

The aim of this report is to describe and analyse how the COVID-19 pandemic affected supply chains for NCD health products, to identify key vulnerabilities and bottlenecks, and to propose key themes and a framework for future policy development.

A convergent, parallel mixed-methods study design is used to untangle the effects and interactions of specific mechanisms of interruptions in a context of significant gaps in data on production and shortages. Data sources included: a scoping review of the published academic literature ([Section 2.1](#)); a desk review of grey literature ([Section 2.2](#)); semi-structured interviews with 38 individuals from United Nations agencies,

humanitarian and non-profit organizations, universities and manufacturers (**Section 2.3**); market data on active pharmaceutical ingredient (API) exported from India (**Section 2.4**); WHO Country Capacity Survey data on medicine availability (**Section 2.5**); and publicly available databases of medicine shortages and their causes in Australia, Brazil, South Africa and the United States of America (**Section 2.6**).

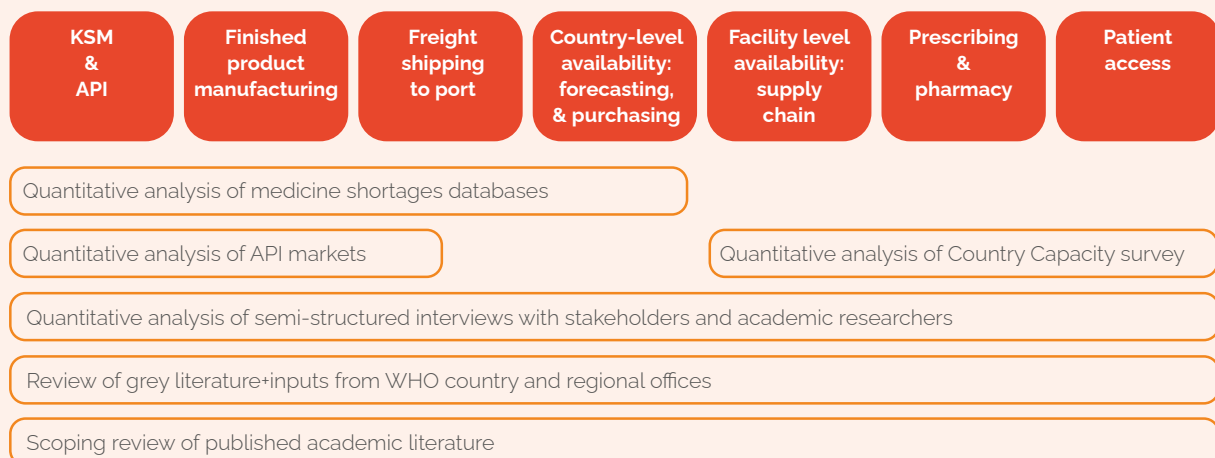
The report considers the full range of upstream and downstream impacts, including those on manufacturing (**Chapter 3**); procurement, importation and last mile delivery (**Chapter 4**); medicine shortages and affordability (**Chapter 5**); and disease-specific issues (**Chapter 6**). From these findings, cross-cutting policy considerations and directions for future research in supply chain resilience are proposed (**Chapter 7**).

2. DATA AND METHODS

Prior to the coronavirus disease (COVID-19) pandemic, there was already limited empirical literature on the resilience of upstream noncommunicable disease (NCD) medicines manufacturing and the cause of shortages. COVID-19 brought into focus the need to expand and strengthen this evidence base. In this study, qualitative and quantitative data are collected in parallel, analysed separately and then synthesized (4). The convergent, parallel mixed-methods design approach pursued in this study was designed to counter some of the data limitations by providing quantitative checks

across the value chain to assess price and availability, complemented by qualitative research to better understand the genesis and interactions between access barriers. Fig. 2.1 summarizes the methodological approach. Collection of both quantitative and qualitative data was undertaken not only to allow complementation and corroboration, but also to generate greater clarity and insight into the research questions than would be possible with any single type of data. There are still significant gaps that could be addressed through future research.

Fig. 2.1. Convergent mixed-methods study design



KSM: key starting material
API: active pharmaceutical ingredient

2.1. Scoping review of published academic literature

The scoping review was conducted in accordance with guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) (5).

The search algorithm was developed from a conceptual model (Fig. 1.1) focusing on the interaction between COVID-19 and availability of NCD medicines across the full access continuum, from upstream manufacturing of key starting materials to manufacturing, distribution, patient access, utilization and affordability. The search strategy was purposely broad to capture

literature across a range of disciplines and include publications that report data on medicine utilization, affordability and stockouts as secondary or incidental outcomes. See **Annex 1** for further details of the scoping review search strategy and queries.

A total of 1997 records of papers were captured through PubMed (851) and Web of Science (1146) searches in July 2021 (Fig. 2.2). A further 19 records were included through snowball addition. Records were imported and screened using Covidence systematic review software, and 49 duplicates were removed. MB screened the remaining 1967 records based on their abstract. AN screened a sample of 10% of records as an independent eligibility assessment. There were three disagreements that were



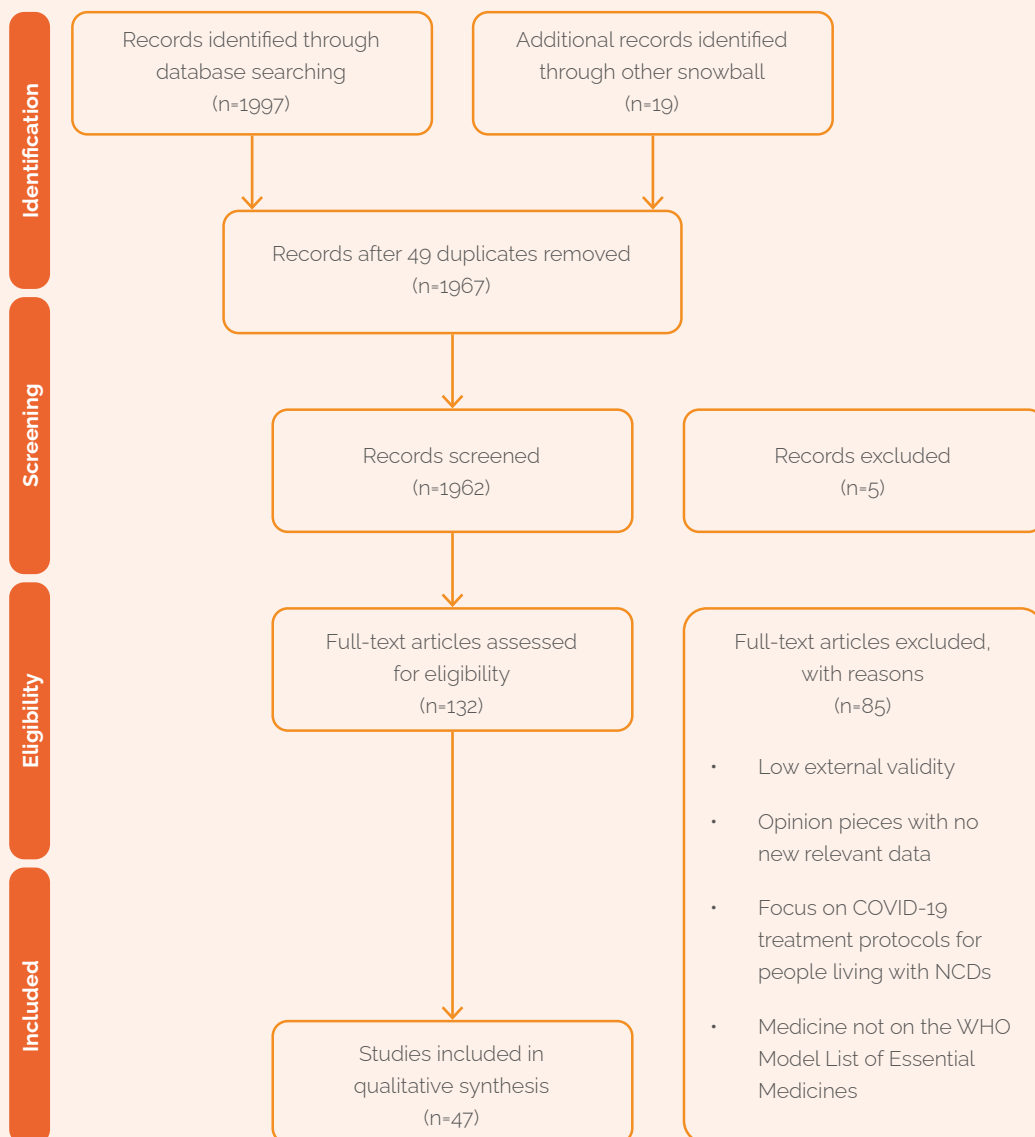
On 12 May 2020 medical and hygiene supplies arrive at the De Martini COVID-19 isolation center in the Banaadir region of Somalia. The facility is supported by WHO. © WHO / Ismail Taxta.

resolved by consensus. For the five papers not available through the Harvard University library, MB contacted the authors to request the text, and received one paper. After abstract screening, the full text of 132 papers was reviewed.

Inclusion criteria were: relevance to the conceptual model (Fig. 1.1); a publication (or online publication) date of 1 January 2020–1 June 2021; and the inclusion of

information on access to NCD medicines, or a description of barriers to or drivers of pharmaceutical systems more widely. Although most systematic reviews only include original research, given the shift in many journals to reporting short pieces because of the emergency nature of the pandemic, perspectives or short news pieces were also included if they contained relevant primary, secondary or incidental access outcome data. Publications with low external

Fig. 2.2. PRISMA flow diagram for literature search



validity were excluded (e.g. surveys with small sample sizes). Publications focusing on COVID-19 medicines or medicines not included in the WHO Model List of Essential Medicines were also excluded [\(6\)](#).

A total of 47 studies were included in the qualitative synthesis (7–53). Table 2.1 summarizes the included publications by pathway and disease category; further results on each pathway are reported in the respective chapters. Data were extracted and charted within the framework of the conceptual mode by MB, following PRISMA guidelines. Risk of bias was not reported. There were no studies with high-quality methods (robust, randomly sampled, sufficiently powered). The review was not pre-registered with Cochrane or Campbell registries. The protocol was critically reviewed across other WHO departments.

In general, the included publications were not designed or powered to answer questions about access and the pharmaceutical value chain, but instead reported these issues as secondary or incidental results. The search algorithm only returned papers published in English, French, Italian, Portuguese and Spanish. This scoping review should be interpreted carefully and cautiously, with expectations that the situation may change and that important themes may not yet be published in academic journals.



Table 2.1.

Results of COVID-19 and NCD medicine access literature review, by pathway and disease category (and number of relevant publications)

Author, year; location or region	No disease focus (14)	NCD (general) (3)	Cardiovascular disease (4)	Diabetes (4)	Chronic respiratory disease (3)	Cancer (8)	Palliative care (0)	Mental health (3)	Other (14)	Manufacturing (7)	Freight/shipping (2)	Procurement, forecasting, purchasing (5)	Stock availability/supply chain (24)	Prescribing (9)	Affordability, availability, utilization (33)
Abdoli 2020; Iran (Islamic Republic of) (7)	X									X		X	X		X
Akande-Sholabi & Adebayo Adebisi 2020; Nigeria (8)	X									X					
Alnajashi & Jabbad 2020; Saudi Arabia (9)									X						X
Alves 2021; Brazil (10)	X												X		
Asadi-Pooya et al. 2020; Iran (Islamic Republic of) (11)									X				X		X
Batu et al. 2020; global (12)									X				X		X
Bell et al. 2020; Australia (13)	X												X	X	X
Burry et al. 2020; NA (14)	X									X		X	X	X	
Charbonneau et al. 2020; France (15)	X														
Ciurea et al. 2020; Switzerland (16)									X						X
Clement et al. 2021; United States (17)	X														X
Cornet et al. 2021; Europe (18)									X				X		X
Cransac-Miet et al. 2020; France (19)			X												X
Deana et al. 2020; Italy (20)	X												X		
Dunlop et al. 2020; NA (21)								X						X	X
Enríquez-Fernández & del Castillo-Rodríguez 2021; France; Germany; Italy; Spain (22)	X									X		X	X		
Ganapati et al. 2020; India (23)									X				X		X
García-Azorin et al. 2021; global (24)								X	X				X	X	
Gul & Atakli 2020; Türkiye (25)									X						X

Gummidi et al. 2020; India (26)		X										X	X
Handfield et al. 2020; United States (27)	X								X		X	X	
Husayn et al. 2020; NA (28)								X					X
Jazieh et al. 2020; global (29)					X					X		X	X
Kostev & Lauterbach 2020; Germany (30)	X												X
Leite et al. 2020; Brazil (31)		X											X
Liang et al. 2020; China (32)				X									X
Liu et al. 2020; China (33)	X								X		X		
Lombe et al. 2020; Zambia (34)					X					X		X	X
Lucero-Priso III et al. 2020; Sudan (35)	X								X				X
Marehin et al. 2020; Gabon (36)							X					X	X
Merks et al. 2020; NA (37)	X												X
Nnaji & Moodley 2021; NA (38)					X							X	
Rathore et al. 2021; India (39)								X				X	X
Riera et al. 2021; global (40)					X							X	X
Saab et al. 2020; Algeria; Armenia; Bahrain; Georgia; Iran (Islamic Republic of); Iraq; Jordan; Kuwait; Lebanon; Morocco; Nepal; Oman; Pakistan; occupied Palestinian territory, including east Jerusalem; Saudi Arabia; Sudan; Syrian Arab Republic; Türkiye; Yemen (41)					X							X	
Saleem et al. 2020; Pakistan (42)								X					X
Schwartz et al. 2021; Uganda (43)			X										X
Shimels et al. 2021; Ethiopia (44)			X	X									X
Singh et al. 2021; India (45)		X	X	X	X			X					X
Traoré et al. 2020; French-speaking Africa (46)					X							X	X
Vasquez et al. 2020; Latin America (47)					X							X	X
Wadasadawala et al. 2021; Mumbai (48)					X								X
Wang et al. 2020; China (49)								X					X
Yan et al. 2020; China (50)				X								X	X
Yeoh et al. 2021; Singapore (51)				X									X
Zhang et al. 2020; China (52)				X									X
Ziadé et al. 2020; Algeria; Egypt; Iraq; Jordan; Kuwait; Lebanon; Libya; Morocco; Oman; occupied Palestinian territory, including east Jerusalem; Qatar; Saudi Arabia; Syrian Arab Republic; Tunisia; United Arab Emirates (53)								X				X	X

NA: not applicable; NCD: noncommunicable disease.

2.2. Review of grey literature

Grey literature was identified through the literature review, from comprehensive searches of United Nations agency databases of published reports, or else suggested by either interviewees (**Section 2.3**) or other WHO staff. Reports include those published by WHO (54–65), the United Nations Development Programme (66–70), other United Nations organizations (or reports co-authored by) (71–75), regional organizations (76–79), the World Bank (80), the World Trade Organization (81–83), various thinktanks (84–88) and others (89–92). The grey literature was not charted alongside the published academic literature; most of the grey literature did not have outcomes specific to NCDs or even medicines, but is instead synthesized in the description and analysis of broader structural factors during the pandemic.

2.3. Interviews with stakeholders and academics

The aim of the interview process was to explore the mechanisms that disrupted access across the full supply chain, from the point of view of those working in production, logistics, and delivery. Qualitative data on

stakeholders' responses to disruptions and risk-mitigation strategies were also collected and analysed.

A total of 38 individuals from 24 organizations participated in interviews (Table 2.2). Interviewees were selected on the basis of having relevant academic or technical expertise, or their involvement in manufacturing, procurement, shipping, logistics, or medicines delivery activities. Organizations were purposively sampled across geographic regions and organizational types. However, the pool of interviewees for whom we were able to obtain contact information and/or were available and willing to be interviewed at the time of writing the report was weighted towards international and donor organizations, rather than small and medium enterprises and local procurement actors. For example, we reached out to a number of Latin American manufacturers both directly and through networks, but were unable to secure an interview.

The global supply chain is vast and heterogeneous; saturation cannot be reached with 38 interviews. Questions for the semi-structured interview were developed through WHO internal collaboration and review. The questions were pilot tested to ensure relevant themes would be covered.



Essential medicines and health products: manufacture of pharmaceutical products. © WHO / Ivan Chernichkin

Table 2.2.

Number of individuals interviewed and organizations, by sector

Sector	No.	Organizations
Academics	3	Center for Value Chain Innovation at University of Michigan Ross School of Business; Harvard Medical School; independent researcher; Institut Européen d'Administration des Affaires (INSEAD)
International aid/donors	6	Bill & Melinda Gates Foundation; Cross Donor Secretariat; The Global Fund; United States Agency for International Development (USAID)
Logistics	2	Imperial Logistics; Imres
Manufacturers and their associations	6	Aspen Pharmicare Holdings Limited; Cipla Limited; International Federation of Pharmaceutical Manufacturers & Associations (IFPMA); Medtronic plc; Novo Nordisk
Multilateral agencies	10	United Nations Development Programme (UNDP); United Nations Population Fund (UNFPA); World Bank; World Food Programme (WFP)
Non-governmental organizations	11	Cancer Alliance South Africa; Clinton Health Access Initiative (CHAI); Intersectoral Forum to Fight NCDs in Brazil (ForumDCNTs); Médecins Sans Frontières (MSF); Santé Diabète; Sociedade Brasileira de Diabetes

Notes from interviews were coded and analysed with a coding tree developed using the same conceptual framework and model as used in the scoping review (Fig. 1.1). Interviews with individuals on behalf of organizations were conducted under the condition that personally or organizationally identifiable information would not be included in the report unless already publicly available. See **Annex 2** for interview protocol and questionnaire for semi-structured interviews.



2.4. Quantitative analysis of Indian API export data

To provide an insight into the effects of COVID-19 on exports of pharmaceutical API, exports from India, a major global API manufacturing hub, were analysed (**Section 3.4**). The analysis of API cost interruptions was limited to Indian export markets as this was the only source of such data; the differential impact on smaller and/or domestic markets within India could not be evaluated with the dataset and methodology. Within export data, the analysis was limited to average effects on API cost per kilogram for individual medicines and across income categories of the importing country. From these data we were unable to assess longitudinal effects on narrower market segments and/or classes of purchasers (i.e. public versus private).

NCD medicines were selected for analysis on the basis of inclusion in WHO Country Capacity Surveys, and included amlodipine, aspirin, bisoprolol, budesonide, gliclazide, human insulin, hydrochlorothiazide, lisinopril, losartan, metformin, nicotine, salbutamol and simvastatin.

2.5. Quantitative analysis of WHO Country Capacity Survey data on medicine availability

Data from the 2019 Country Capacity Surveys provide a baseline for NCD medicine availability before the COVID-19 pandemic (**Section 5.2**). In these surveys, Member States report whether priority medicines are available, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aspirin, benzathine penicillin, beta blockers, bronchodilators, calcium channel blockers, insulin, metformin, nicotine replacement therapy, oral morphine, statins, steroid inhalers, sulphonylureas and thiazide diuretics. This survey was repeated from May to September 2021 during the pandemic. All 194 Member States responded to both rounds of the survey. Data on medicine availability and changes between 2019 and 2021 are reported in **Annex 3**, with disaggregation by WHO region and 2020-2021 World Bank income group.

It should be noted that WHO Country Capacity Surveys only provide data on high-level indicators of medicine availability; from these data, we receive country-level insights which cannot determine subnational disparities within countries, for example, by urban/rural location, socioeconomic status, ethnicity, sex or disability.



Essential medicines and health products: manufacture of pharmaceutical products. © WHO

2.6. Quantitative analysis of medicines shortages databases

Assessing global API interruptions and/or shortages would require manufacturers to report interruptions. No system for this currently exists, and manufacturers may not voluntarily report shortages data, as some may view this information as commercially sensitive. Reporting is sometimes voluntary. Even in jurisdictions where reporting is mandatory, enforcement may be limited by resource constraints of relevant authorities. Low fines may not be sufficient in incentivizing compliance; there is no empirical evidence evaluating the level of fine (or other sanction) needed to incentivize compliance by most firms. The threshold for reporting is also subjective, and there is likely a wide range of views within firms about what constitutes a large enough potential problem to merit reporting. Although there are no direct data on API shortages, indirect inference can be made from publicly available medicines shortages databases.

Interviewees generally agreed that interruptions in the production of API and finished pharmaceutical product (FPP) were resolved after the first 6–8 weeks of the pandemic. To test this consensus

view, quantitative data were collected from national shortages databases in Australia, Brazil, South Africa and the United States according to methods described in **Annex 4**. Shortages databases from these countries were selected because they are (i) publicly available and (ii) report the specific causes of shortage events (e.g. problems with API, logistics, manufacturing, packing, regulatory delays, unanticipated demand increases and commercial decisions). The included countries represent large, competitive markets; if these markets experienced upstream challenges in API markets, it is likely that the underlying mechanism also contributed to shortages in other countries. However, smaller markets were likely disproportionately affected, and using large markets as a signal would therefore underestimate the effect of interruptions in small markets. In terms of external validity, this approach can at best provide a signal of potential global effects.

NCD medicines for which a problem in the supply of API was reported as the cause of shortages are examined in **Chapter 6**, with overlapping shortages in multiple countries highlighted through Venn diagrams. These medicine, shortage cause and country comparisons are helpful signals for further research and exploration in likely upstream shortages in 2020–2021.



3. MANUFACTURING

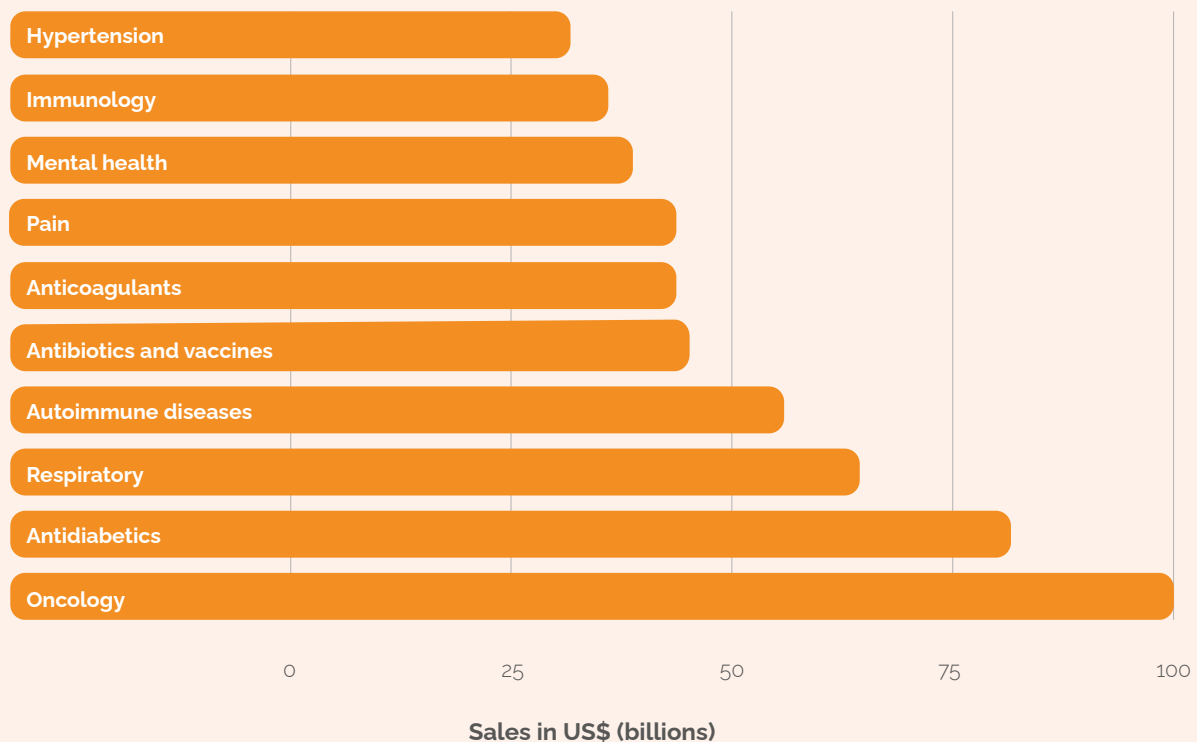
3.1. Background

The global market for pharmaceuticals reached 1.26 trillion United States dollars (US\$) in 2020 (93), and medical products accounted for approximately 5% of world trade (94). Globally, more is spent on medicines for noncommunicable diseases (NCDs) than any other therapeutic class (Fig. 3.1) (96).

Disruptions in the supply chain for a single component used in manufacturing have the potential to lead to manufacturing delays, especially when few alternative suppliers exist. The manufacturing of a finished pharmaceutical product (FPP) depends on the resilience of the global

supply chain for all key inputs. For example, a metered dose inhaler for the treatment of asthma comprises the plastic spacer, metal canister, the active pharmaceutical ingredient (API) and its key starting materials, and packaging, which are often produced in different countries and by different firms. Localized disruptions in manufacturing have affected the supply chain of many products, including of small-volume saline bags (250 mL or less) after Hurricane Maria hit Baxter's pharmaceutical plant in 2017 (97) and of piperacillin-tazobactam after an API factory fire in China in 2017 (98). One of the first studies conducted by the World Health Organization (WHO) was assessing the impact of the Second World War on insulin supply (Box 3.1).

Fig. 3.1. Top 10 therapeutic classes by estimated global pharmaceutical sales in 2018 (95)



Source: IQVIA



After the checkup a woman came to collect free medicines at Basic Health Unit (BHU) No 10, Hyderabad district. © WHO / Asad Zaidi

The most significant barrier to assessing interruptions to global manufacturing capacity is that there are no robust, systematically collected data. Essential questions – for example, how many producers are there of a given medicine and where are they; how many medicines are directly or indirectly available from a single source – cannot be answered with existing data. Some stringent regulatory authorities (SRAs) collect data and try to proactively identify shortages or future interruptions, but are limited by the availability of public data and voluntarily shared market information. For-profit firms such as IQVIA (previously IMS Health) sell some related data, but these sources have not been audited and their quality is indeterminate.

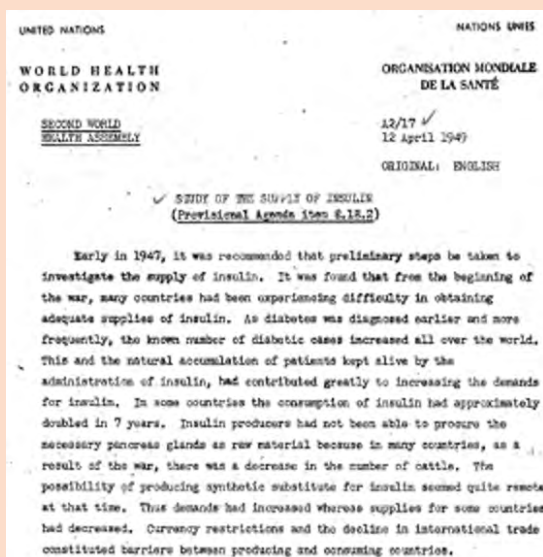
This chapter synthesizes evidence from the scoping review of academic literature, the desk review of grey literature, qualitative data from interviews with stakeholders and academics, and quantitative data from analysis of API import–export data from

India. Through the interview process, key informants were asked if they were aware of any interruptions or delays in API or FPP production or sourcing and, if relevant, what strategies were put in place to maintain production (see the questionnaire in **Annex 2: Production and manufacturing**). Where possible, this information was then validated through other sources, including trade reports, press materials and statements by manufacturers and trade associations. Analysis focuses on, but is not limited to, generic manufacturing.

First, manufacturing challenges are outlined (**Section 3.2**), followed by an analysis of medicine shortages reported to be caused by manufacturing issues (**Section 3.3**). These findings are triangulated with data on upstream interruptions in API markets (**Section 3.4**). Finally, stakeholder responses to address and mitigate against manufacturing disruptions are described (**Section 3.5**).

Box 3.1. The first analysis of the effects of a global interruption (Second World War) on insulin production

At a time when few medicines used today were commercially available, the second World Health Assembly (1949) reviewed the results of a fact-finding study on the “difficulty encountered in obtaining insulin” as a result of the Second World War [\(99\)](#).



The 1949 investigation collected data on insulin production from 47 states and found that the war had interrupted procurement of pancreas glands because of a decrease in the number of cattle. (At the time, insulin was manufactured by purifying insulin extracted from the pancreases of animals.) As in 2020, currency restrictions and trade barriers also affected production. Unlike 2020, the report was able to gather sufficient data to estimate upstream insulin production capacity.

The recommendations of the study were broad but continue to be relevant in 2020: “The encouragement of production in countries possessing the raw material, the making available of raw material to producing countries and the overcoming of currency restrictions are basically economic problems. It would be the function of WHO to assist Governments in utilizing existing international economic machinery in such a way to bring about a maximum improvement.” [\(99\)](#)

3.2. Drivers of interruptions to pharmaceutical manufacturing

3.2.1. Raw material availability at key global manufacturing sites

China is the largest global producer of key starting materials (KSMs) used to manufacture APIs. The majority of API production occurs in China and India, with other generic manufacturing hubs in Brazil, Indonesia, Italy, Mexico, the Russian Federation, South Africa and the United

States of America. Manufacturing for patented NCD medicines is concentrated in Ireland and Puerto Rico, and in the Basel, Switzerland area. Factories that convert raw API to FPP require lower capital investments and are distributed more widely across the world.

The first cases of novel pneumonia, later identified as coronavirus disease (COVID-19) infection, were reported in Wuhan, China on 31 December 2019 [\(100\)](#). Cases in Wuhan were reported to have peaked on 12 February 2020 [\(102\)](#). In late January 2020, the government ordered most factories to shut down for several weeks [\(102\)](#). This,

along with the shutdown of airports in China, resulted in supply disruptions to KSMs used to manufacture APIs (72, 103). This study was not able to assess the impact of disruptions to the manufacturing of KSMs and APIs on global supply because of insufficient data. However, there was agreement among key informants that manufacturing in India experienced an initial shock in March 2020, largely because of shortages of raw ingredients normally imported from China.

Interviewed manufacturers reported that production interruptions in India were largely resolved by April–May 2020. India is a key manufacturer of generics globally, supplying, for example, 80% of HIV medicines used in Africa (72). There is no survey of manufacturers of NCD medicines and production challenges during this period in India. However, the WHO Regional Office for South-East Asia conducted a preliminary assessment of Indian antiretroviral medicine

manufacturers in March 2020, followed up with a questionnaire-based survey in May 2021 (104). Manufacturers reported that by May 2020 they had adequate stock of APIs required for antiretroviral medicine manufacture (104). One manufacturer reported that API shortages resulted in a 20–30% decline in production capacity, while others reported that they were not affected (104). Respondents cited concerns about increasing costs of APIs, and planning challenges resulting from the indefinite uncertainty of supply shortages (104). Although respondents to this survey were manufacturers of antiretroviral medicines, most antiretroviral medicine factories produce other products, and these findings are likely broadly generalizable to factories producing NCD medicines. These findings are also in line with reports by manufacturers and other stakeholders from interviews.



Quote 3.1: non-governmental organization

“During the period of peak need, the price of dexamethasone doubled, but only for a short period of time when everyone wanted the API. We wanted to get back to normal. For paracetamol we have experienced a crazy increase [in price], and that’s still the case now.”



The impacts of the supply shocks from India and China had downstream effects for smaller markets. Manufacturing in Indonesia, which depends on imports from India and China for 90% of APIs used in domestic pharmaceutical manufacture, was more severely and lastingly disrupted. The Indonesian Chamber of Commerce and Industry estimated that pharmaceutical firms were operating at only 55–60% capacity in May 2020 as a result of disruptions from the COVID-19 pandemic (105, 106). Many different factors may explain differences in how rapidly pharmaceutical manufacturing systems in India and Indonesia were able to recuperate, including redundancy of supply, duration of public health measures and regional dispersion of production, which enabled some provinces to continue manufacturing when others were experiencing higher levels of public health measures.

Similarly, Bangladesh relies on Indian and Chinese API imports for its manufacturing sector, and as a result experienced a significant and durable interruption in production in the early weeks of the pandemic (107). Bangladesh manufactures medicines for a sizeable domestic market, but is also a key producer of medicines exported to other least developed countries (LDCs). Bangladesh is the only LDC with a significant pharmaceutical manufacturing industry. As an LDC, Bangladesh is exempted until at least 2033 from sections 5 and 7 of part II of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) that require countries to protect pharmaceutical patents and clinical trial data. It is therefore likely that the interruption to manufacturing in Bangladesh disproportionately affected medicine markets in import-dependent LDCs, but this study did not have adequate data to test this hypothesis.

With 112 manufacturing facilities and 18 public pharmaceutical manufacturers capable of producing 16.6 billion pharmaceutical units per year (108), Brazil has the seventh-largest manufacturing sector in the world; however, the pharmaceutical sector imports 90% of raw materials (109). While there are no systematic data published on the effect of COVID-19 on production in Brazil, the reliance on imported APIs likely explains the sharp increase in

notifications of medicine discontinuations during 2020–2021 (see **Chapter 5** for more detailed analysis on Brazilian discontinuation data).

Nigeria has a relatively large pharmaceutical sector with more than 100 companies. However, there is little domestic API production, and more than 70% of prescribed medications are manufactured with APIs sourced from China and India (8). It is likely that these firms were affected by interruptions, but this study was not able to locate any comprehensive data on interruptions (8).

Sudan's pharmaceutical sector was significantly affected by COVID-19, which was exacerbated by challenging economic conditions (35). The Ministry of Trade and Industry reported that 19 of the country's 27 pharmaceutical factories that cover 45% of consumption were operating at only half of their production capacity (35).

3.2.2. Aseptic pharmaceutical product manufacturing

The manufacture of aseptic pharmaceutical products (i.e. intravenous and intramuscular products) and biotherapeutics was more sensitive to shortages and fluctuating supply of key inputs in the global supply chain. A review of medicine shortages during previous disasters found that limited diversification in API supply, especially for medicines that are complex to manufacture, is a driver of supply vulnerability during disasters (14). In addition to being more complex to manufacture, these products often rely on components that are also used in vaccine manufacturing, such as cell culture media, buffers and vials, as well as personal protective equipment (PPE), high-efficiency particulate absorbing (HEPA) filters and disinfectants to maintain aseptic areas.

Many countries imposed export restrictions on PPE with the intention of ensuring an adequate national supply for health workers, but these restrictions also had effects on sterile medicine product manufacturing, which requires PPE for aseptic processing. It is worth noting that even before the COVID-19 pandemic, the supply of injectable medicines was known to experience shortages more often than other formulations (110, 111).



Quote 3.2: manufacturer or their associations

“In our normal supply chain we would buy PPE and ship it to manufacturers because it's part of the gear that you need to wear in aseptic production. Suddenly Europe put a hold on PPE export. We had to put letters, to say that this was needed in our production plan here are associated supply chains that need to be put in place, so we don't experience disruptions.”

Manufacturing processes requiring PPE were also affected by the increase in its global cost. Increased global demand led to price increases of more than 20 times historical levels for some items of PPE [\(112\)](#).

3.2.3. Biotherapeutic manufacturing

Biotherapeutics (also known as biologics) have specific, additional manufacturing requirements that may create particular challenges in the context of supply chain disruptions or rapid increases in demand volume. Biotherapeutics are medicines that are manufactured using genetically modified living organisms. Examples of biotherapeutics include numerous oncology and rheumatology medicines, such as trastuzumab for breast cancer, infliximab for rheumatoid arthritis and insulin for diabetes.

The manufacture of biotherapeutics is significantly more complicated than the manufacture of non-biotherapeutic medicines (small-molecule medicines or SMDs) because of the larger number of steps involved, the specialist machinery required and vulnerability to small variations in manufacture [\(113, 114\)](#). Key biotherapeutic manufacturing sites include Argentina, Canada, China, Germany, India, Israel, Japan, Poland, Republic of Korea, Switzerland and the United States [\(115\)](#). Biologics are in general significantly more expensive than SMDs, and their use is concentrated within high-income countries. A small but growing number of biotherapeutics are included in the WHO Model List of Essential Medicines (EML).

There are limited data on the effects of the COVID-19 pandemic on biotherapeutic manufacturing. This theme was not discussed in the academic or grey literature, or during the interviews. Among countries where shortages data were analysed (Australia, Brazil, South Africa and the United States), there were no reports of shortages caused by manufacturing issues for any biotherapeutic medicine included in the WHO EML [\(6, 116-119\)](#) (see also **Chapter 5** for a more detailed analysis of shortages data reported in national databases). Expanding the scope to include biotherapeutics not included in the WHO EML, but with marketing approval in their respective jurisdictions, led to the identification of a small number of isolated reports. In Australia, there was a shortage notification lasting from May to July 2021 for dupilumab, a monoclonal antibody (mAb) licensed in Australia for atopic dermatitis [\(116, 120\)](#). Australia, Brazil and the United States reported shortages of tocilizumab as a result of increased demand [\(116, 117, 119\)](#). Tocilizumab, a mAb marketed in some countries for rheumatoid arthritis, is now recommended by WHO for use in the treatment of COVID-19 in patients with severe or critical COVID-19 [\(121\)](#).



Although there are insufficient data to draw conclusions on the impact of COVID-19 on biotherapeutics, a number of unique features of biotherapeutic manufacturing make it more susceptible to the effects of pandemics and/or natural disasters compared with SMDs. Biotherapeutics are generally more sensitive to storage and handling conditions (122). In general, biotherapeutic manufacturing plants are fewer, larger and have greater up-front construction costs compared with those for SMDs (123, 124). This implies that disruptions to the functioning of one plant could have a significant effect on global supply. Biotherapeutic manufacture also requires a range of specialist input materials (e.g. chromatography media) that are often sourced from a single supplier. As an example of the challenges associated with mono-source inputs, the manufacturing of N,N'-methylenebisacrylamide, an ingredient in Sephacryl chromatography media, was affected by the 2011 tsunami in Japan (125). The company moved manufacturing to another site and was only able to offer a validated product 2 years later (125).

Biotherapeutic manufacturing is also more vulnerable than SMD manufacturing because it depends on the safety and stability of a cell bank. In biotherapeutic manufacturing, a master cell bank (MCB) is expanded to generate a working cell bank (WCB) that produces the cells used for large-scale production. WHO good manufacturing practices for active pharmaceutical ingredients, based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), recommends that "manufacturers should carefully consider the steps that can be taken to provide for protection from catastrophic events that could render the cell bank unusable[.] Manufacturers should describe their plans for such precautions; for example, these may include redundancy in the storage of bank containers in multiple freezers, use of back-up power, use of automatic liquid nitrogen fill systems for storage units, storage of a portion of the MCB and WCB at remote sites, or regeneration of the MCB" (126, 127). There

are a number of private services for off-site cell banking. However, there is currently no requirement for the number of redundant cell banks and the breadth of geographic distribution in the case of emergency. Regulatory authorities do not routinely collect master and working cell banks.

3.2.4. Primary packaging

Primary packaging includes all packaging that is directly in contact with a medicine (e.g. blister pack, vial or ampoule). For many parenterally administered medicines, the preferred material for primary packaging is glass (128). There was agreement among interviewees that, during the early months of the pandemic, there was an unprecedented rise in global demand for type I borosilicate glass (used in most medical vials and vaccines), which led to stockpiling, uncertainty and disruptions in the market. At least one major global supplier of vials diverted reserves of medical glass to vaccine production (129).

3.2.5. Human resources

Absence because of self-isolation by those infected with COVID-19 or quarantining following a (potential) COVID-19-positive contact affected the workforce. In a survey conducted by the WHO Regional Office for South-East Asia, antiretroviral manufacturers reported that they were operating with 50–80% of the normal workforce, which affected work in production plants as well as loading trucks (104). This was further exacerbated by the lack of ground transport needed to reach warehouses (104).

Physical distancing measures affected the number of workers available or permitted to work. The Joint United Nations Programme on HIV and AIDS (UNAIDS) undertook a situational analysis in May 2021, interviewing eight generic manufacturers in India as well as manufacturers in seven other countries. Their analysis found that plants in India were limited to approximately half of normal staffing levels because of national physical distancing measures (72).

In a number of countries, physical distancing policies included exceptions for workers in plants manufacturing essential goods. In India for example, manufacturing sites for pharmaceuticals, medical devices, relevant raw materials and intermediates, as well as packaging, were included in exceptions to closures of industrial establishments [\(130\)](#).

3.2.6. Quality assurance

Planned in-person inspections of facilities for good manufacturing practice (GMP) and other quality assurance certifications were delayed by the pandemic. Some actors adapted normal practices to minimize knock-on effects: for example, the United Nations Population Fund (UNFPA) used virtual inspections, and some SRAs temporarily postponed facility inspections.

About 1 month after the declaration of a COVID-19 pandemic, the United States Food and Drug Administration (USFDA) announced that it would “temporarily [postpone] all domestic and foreign routine surveillance facility inspections” [\(131\)](#). Among other effects, travel restrictions delayed inspections of Chinese pharmaceutical manufacturing facilities, with the effect of

delaying API exports that await certification [\(132\)](#). The USFDA resumed “mission critical” and “prioritized domestic” inspections about 6 months later [\(131\)](#).

3.2.7. Small and medium enterprises

The interview and export data used in this analysis are not likely to capture the experience of small and medium enterprises (SMEs) that have production primarily directed at the domestic market. More generally, a systematic review by Chowdhury et al. [\(133\)](#) demonstrates that there is limited literature on SMEs across sectors and supply chain interruptions. There is a number of reasons to expect SMEs to be less resilient to employ compared with large, multi-site API producers, including lower capital availability, less fluid inventory and/or capacity buffers, less market power to negotiate with back-up suppliers, and less product and process flexibility [\(133-137, 182\)](#). Further research is needed to describe and analyse the challenges to supply chain resilience that are unique to SMEs.



As the health system mobilizes its scarce resources to respond to the COVID-19 pandemic, shortages of essential drugs and disposables have reached critical low levels and are affecting provision of critical health services for patients with chronic conditions in Gaza Strip. The World Health Organization handed over life-saving hemodialysis drug supplies to the local health authorities in the Gaza Strip. These essential drug supplies will help maintain life-saving support for up to 900 patients, including at least 821 regular hemodialysis patients. This delivery was made possible with the generous support of the Government of Czech Republic. © WHO

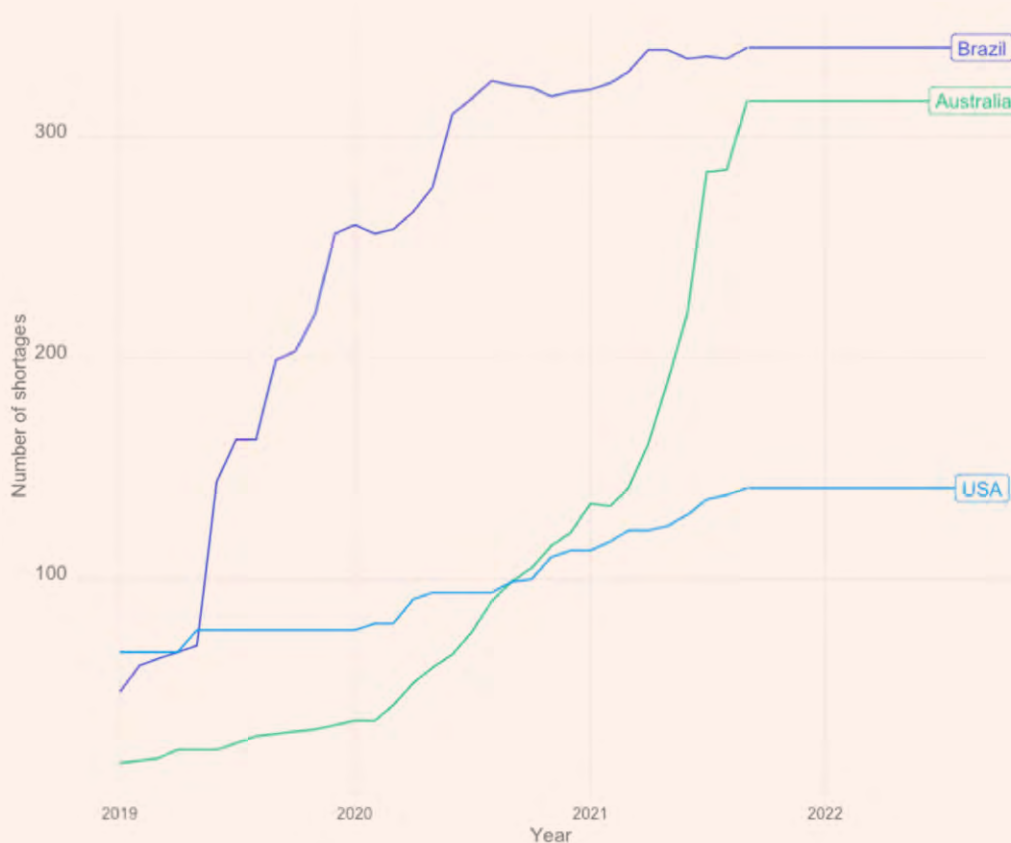
3.3. Did upstream manufacturing interruptions cause shortages?

Qualitative data from interviews and quantitative data from shortages databases were divergent in their assessment of the duration and degree of upstream manufacturing interruptions. According to interviewees representing procurement or supply chain roles and from the private sector, significant interruptions to manufacturing of SMDs were likely resolved by June or July 2020. However, data from national shortages databases in Australia, Brazil and the United States indicate an increase in manufacturing interruptions that led to medicines shortages throughout this period (Fig. 3.2). These shortages databases include records of notifications by manufacturers and wholesalers to national regulatory authorities of anticipated shortages and the causes. Shortages

databases from these countries were used because they are publicly available and report the specific cause of shortage events. The experiences of these countries cannot be generalized globally to all markets. However, as large, affluent markets, they are likely to be indicative of broader global trends. See **Chapter 5** for a more detailed analysis of shortages data reported in national databases.

Manufacturing and API-attributed shortages increased by more than 15 fold in Australia between March 2020 and September 2021 (the last available data). The number of shortages attributed to API supply or manufacturing was increasing prior to the pandemic, and continued at a similar rate until 2021 when the rate of increase plateaued but remained high in absolute terms. In the United States, there was a sharp discontinuity in March–April 2020 followed by a gradual increase until the last available data in late 2021.

Fig. 3.2. Drug shortages attributed to API or manufacturing problems



Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, and United States Food and Drug Administration.

3.4. Did manufacturing interruptions affect the price of APIs?

Interview data include self-reported assessments of interruptions by pharmaceutical manufacturers and purchasers. Shortage data provide a lens into the effect of these interruptions in large markets.

To understand the impact of manufacturing interruptions during intermediate stages of the production process, data on API exports from India were analysed to identify changes in prices in raw materials. Smaller production markets are likely to have had more significant interruptions, but a shock in prices in India is likely to indicate a shock in global market prices for APIs. Although India and China produce the majority of APIs used globally, only API data from India are analysed as data were not available for exports from China.

The NCD medicines analysed were selected from the core basket of essential medicines and those included in WHO Country Capacity Surveys, namely: amlodipine, aspirin, bisoprolol, budesonide, gliclazide, human insulin, hydrochlorothiazide, lisinopril, losartan, metformin, nicotine (for nicotine replacement therapy), salbutamol and simvastatin (137). No data were available for benzathine penicillin and oral morphine.

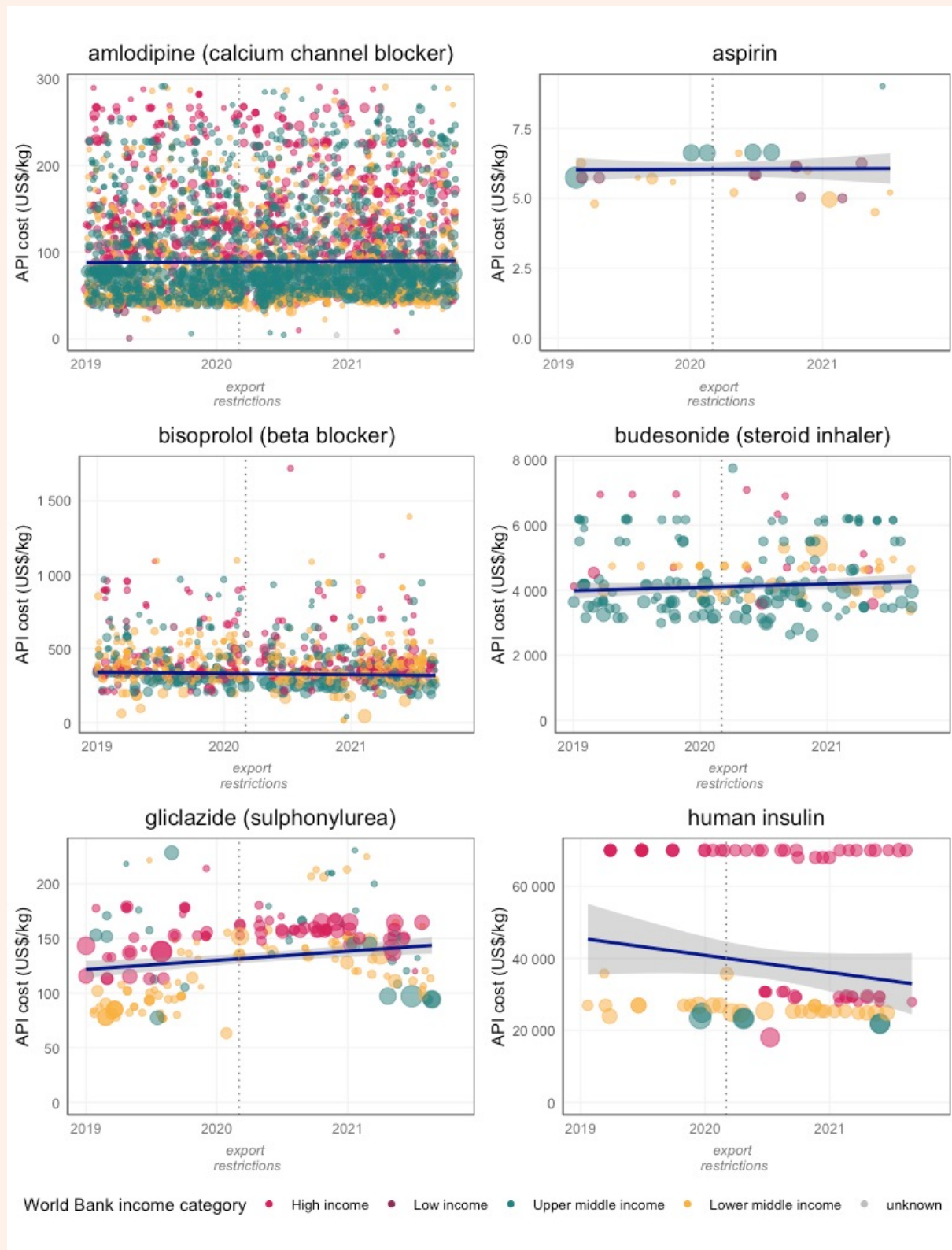
Data on API shipments exported from India were extracted from a commercial customs database. The database provides data as reported in Indian customs declarations, including: the date of shipment; a short description of the shipment; quantity and measurement units (e.g. 100 kg); the declared value of the shipment in Indian rupees and US dollars; and destination country.

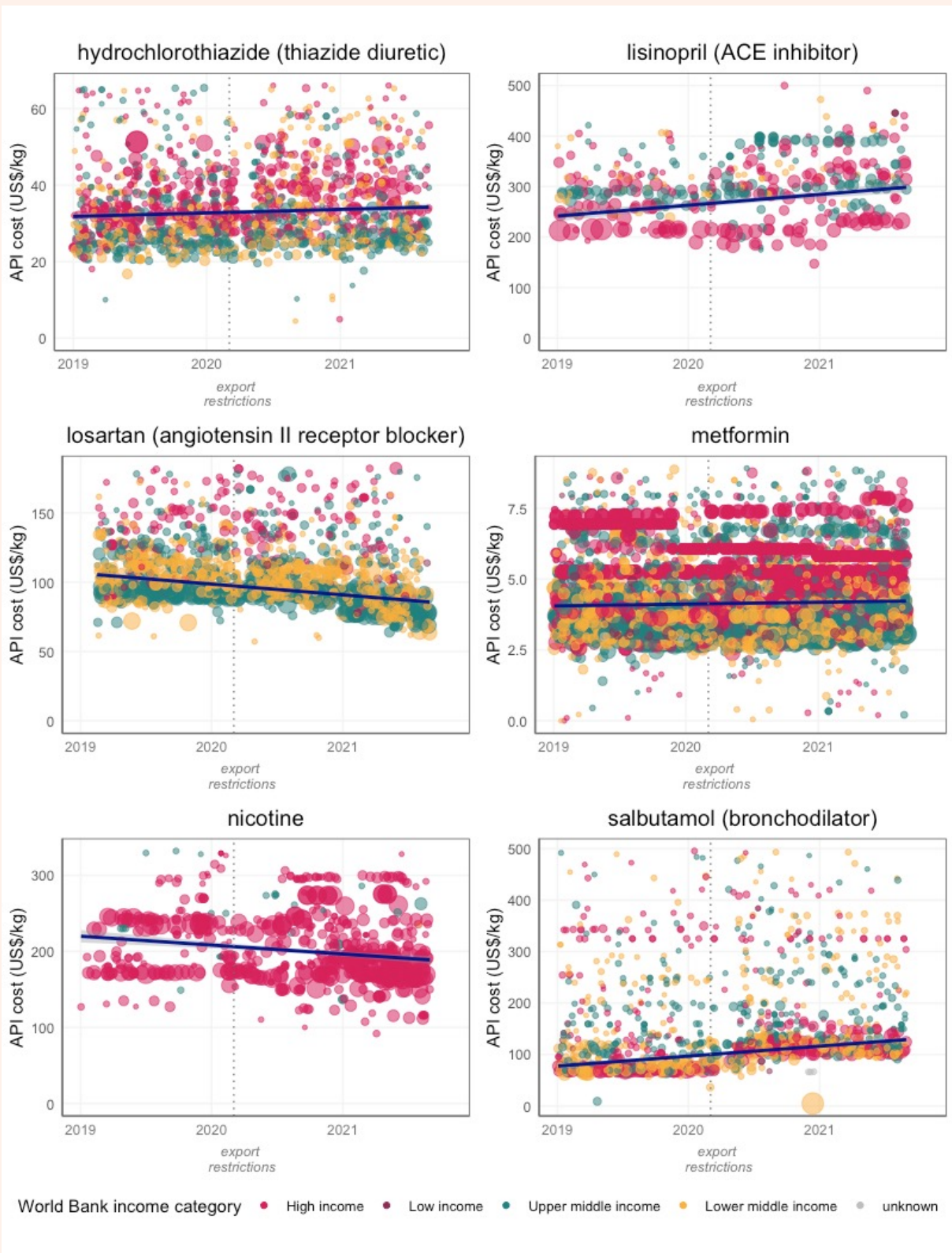
API exports were identified by querying the database using the international nonproprietary name (INN) of each of the 13 medicines. Exports were limited to those dated between 1 January 2019 and 1 October 2021. Data were manually cleaned to remove entries that likely do not represent pure APIs and to remove statistical

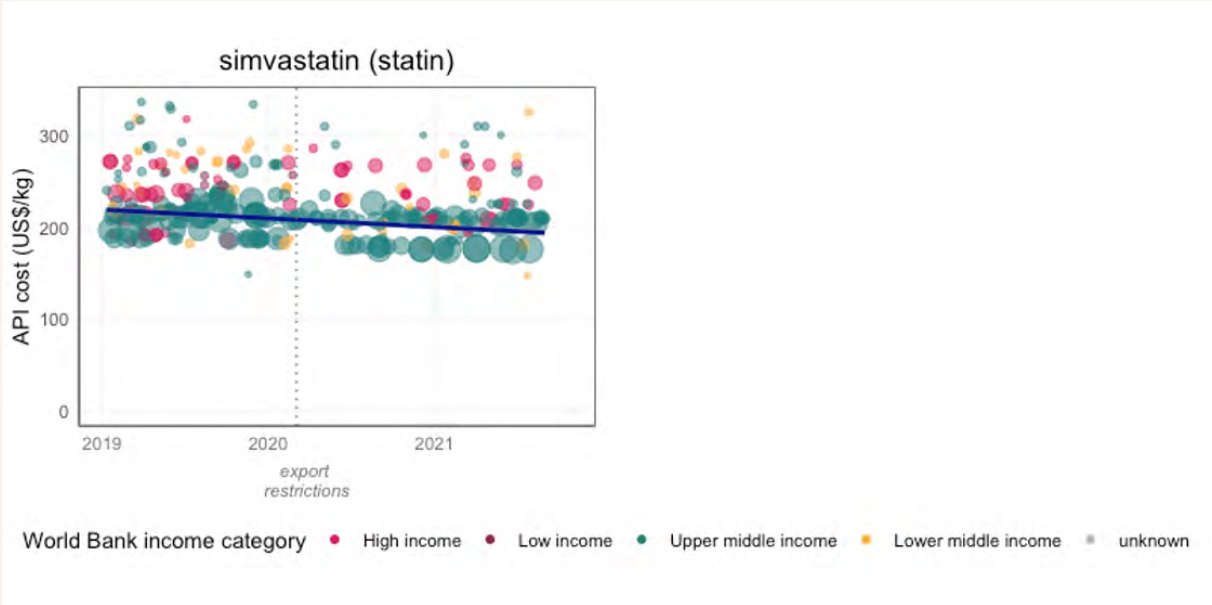
outliers, following methods published in earlier analyses of pharmaceutical API exports (138). The visualizations in Fig. 3.3 show a variety of trends in prices of APIs exported from India. Larger bubbles correspond to larger shipments, and the colour of bubble corresponds to the income category of the destination country for each individual API shipment. A model of API price trend was then calculated through least-squares regression weighted for shipment size, using R version 4.1.2.



Fig. 3.3. Cost (US\$/kg) of key NCD medicine API exported from India, 2019–2021







Getnet Hailu,26, is photographed in a pharmacy at Yeka health center in Addis Ababa, Ethiopia. © WHO / Maheder Haileselassie

Table 3.1.

Cost (US\$/kg) of key NCD medicine APIs exported from India, 2019–2021

Medicine ^a	Export records meeting inclusion criteria		Coefficient (change in US\$/kg/year)	2019 average cost (US\$/kg)	Relative change from 2019 to 2020 (%)	2020 average cost (US\$/kg)	Relative change from 2020 to 2021 (%)	2021 average cost (US\$/kg)
	No. records	Total quantity (kg)						
amlodipine	3,549	977,439	+0.75	90	-3	87	+3	90
aspirin	26	67,450	+0.02	6	0	6	-17	5
bisoprolol	932	62,897	-7.97	335	0	335	0	334
budesonide	211	1367	+104.17	4145	-2	4062	+5	4276
glucilazide	192	55,762	+8.31	121	+27	154	-14	133
human insulin	92	1018	-4746	43 904	-16	36 686	-2	35 997
hydrochlorothiazide	1,502	561,415	+0.93	33	0	33	+3	34
lisinopril	399	90 022	+21.35	253	+7	271	+8	294
losartan	1,766	1 748 635	-7.76	100	0	100	-15	85
metformin	5,835	60,608,365	+0.06	4	0	4	0	4
nicotine	577	324,845	-11.67	214	-3	207	-9	188
salbutamol	1,231	195,482	+19.29	83	+34	111	+10	122
simvastatin	322	153 203	-9.44	214	-5	204	-4	196

US\$: United States dollars.

^a No data were available for benzathine penicillin and oral morphine.

For many APIs, a clear interruption can be seen in the first quarter of 2020, corresponding to the start of the COVID-19 pandemic beyond China (Table 3.1). The amount of total APIs exported (kg) as well as the number of individual shipments varied widely between medicines, with aspirin having the fewest individual shipments and metformin having the most. A lower number of shipments implies that there was little export of the API in question. However, this does not imply that there was no substantial export of the medicine in question from India. Exports of FPP, such as aspirin tablets, may well be far greater; these data only reflect cases in which the API is exported from India to be formulated into a FPP elsewhere. The APIs examined here resumed export at essentially the same price as before the interruption in the first quarter of 2020, with the exception of one: salbutamol demonstrated a pronounced stepwise increase in price at the time that governments began instituting restrictions in response to the COVID-19 pandemic. It is noteworthy that, among the APIs included here, there were reports that salbutamol was used for treating COVID-19 symptoms; this was not a WHO-recommended treatment.

Fig. 3.3 also illustrates the distribution of API exports by income level of destination countries. APIs such as losartan and amlodipine show clear market segmentation: the least costly APIs are shipped to lower-middle-income markets, followed by upper-middle-income markets, with the costliest APIs going to high-income markets. There is little API from India shipped to low-income markets, likely because (with the exception of Bangladesh) no low-income markets have significant pharmaceutical manufacturing sectors to process API into FPP.

The disaggregation by income category reveals differential impacts for some products. Looking closely at the effect of export restrictions on prices of API for simvastatin, high-income markets were not affected but upper-middle-income purchasers experienced a sharp increase in price and drop in volume throughout the first quarter of 2020. While not conclusive, this suggests that (i) low-income market segments were disproportionately affected; (ii) manufacturers prioritized contracts with

higher margins; and/or (iii) contracts in lower-middle-income countries were put on hold or cancelled.

3.5. Actions taken by stakeholders to anticipate, prevent and mitigate manufacturing disruptions

A review of the academic literature and information gathered from interviews gives some insight into the risk mitigation activities undertaken by manufacturers, wholesalers and states to avert disruptions to pharmaceutical manufacturing during the COVID-19 pandemic. Effective risk mitigation strategies are context specific; these findings should be interpreted as a review of what happened during the first year of the pandemic, rather than a review of strategies that are universally applicable or effective.

3.5.1. Scoping review

Without a precedent for an event of this scale, the published literature on worldwide manufacturing and coordination interruptions is non-existent. A limited number of previous studies of supply chain crises have focused on regionally isolated shocks or individual manufacturing facility shutdowns. The scoping review did not identify any papers with manufacturing pathways as a primary outcome. Six papers addressed secondary and incidental outcomes. The literature does not address underlying mechanisms that interrupt manufacturing pathways, but rather documents specific examples of API shortages or API shortage surveillance strategies. See **Table 2.1** for a summary of included papers by pathway, disease category and location.

The scoping review identified a number of actions taken by states to stabilize manufacturing of priority medicines. Abdoli [\(7\)](#) summarized the indirect and direct effects of economic sanctions against the Islamic Republic of Iran on the pharmaceutical manufacturing sector. Enríquez-Fernández and del Castillo-Rodríguez [\(22\)](#) described special powers and orders passed in Italy

and Spain relating to information sharing between manufacturers and regulators, as well as prioritization of manufacturing key medicines. Handfield et al. (27) described the failures of the United States Strategic National Stockpile (SNS) and recommended advance contract agreements for key materials as a risk mitigation strategy. Liu et al. (33) described upstream-focused risk mitigation actions undertaken by regulatory authorities to avert shortages of key medicines, including expedited review and import permissions for new API suppliers.

3.5.2. Risk mitigation and manufacturing: perspectives from interviews

While no firm anticipated the effects of COVID-19, common themes from interviews were the importance of risk mitigation plans made in advance, prioritization, coordination and increased information sharing across firms and sector.

3.5.3. Risk assessment across raw material sources: mapping critical infrastructure and simulating possible scenarios to identify vulnerabilities

Some pharmaceutical manufacturers mapped their network of critical raw materials and suppliers as part of routine risk mitigation efforts. These maps were used to (i) assess geographical diversity of suppliers and (ii) build models of the flow and timing of shipments. These models were then used

to simulate the effects of the collapse of any given node on other nodes, as well as the supply chain network as a whole, to identify potential vulnerabilities and bottlenecks. From this information, some manufacturers reported that they were able to prioritize the supply of certain manufacturing components or medicines for additional back-up, and secure advance agreements and quality assessments with potential so-called surge suppliers.

One key benefit of mapping is obtaining a better understanding of the ultimate source of components. Many FPP producers purchase APIs from other firms, and some API producers are in fact re-selling imported APIs. There is no comprehensive source documenting the number of API suppliers for medicines. Purchasers can stipulate that manufacturers share information about upstream sources as a contract term, but this needs to be done in advance of purchase, regularly re-assessed and results integrated into a risk mapping model. Some APIs are only produced by one firm globally; in these cases, higher levels of safety stock (also known as security or buffer stock) are needed to adjust for the higher risk of manufacturing interruptions and stockouts. With single-supplier medicines, higher safety stock is never a guarantee. A minimum of 6 months to 1 year (and frequently longer) is required for a new firm to receive authorizations necessary to begin production and export. Few health systems can purchase and store the volume of safety stock that would be required if a monosource producer suddenly went offline.



Quote 3.3: non-governmental organization

"We try to know the API location for each product. Sometimes the manufacturers say it's confidential...for some molecules, you can have ten different offers, but the API at the beginning is the same. It's a domino effect, it's a stockpile strategy... if monosource has a quality issue, everyone struggles."

Although modelling can help anticipate brittle points in the supply chain and optimize outcomes in a context of high levels of uncertainty at multiple nodes, it is not without its shortcomings in an emergency context. First, the probability of unlikely events such as a pandemic or natural disaster affecting a key manufacturing site such as Wuhan could not have been predicted with any accuracy. Second, the most sensitive parameters in a model are likely to be dynamic and affected by political choices, for example, whether countries close borders or if other firms buy out the market of raw supplies. With such a small sample of manufacturing interruptions at the global scale, the experience and responses of countries and manufacturers during the COVID-19 pandemic will weigh heavily in the future models, parameters and sensitivity analyses that structure risk analysis and mitigation plans.

3.5.4. Increasing safety stock of vital components for manufacturing

One useful output of mapping exercises is the identification of critical materials with a narrow and/or risky supplier network. Pharmaceutical companies report the approving of new suppliers, such as those for packing and packaging, and renting additional warehouse storage. Reports from both the grey literature and the interviews describe the challenges of storing finished product at times of reduced downstream distribution (72). One firm reported renting extra warehousing to store 6 months of safety stock, up from 3 months before the pandemic. Rented warehousing was also needed to store increased stockpiles of critical raw materials. Firms with factories in different districts or countries could relocate production according to the changing effect of the pandemic at particular sites, shifting materials where needed. When some factories were shut down because of quarantine, others were running overnight and at weekends with staff working overtime.

Firms with sufficient resources to secure large volumes of stock of critical materials were able to protect their own operations, but this had knock-on effects across the supply chain and led to inefficient allocation of raw materials as well as medicines. The inequity in distribution in the event of a shock in supply and demand, such as during a global pandemic, was not

unexpected; one review on local manufacturing in Africa during COVID-19 reports, “many African stakeholders have been warning for years that in a global pandemic, African needs would be sidelined in a global nationalistic rush to buy up essential supplies [; in] 2020, it happened” (87). The same review describes the experience of a large East African manufacturer, whose routine order of bulk chloroquine API from India increased from an accepted bid of US\$ 32 per kg in November 2019 to US\$ 260 per kg in January 2020, forcing the recipient to cancel the order (87). One interviewed organization, which undertakes significant procurement, reported challenges in acquiring medicines that were advertised but not available. In that case, the originator offered a set price, but the licensed distributor would not honour the price, citing import taxes and other mark-ups. As a result, public authorities were unable to purchase the needed medicine.

3.5.5. Local production

After an overall decline in recent years, policy interest in local production to improve access to medicines was revived during the COVID-19 pandemic. The 2019 interagency statement (The Global Fund to Fight AIDS, Tuberculosis and Malaria; UNAIDS; United Nations Conference on Trade and Development (UNCTAD); United Nations Children’s Fund (UNICEF); United Nations Industrial Development Organization (UNIDO); and WHO) noted the role of local production in improving access to quality-assured medical products and achieving universal health coverage. The signatory organizations will “aim to work in a collaborative, strategic and holistic manner in partnership with governments and other relevant stakeholders to increase local production” (139). World Health Assembly resolution 74.6 Strengthening local production of medicines and other health technologies to improve access notes that local production of medicines can enable greater sustainability of supply chains, especially during public health emergencies (140).

Examples of local production during the COVID-19 pandemic include starting or scaling up production of azithromycin, dexamethasone and paracetamol (87). Local production of health equipment also increased, including sanitizers, masks, gloves, overshoes, face shields, medical scrubs, PPE, ventilators, viral transport media and test kits (87). Although local manufacturing

was important in some countries for COVID-19 commodities, it was not a risk mitigation strategy employed during the pandemic to address NCD medicine availability. The length of time and quantity of resources required to establish or repurpose manufacturing sites and secure regulatory approval is substantial; as a result, local production can have a role to play in long-term supply resilience strategies, but is not a pragmatic or efficient reactive measure in the short term, for example, to address shortages or increased demand during an emergency.

A 2011 WHO review of local production for access to medical products found mixed benefits for cost savings: in some countries, locally produced medicines are less expensive than foreign-made counterparts (Bangladesh; India; and occupied Palestinian territory, including east Jerusalem), but they were found to be more expensive in other countries (Brazil, Malaysia, Türkiye, United Republic of Tanzania and Viet Nam) (141). The review found evidence of local production having a positive effect on supply reliability and quality standards in high-income countries, but no evidence in either direction in low- and middle-income countries (141). Although local production can improve supply diversification and stability, there are a number of challenges. Depending on the economic and political environment, local production may not be more cost-effective or reliable than relying on imported medicines (142). Economies of scale may not be achievable in local markets. Similarly, some products with relatively small patient populations may not support efficient production by many actors. Many countries allow for tariff-free importation of FPP medicines and vaccines, but apply tariffs to API or component imports. Smaller manufacturing sites are also more vulnerable

to changes in demand. These added risks may affect the ability of local firms to secure needed credit or financing for initial capital costs. Other sources of financing have included public ownership, public-private partnerships and loans from multilaterals such as the World Bank.

Technology transfer is an important driver of feasibility and cost-effectiveness. An UNCTAD review of local production notes that countries “that demonstrated the most advanced levels of production had absorptive capacity (human skills and scientific infrastructure) that was strengthened consistently through technology transfer” (143). The first COVID-19 mRNA vaccine technology transfer hub was established by WHO, the COVID-19 Vaccines Global Access (COVAX) Facility partners, a South African consortium comprising Biovac and Afrigen Biologics and Vaccines, a network of universities, and the Africa Centres for Disease Control and Prevention (144). Another global training hub has been announced in Seoul, Republic of Korea, serving all low- and middle-income countries seeking to manufacture biologicals, including vaccines, insulin, mAbs and cancer treatments (145).

Some of these parameters were already changing before the pandemic, with new technologies and processes reducing the costs of manufacturing and capital required in some instances. Global shortages of key products, high prices for inputs, and slow and costly freight in the context of the COVID-19 pandemic have contributed to a further re-evaluation of the business and public health cases for local production. Policy discussions on the economic case for local production may use the experience of COVID-19 to refine parameters to estimate risk in cost-effectiveness analyses evaluating local production in a given context.



Quote 3.4: non-governmental organization

“The main thing that we need to start looking at is local production... It is [emphatically untrue] that we do not have the knowhow or capacity. People question me, who says we can't manufacture a medicine cheaper?”

“We put all our eggs into one basket, and we never thought that this was going to hit us. But now that it has, we're starting to look at local production.”

Summary: Manufacturing

Pharmaceutical manufacturing was moderately to severely disrupted in the early weeks of the pandemic (January 2020 in China, March to April 2020 in most other countries). Disruptions were the result of turbulence in the upstream and downstream supply chains as well as the unpredictable operating environment brought about by the COVID-19 pandemic. Most manufacturing risk mitigation plans did not anticipate the magnitude of global supply interruptions, including the multiple export bans and other policy responses implemented by governments. Mitigation measures such as compensating or shifting operations in response to reduced capacity or limited manufacturing inputs were only partially successful. Manufacturing that depends on imported active pharmaceutical ingredients (API) was particularly sensitive to supply chain interruptions.

According to interviews with professionals working in procurement and in the private sector, there were more API-related shortages after April 2020 than in a typical year, but manufacturing delays had largely been resolved by May 2020. Reports from selected national shortages databases that document the cause of the shortage gave a slightly different picture: from the start of the pandemic to early 2021, there were increases in the rates of shortages related to manufacturing and API supply (data covering Brazil, South Africa, and the United States). Average prices of API exported from India increased over 2020-2021 for budesonide, gliclazide, lisinopril, and salbutamol. API prices remained stable for amlodipine, aspirin, bisoprolol, metformin, and hydrochlorothiazide, and decreased for human insulin, losartan, nicotine, and simvastatin. Of these medicines,

the most pronounced price change during the start of the pandemic was seen for salbutamol. For some medicines, data suggests that low-income market segments were disproportionately affected.

NCD pharmaceutical manufacturing plants were affected by shortages and delays in sourcing of manufacturing input materials (e.g. KSM, API, machine components, glass, vials, packaging, personal protective equipment needed for aseptic manufacturing). Obtaining key input materials was further complicated by delays in cross-border transit of goods and export/import restrictions in some jurisdictions: while medicines were generally classified as 'essential' and permitted to pass through priority lanes where available, key manufacturing components were not. The manufacturing workforce was also affected by a) illness or caring responsibilities, b) curfew, quarantine, or stay-at-home measures and c) physical distancing requirements within workplaces. Physical inspections of pharmaceutical manufacturing plants, required for regulatory approval, were in some cases delayed.

Risk mitigation strategies to address manufacturing interruptions included:

- Implementation of pre-existing risk management plans and protocols
- Supply chain mapping for critical raw materials and suppliers, as well as vetting of diverse backup suppliers
- Domestic API manufacturing, especially for countries particularly affected by border closures
- Information collection and sharing to identify shortages and expected resolution



Female pharmacist at work in a pharmacy during the COVID-19 pandemic. © WHO

Policy Considerations: Manufacturing

Regulatory authorities in collaboration with the manufacturing entities could consider strengthening data and reporting mechanisms including reporting any anticipated interruptions to supply and/or demand increases, the availability of critical infrastructure, supply sources, and manufacturing capacity, the cause of interruptions and expected duration. Furthermore, risk evaluations could be conducted and risk management plans and mitigation measures being

implemented with a transparent prioritization process.

Subsequently, global actors should also consider developing reporting standards and data indicators for health product shortages, to enable comparability and upstream visibility of global production and supply, leverage local manufacturing, and institute market-shaping interventions to diversify supply and improve access to NCD medicines.

4. PROCUREMENT, IMPORTATION, AND LAST MILE DELIVERY

4.1. Background

This chapter integrates evidence from the scoping review of academic literature, the desk review of grey literature, and qualitative data from interviews with stakeholders and academics. Through the interview process, key informants were asked about changes in freight charges, lead times, purchasing schedules and procurement volumes as a result of the coronavirus disease (COVID-19) pandemic. They were also asked to describe challenges in customs clearances, the effect of confinement rules on freight in supply chains, the impact of currency fluctuations and budget re-allocations, and strategies to modify standard dispensing to promote facility- and patient-level access (see the questionnaire in **Annex 2: Procurement and importation; Distribution**). Where possible, this information was then corroborated through other sources, including trade reports, press materials, and statements by manufacturers and trade associations.

First, supply chain challenges are outlined (**Sections 4.2–4.9**), followed by an overview of interventions made by different actors to anticipate, prevent and mitigate these disruptions (**Section 4.10**).

4.2. Export restrictions

The World Trade Organization (WTO) estimated that, as of April 2020, 20 countries

and customs territories had introduced export restrictions on medicines in response to COVID-19 (146). Most export restrictions covered personal protective equipment (PPE) and COVID-19 diagnostics. Some export restrictions required exporters to demonstrate that goods to be exported were being used for the production of essential goods in the importing country. However, there is no global standard for goods to be considered essential; even where governments have given national definitions for essential goods, these definitions have sometimes been ambiguous or changeable.

India's Directorate General of Foreign Trade (DGFT) issued a notification on 3 March 2020 restricting the export of 26 active pharmaceutical ingredients (APIs) and formulations, affecting 10% of India's overall pharmaceutical industry (84, 147) (Box 4.1). Restrictions were announced in response to a review by the Department of Pharmaceuticals on the availability of API stocks (148). It is reported that 70% of raw materials used in Indian pharmaceutical manufacturing was sourced from China before the pandemic, with Hubei as a key manufacturing province. Restrictions on API exports were implemented to anticipate the expected supply shock from China, although China did not at any time implement export bans on bulk API. In addition to export bans, Indian missions in six countries were asked to explore other sources of raw materials in their respective countries (148).

Box 4.1. Timeline of pharmaceutical export restrictions in India

3 March 2020:

India's DGFT restricts the export of 26 APIs and formulations. Restricted APIs included: acyclovir, chloramphenicol, clindamycin, erythromycin, metronidazole, neomycin, ornidazole, paracetamol, progesterone, tinidazole, and vitamins B1, B6, and B12, both in raw form and as formulations.

20 March 2020:

Clarification allows planned exports of APIs with advanced licenses for export issued before the 3 March announcement (149). Factories in SEZs were permitted to continue to export restricted APIs (149).

25 March 2020:

Amendment prohibits the export of hydroxychloroquine and its formulations (150).

4 April 2020:

Exceptions to restrictions on the export of hydroxychloroquine are extended to remove exceptions, including on humanitarian grounds and for product produced in SEZs (151).

6 April 2020:

Restrictions are lifted on the export of acyclovir, chloramphenicol, clindamycin, erythromycin, metronidazole, neomycin, ornidazole, progesterone, tinidazole, and vitamins B1, B6 and B12, both in raw form and as formulations.

11 April 2020:

Amendment from DGFT prohibiting the export of remdesivir API and injections (152).

28 May 2020:

Restrictions on the export of paracetamol API are lifted, but restrictions remain on export of paracetamol formulations (153).

14 June 2020:

The prohibition on the export of remdesivir is amended to a restricted status.

18 June 2020:

↓ All restrictions on hydroxychloroquine export lifted (154).

API: active pharmaceutical ingredient; DGFT: Directorate General of Foreign Trade; SEZ: special economic zone.

Given their role in the overall pharmaceutical supply chain, production interruptions or export restrictions in India and China have received the most attention in risk assessments by purchasers. However, it is worth noting that for some categories of medicines, such as patented cancer medicines, a large proportion of global manufacture occurs in Europe and North America. Regional and local production play

a key role in generic purchasing for at least some products in nearly all countries.

Many other countries issued export bans or additional export licensing requirements for medicines in response to COVID-19, including Algeria, Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Greece, Hungary, Kuwait, Nepal, Norway, Pakistan, Poland,

Romania, the Russian Federation, Saudi Arabia, Serbia, Slovakia, the United Kingdom and Viet Nam (this list should not be considered as exhaustive). Some restrictions included humanitarian exceptions. However, one interviewee who was trying to export pain and palliative medicines through a humanitarian exception noted that, in practice, the exception still resulted in delays of many months.

4.3. Effect of border measures and customs delays

Export bans and/or added border checks and restrictions also prevented shipments of medicines from the unloading port to their final destination. The World Health Organization (WHO) Regional Office for South-East Asia conducted a preliminary assessment of Indian antiretroviral medicine manufacturers in March 2020, followed up by a questionnaire-based survey in May 2021 (104). All respondents reported that disruptions in international air traffic and sea shipping had affected operations and caused an increase in lead times (104). Although this assessment focused on major firms that manufacture antiretroviral medicines, the interruption in shipping would also have affected manufacturers seeking to export medicines for noncommunicable diseases (NCDs).

Landlocked countries were particularly affected by the intersection of increased border measures and interruptions in air cargo, as they rely on efficient cross-border transport from ports in other countries.

For example, in Uganda most imported medicines arrive by truck from the seaport of Mombasa, Kenya. Truck drivers were tested for COVID-19 and given certificates for negative results. However, delays introduced by this process led to traffic jams reported to be as long as 80 km, with drivers waiting days for testing and permission to enter. These delays incurred substantial costs in fuel, wages and COVID-19 tests (around 6000 Kenyan Shillings or 55 United States dollars in total per truck) (155).

In Zimbabwe, most imported medicines arrive by truck from seaports in South Africa or, to a lesser extent, Mozambique. A number of lockdowns and border closures on either side of the border led to significant delays in the flow of commercial traffic. Borders were closed in March 2020 and only partially reopened in November 2020 (156). Truck drivers entering South Africa were required to show COVID-19 test results obtained within the last 72 hours. The extended lockdown in Botswana added to pressure at the Beitbridge border crossing, already the busiest road border crossing in sub-Saharan Africa, because all traffic normally routed through Botswana was forced to re-route via Zimbabwe (157).

Lombe et al. (34) described the impact of COVID-19 on the management of cervical cancer patients in Zambia. Zambia imports radioactive isotopes for brachytherapy, and the suspension of commercial airline services led to a disruption in supply. The authors described flight chartering as a potential solution, but noted that source transportation licensing and in-country budget constraints prevented realization.

Customs clearance in some countries was delayed by a surge in demand, remote working by customs workers and shortages of workers to unload ships. Countries with significant existing trade barriers, such as those under sanctions, experienced cascading effects (Box 4.2).



Box 4.2. Intersecting impact of trade embargos and global disruptions in trade: the case of the Islamic Republic of Iran

A number of countries, including Afghanistan, Cuba, the Democratic People's Republic of Korea, the Islamic Republic of Iran and Venezuela (Bolivarian Republic of), are the subject of sanctions from other Member States, multilaterals and/or the United Nations Security Council. In most cases, sanctions have humanitarian exemptions that include certain medicines. Interviewees emphasized that, despite humanitarian exemptions, there are still key medicine shortages resulting from economic sanctions, bringing indirect economic, regulatory and administrative effects.

The Islamic Republic of Iran exemplifies the interaction and overlapping of baseline challenges from sanctions and the shock of the COVID-19 pandemic. There is significant domestic pharmaceutical manufacturing capacity, with 85 manufacturers and 20 API manufacturers (158). A total of 96% of medicines consumed in domestic markets is produced domestically.

Although the import of medicines is covered under humanitarian exemptions, the import of key components for manufacturing is not. Furthermore, firms are also unable to transfer money to Iran in foreign currency, and instead must accept foreign currency and/or barter for goods (159). Former United

Nations General Secretary Ban Ki Moon noted that "even companies that have obtained the requisite license to import food and medicine are facing difficulties in finding third-country banks to process the transactions" (160). As one example, while a US\$ 60 million order for an anti-rejection medicine for liver-transplant patients was in compliance with licensing from the United States treasury and was fully legal, no bank would facilitate the transaction and attempts to import the medicine were abandoned (159).

A review of medicine shortages in the Islamic Republic of Iran found that 89% of shortages were for medicines used to treat NCDs (158). Firms that previously produced medicines for heart disease, lung problems, kidney disease, multiple sclerosis and cancer have closed or faced bankruptcies, leaving patients to rely on imports of expensive specialist medicines (158). These pressures have contributed to a 30-fold rise in the cost of cancer treatment (7). During the COVID-19 pandemic, there was a shortage in reusable insulin pens. Imports from abroad, especially from manufacturers based in the United States, have only become more challenging during the pandemic as unpredictability and costs in the supply chain have increased.

API: active pharmaceutical ingredient; COVID-19: coronavirus disease; FPP: finished pharmaceutical product; NCD: noncommunicable disease; US\$: United States dollars.

4.4. Cold chain

The collapse of commercial airline routes in March–April 2020 also had a significant impact on the global distribution of temperature-sensitive medicines and health products (161). Of particular concern to interviewees working in logistics was preserving the cold chain for insulin. One interviewee reported that a cargo shipment of insulin had to be destroyed as a result of pandemic-related delays in unloading a cargo plane.

The availability and uptake of childhood vaccines, which require end-to-end cold chain storage and transportation, were also particularly affected by the global supply chain and transport disruptions. The United Nations Children's Fund (UNICEF), which procures about 45% of the global supply of vaccines for children aged < 5 years in about 100 countries, estimated there was a 70–80% reduction in planned vaccine shipments because of the dramatic decline in commercial flights and the limited availability of charters at the start of the global pandemic in March 2020 (162). In June 2020, UNICEF began organizing multi-stop charter flights to address the lack of available commercial flights to smaller countries where flights had been suspended as a part of their vaccine supply chain response (112).

Despite a gradual recovery of vaccine shipments to pre-pandemic levels from May 2020, widescale disruptions in routine vaccination campaigns were observed globally. In early May 2020, 99 countries reported the suspension of immunization campaigns for cholera, measles/measles rubella, meningococcal A, polio (including for vaccine-derived polio virus response activities), tetanus/diphtheria, typhoid and yellow fever (163). WHO and UNICEF data revealed that 23 million children missed out on basic childhood vaccines through routine health services in 2020, the highest number since 2009 and 3.7 million more than in 2019 (164).

4.5. Increase in freight costs because of reduced commercial options

Nearly all interviewees emphasized the rise in air and sea freight costs as one of the most significant disruptors to supply chains for medicines. Interviewees estimated that freight charges had increased from pre-pandemic costs by a factor of 2–6. Interviews were conducted before the more significant supply chain interruptions of late 2021, and freight charges may have further increased. Intranational and intraregional costs increased, although to a lesser extent, with interviewees reporting an increase of around one fifth compared with pre-pandemic levels.

International cargo transport of essential goods was not banned. However, cargo space in commercial passenger flights contributes a significant proportion of global air freight capacity. The cancellation of a large proportion of passenger flights led to volatility and unpredictability in air cargo availability, increased demand for remaining capacity, complete collapse for some routes and decreased cost efficiencies. Routes that require multiple connecting flights were particularly affected by cascades of delays and cancellations. Manufacturers reported that one effect of the reduced air cargo availability was that cargo companies were less likely to accept bookings for small-volume orders (104). This would have disproportionately affected small and medium enterprises (SMEs) and manufacturers serving small markets (e.g. treatments for rare diseases, paediatric formulations or less populous countries).

Maritime transport was also disrupted. Changes in port protocols included port closures, crew-change restrictions, changes in documentation requirements, and physical examinations of vessels and crew members (82). In some cases, vessels were required to quarantine prior to entry. In a sample of 125 jurisdictions across all regions, the Organisation for Economic Co-operation and Development (OECD) estimated that the technical and bureaucratic burden of additional border controls and clearance requirements peaked in March and April 2020, but had, on average, reverted to pre-pandemic levels by June 2020 (165).

4.6. Decreased payment flexibility

The economic shock of the early weeks of the pandemic reduced revenues for some manufacturers and wholesalers. Health financing was also disrupted in some cases, with funds re-allocated for emergency use. For health budgets where co-payments are a significant source of financing, revenue

decreased unexpectedly as many people shielded and elective care was postponed.

The rules and norms around payment contracts also shifted in some cases, with some manufacturers requiring full payment upfront despite not having previously required this. One interviewee, speaking about the experience of procurement in a low-income country, outlined the challenge.



Quote 4.1: non-governmental organization

“COVID was a situation [where] the cashflows of even big companies are also in difficulty, so they ask for money quickly...With the crisis, central medical stores had a big problem in paying the bill of the manufacturers [that are] outside of the country, [because] they say [that] they will answer the tender exclusively if you give [payment] up front. But in national procedure, payment is not allowed at the beginning. With [redacted insulin manufacturer] it was a big problem.”

Challenges relating to manufacturers changing norms and expectations for contracts and health systems suffering financing shocks are not unique to COVID-19. One interviewee recounted that the same challenge had occurred recently in the context of a coup, leading to a temporary suspension in the ability of the ministry of finance to release funds needed to purchase medicines on the agreed-upon schedule. The shock of COVID-19, however, exacerbated these existing challenges, subjecting health systems to cascading financing stresses. Two interviewees described specific situations where late payments to medicine suppliers caused the suppliers to demand full payment up front for other orders. In one case, the supplier bid on a number of other tenders, and did not release the ordered supply for any of the tenders until all outstanding balances were paid.

4.7. Inefficiencies from greater variability in anticipated demand

Levels of safety stock should correlate positively with expected risk and variability at any level of the supply chain. Where variability in demand is high, higher levels of safety stock are needed to prevent stockouts. Even with well executed stock rotation and no losses, maintenance of safety stock incurs storage costs, and most supply chains use lean methodologies to keep safety stocks at the lowest levels possible to guarantee supply, given anticipated shocks.



Quote 4.2: multilateral agency

“The problem is the money not the capacity. It’s not ‘How do I forecast?’, it’s ‘How do I know the demand?’”

In a push-based system, manufacturing responds to expected future demand; in a pull-based system, production responds to actual demand. Many systems are a hybrid. In the context of rapid and exponential changes in demand patterns for medicines during the pandemic, push-based systems were slow to react. Most pharmaceutical firms use some version of material requirements planning (MRP) and push-based planning. MRP schedules production and purchasing of raw materials, and requires detailed and accurate data on demand, quantities of raw materials and stock on hand, lead times from purchasers and time to manufacture goods. MRP systems are often configured to allow transfer of materials where needed within or across factories. Newer systems will optimize necessary buffer levels of raw materials and finished stock levels, taking into account variability.

In any supply chain management system, unexpected changes in human resources, export controls and stockouts of raw materials severely test even the most sophisticated resource planning and management system. The Forrester effect (also known as the bullwhip effect) describes the propensity for demand distortion to increase at each level of the supply chain.

In the context of the COVID-19 pandemic, anticipated higher demand globally led many medicine purchasers to increase orders upstream. Each link in the chain expects higher demand, from individual pharmacies to central medical stores to wholesalers to pharmaceutical manufacturers to API producers to raw materials producers. When uncertain anticipated demand information is passed along each stage of the chain, the variance increases. With high variance, each level of production is more likely to purchase the wrong quantity of materials, leading

to surpluses for some firms and stockouts for others. Relative to capacity, the global system performs less efficiently when demand is uncertain than it might if demand were steady, and this inefficiency is increasingly compounded at every level of the supply chain.

4.8. Last mile delivery

Due to increased health service demand, budget constraints and other capacity challenges, governmental and nongovernmental organizations supporting the public health sector face pressures to improve the distribution of medicines and health products to patients and end-users, more commonly called last mile delivery. The supply chain and health service delivery disruptions during the COVID-19 pandemic have made the exploration and implementation of innovations at the final and most important component of the medicine supply chain even more urgent.

The optimization and continuous improvement of transport delivery routes is a key focus area in the strengthening of last mile delivery systems. Mobile, global positioning system (GPS) and cloud-based data management technologies have enabled the development and implementation of more advanced, data-driven dispatching and route-planning decision-making tools. Route planning that considers multiple parameters such as delivery locations, fleet performance, real-time vehicle locations, traffic and weather allows for a more dynamic and flexible approach to the medicine and health product distribution process (166). By potentially reducing delivery times and distances, as well as the workload of warehouse packers, dispatchers and drivers, dynamic route planning introduces system efficiencies to improve last mile delivery.

The use of unmanned aerial vehicles (UAVs) in the distribution of medicines and health-related commodities has also been proposed to address certain last mile challenges. Although a relatively new technology under pilot testing in various countries, UAVs are seen as uniquely positioned to provide advantages in the distribution or collection of medicines and health products, particularly laboratory samples, in remote areas with difficult terrain, areas experiencing humanitarian challenges and where rapid delivery is critical (167). Due to their low operating costs and ability to be quickly and routinely deployed, UAVs have also been proposed to potentially support the care of older and less mobile people requiring emergency services for chronic diseases (168).

A notable example of an initiative to strengthen last mile delivery systems for chronic care medicines is the Central Chronic Medicines Dispensing and Distribution (CCMDD) programme implemented by the South African Department of Health. CCMDD allows clinically stable clients to collect antiretroviral therapy (ART) medicines, as well as medication for chronic NCDs, at external pick-up points (e.g. private pharmacies, adherence clubs) or public health pick-up points (in designated so-called fast lanes), and to visit public health facility providers less frequently (169). By reducing the frequency or distance required for patients to collect their chronic care medications, the CCMDD model aims to reduce patient transport costs and health care facility patient burdens, while also providing a more patient-focused, differentiated care model with benefits that go beyond product distribution and last mile operational efficiencies.

4.9. International governance on supply chains in public health emergencies

International health regulations (IHR) aim "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade" (170). IHR include provisions for infection control and transit of ships, aircraft, civilian lorries, trains and coaches. However, the scope of Core capacity requirements for surveillance and response (170, annex 1) includes as part of public health response capacities "to establish, operate and maintain a national public health emergency response plan, including the creation of multidisciplinary/multisectoral teams to respond to events that may constitute a public health emergency of international concern". In practice, this regulation has not been implemented to include monitoring of markets to anticipate or prevent shortages of medicines resulting from health crises. Future updates of IHR and other similar regulations may consider the need to stabilize and protect medicine supply chains within core capacities and transit guidance.

It is also necessary to consider international law and trade agreements governing intellectual property in responding to supply challenges (Box 4.3).



Box 4.3. The role of intellectual property in procurement

Intellectual property rights, especially patents, are a key determinant of access to health technologies globally. These legal instruments dictate who can manufacture and sell a product, and therefore determine whether the product is subject to a monopoly or market competition. Where patent protection monopolies exist, health technologies have in many cases been unaffordable and access has been limited to the wealthy (73).

Recognizing the potential importance of intellectual property rights in this context, a number of countries have passed new legislation or policies aimed at ensuring access to medicines and other health technologies for COVID-19. Certain private actors have shared intellectual property through a variety of mechanisms, enabling generic (non-proprietary) manufacture before the expiry of patents. The WHO COVID-19 Technology Access Pool (C-TAP) provides a platform for developers of COVID-19 therapeutics, diagnostics, vaccines and other health products to voluntarily share their intellectual property, knowledge and data with multiple quality-assured manufacturers (184).

The trilateral cooperation between WHO, the World Intellectual Property Organization (WIPO) and the WTO has highlighted a number of intellectual property considerations in the context of COVID-19 and access to health technologies (74,83). These include, for example, flexibilities in Trade-Related Aspects of Intellectual Property Rights (TRIPS) such as compulsory licensing and government-use licensing, as well as TRIPS exemptions under the transition period for least developed countries, allowing generic manufacture of medicines that are patented in other countries (73). The WTO maintains a database of intellectual property policy interventions that governments have made in response to COVID-19 (83). Initiatives by the Medicines Patent Pool (MPP) (171) and WIPO

aim to improve transparency in information on patent coverage for medicines, vaccines and other health technologies used to fight COVID-19.

Medicines with a single source are inherently more vulnerable to shortages. Intellectual property rights can be a factor of medicines shortages where they limit the number of suppliers. Where a patent holder is not able to meet necessary volumes, timelines or technical specifications, or does not offer an affordable price, buyers will not have other sources immediately available to them. Although governments may in these cases pursue government-use licensing, such processes are often lengthy and still require that a generic source is available anywhere in the world.

The TRIPS Agreement forms a cornerstone of the international legal framework for intellectual property protection, and requires all WTO members to grant patents on pharmaceuticals. Article 31 of the TRIPS Agreement allows governments to permit use of a patented technology without the authorization of the patent holder: this is often referred to as compulsory licensing or government-use licensing. Compulsory licensing has been used by a number of countries in order to ensure access to affordable medicines, for example, HIV, cancer and cardiovascular medicines (73). Compulsory licensing may also be used in the case of shortages or supply constraints; for example, in March 2020 the government of Israel issued a government-use licence for lopinavir/ritonavir for the treatment of COVID-19 because AbbVie was unable to supply the requested quantities (172) (WHO made a strong recommendation against the use of lopinavir/ritonavir for COVID-19 in December 2020 (173)). Compulsory licences were issued for remdesivir, a treatment for COVID-19, in Hungary and the Russian Federation (83). An Indian generics company has filed a request for a compulsory licence to be granted on baricitinib, a medicine



WHO logistics hub airlifts its largest single shipment of humanitarian cargo to Ethiopia - September 2021. © WHO

originally approved for treating rheumatoid arthritis that is now recommended for patients with severe or critical COVID-19 [\(174, 175\)](#).

During the early months of the COVID-19 pandemic, a number of countries passed or amended existing legislation to create or extend mechanisms for compulsory licensing in their national law, including Canada, Germany, Hungary, Indonesia and Italy [\(83\)](#). Compulsory licences have been issued to enable importation or manufacture of potential treatments for COVID-19, for example, by Israel and the Russian Federation [\(83\)](#). In view of the COVID-19 pandemic, the European Commission has recognized the “need for better coordination of compulsory licensing in EU-wide emergencies” [\(176\)](#).

Many countries do not have domestic manufacturing capacity for certain health technologies and rely on imports. For such countries, a compulsory licence issued by their government may not be sufficient to enable access to the health technology in question if that technology is still patented in countries where it is manufactured. Article 31bis provides for a Special Compulsory Licensing System to address this challenge [\(177\)](#). Under this system, governments can provide for a “compulsory licence for export” in their national law. For example, under this system Canada issued a compulsory

licence for export of an HIV medicine to Rwanda in 2007. While this medicine could not be sold as a generic within Canada, it could be legally exported to Rwanda [\(73\)](#). To date, Antigua and Barbuda as well as Bolivia (Plurinational State of) have formally notified the TRIPS Council of their intention to use the Special Compulsory Licensing System for the importation of COVID-19 treatments and vaccines [\(178, 179\)](#). A Canadian company has indicated its intention to produce a version of Johnson & Johnson’s COVID-19 vaccine for export to Bolivia [\(180\)](#).

At the time of adopting the 31bis amendment, a number of WTO members opted out of the system, noting that they will not use it as importing members. These included Australia, Canada, Iceland, Japan, New Zealand, Norway, Switzerland and the United States, as well as the European Union and its Member States [\(177\)](#). Members who have opted out constrain their ability to import medicines, and concerns have been voiced that the EU would not be able to import additional supplies of COVID-19 treatments in the event of a shortage because of, among other things, the EU opt-out of 31bis [\(181\)](#). In the highly interdependent global supply chain, members who opt out also constrain potential global markets by reducing the ability of exporting countries to benefit from economies of scale.

4.10. Actions to anticipate, prevent and mitigate supply chain disruptions

A review of the academic literature and the information gathered from interviews provided some insight into the risk mitigation activities undertaken by stakeholders across the supply chain to avoid disruptions, mitigate the public health impacts of delays and manage demand where possible. Effective risk mitigation strategies are context specific; these findings should be interpreted as a review of what happened during the first year of the COVID-19 pandemic, as opposed to guidance on what strategies are effective or universally applicable.

4.10.1. Scoping review

More published analyses focused on procurement challenges than on manufacturing. The majority of studies describe patient-level utilization and access challenges collected through surveys. The scoping review identified 26 published analyses of health product supply chain challenges, with analyses falling into two categories: stock availability and supply chain at the district to facility level (23 studies); and prescribing practices at the facility or health care provider level (eight studies). Five studies reported on both these categories. See **Table 2.1** for a summary of included papers by pathway, disease category and region.

4.10.2. Implementation of priority lanes for expediting customs clearance of medicines

Nearly all border restrictions still permitted the transport of essential goods, including medicines, and many countries instituted priority lanes for key products. Nevertheless, despite national policies often including priority lanes for medicines, many interviewees reported substantial barriers in ensuring that medicines received expedited processing in practice.

One challenge was that there is no global definition of essential goods, and therefore uncertainty in some cases concerning eligibility. Some national governments maintain essential goods lists (often under the auspices of disaster management authorities), but others do not or leave the definition of essential goods to the discretion of customs officials. Intergovernmental organizations have designed tools to support governments in designing national essential goods lists in the context of COVID-19. These include the World Customs Organization (WCO) tool HS classification reference for COVID-19 medical supplies [\(89\)](#), the WHO Disease commodity package - Novel Coronavirus (COVID-19) [\(63\)](#) and the joint WCO-WHO List of priority medicines for customs during COVID-19 pandemic [\(185\)](#).

Where such priority lists were successfully implemented, shipments of included products underwent priority customs clearance. However, even where medicines were included in priority lists, key components for manufacturing or packaging medicines were often not included, with one interviewee attributing this to disruptions to downstream manufacturing.



Quote 4.3: manufacturer or their associations

"Governments and authorities are just focusing on the product itself – there are associated supplies that have to move. We had to literally produce letters that say, it might be plastic components, aluminium, rubber, etc., but they are also 'critical transport!'"

Interviewees emphasized that although complying with increased requirements for customs clearance posed challenges, the greatest challenge was the frequent changing and unpredictability of policies and their enforcement. One procurement specialist illustrated the lack of information about the degree of congestion at one border crossing point by highlighting their reliance upon reports on the Twitter social media platform to estimate delays for truck crossings.

4.10.3. Emergency chartered and/or humanitarian transport

During the pandemic, the costs of transporting medicines increased globally. Some routes ceased to be profitable, leading to private sector withdrawal. In a context of strained global supply of transport capacity, the lowest-margin routes suffered disproportionately. The private sector collapsed entirely for some routes, a situation rarely seen outside the context of humanitarian emergencies. Interviewees reported that in early 2020 it was extremely challenging to organize delivery to small islands.



Quote 4.4: multilateral agency

"When there's a crisis, private sector services and assets are usually disrupted, leaving a vacuum left to humanitarian organizations to fill and keep delivering assistance to people in need."

The World Food Programme, which is uncommon among humanitarian actors in maintaining its logistics footprint of trucks, amphibious vehicles and chartered aeroplanes, ships and helicopters in more than 120 countries and territories provided transport and logistics support for some routes to the rest of the humanitarian community, with a focus on routes not operated by the private sector anymore due to the pandemic. In the context of the COVID-19 pandemic, there was an increase in the number of humanitarian routes needed to deliver essential medicines.

Although emergency-chartered air freight transport was a key option that was used in some cases, it was a costly alternative to traditional air freight and far from sufficient to address global need.

4.10.4. Risk assessments and scarce resource prioritization

Most interviewees working in logistics reported the pre-pandemic existence of a risk assessment framework, which identified the most at-risk products in terms of stockouts and clinically vulnerable patients. Nevertheless, COVID-19 posed a challenge beyond the limits of most risk planning, as prices for some essential goods increased far beyond historical expectations and commercial freight for some routes completely disappeared. Dynamic parameters such as border closures and export restrictions further complicated updates to risk assessments.

Interviewees involved in service planning and provision emphasized risk assessment plans that prioritized products according to clinical need. Of all NCD services provided, maintaining stable supplies of insulin for type 1 diabetes was the top priority. Although existing risk assessments to identify vulnerable points in the supply chain were helpful for many issues, other challenges remained unpredictable or were dependent on the decisions of other actors. Actors were forced to operate with limited information. How long will a delivery route remain closed? Are promised stocks going to be delivered on the promised timetable?

Public health logisticians can rank their products and patient groups in terms of vulnerability, but they are in turn sometimes ranked by commercial suppliers in terms of profitability: although private sector firms sought to honour contracts and limit stockouts, some also described the prioritization of their most profitable products when production capacity was reduced. One stakeholder was frank about how operations were managed during the most turbulent early phase of the pandemic. In the context of diminished capacity, they described a risk assessment and planning process where products were ranked in terms of profitability.

Those few product lines that generated the majority of profits were placed on a priority list, and the planning, production and management of inputs in short supply was managed accordingly. While not illustrative of the sector, such examples offer a rare glimpse into some business decision-making processes and considerations during a crisis.

Risk assessment and prioritization were also strained by a sometimes abrupt contraction in already limited resources as they were diverted to address COVID-19. The occurrence of occupational moral injury, defined as "the profound psychological distress which results from actions, or the lack of them, which violate one's moral or ethical code", was observed in frontline health care workers who experienced moral distress from making difficult clinical decisions and allocating scarce resources in the context of COVID-19 (186). This was a recurrent theme as actors in logistics described the challenges of feeling powerless in addressing supply issues in a rapidly deteriorating situation with no good options. In response to a question about continuity in resources for medicines, one interviewee described the stress of prioritization decisions in the context of unexpected and abrupt scarcity.



Quote 4.5: non-governmental organization

"It is important to say that the health system has collapsed completely. Regardless of the disease, diabetes, mental health – actually people still have access to HIV/TB [medicines and services] – but the rest, it's about non-existing. To come back to [region X], they are now experiencing, because the health system has collapsed, they have limited funding for extending cancer services. The head of health made the point that I don't even have money to buy food for my patients. What must I do? How must I prioritize?"

A third dimension influencing prioritization is the financing source. Donor funding has been critical in scaling up treatment of communicable diseases, most notably scaling up family planning, reproductive health, and the treatment of HIV, tuberculosis and malaria. Compared with communicable diseases, there is very little donor support for NCDs, and almost no support for supply chain work specifically for NCD medicines. Donor funding for some programmes may have unintended effects across the health system. Where investments for communicable diseases are targeted to support broader health system strengthening, there can be synergies with NCD programmes. The source of funding may influence prioritization decisions by health authorities, especially in countries where donor funding constitutes a significant proportion of the overall health budget.

Challenges in the practical execution of prioritization governance and administration can be further complicated where financial resources, domestic priorities and administrative capacity are strained, as occurred during the COVID-19 pandemic. Some interviewees expressed frustration that, in the early days of the pandemic, there were a number of high-level emergency meetings to stabilize supply for donor-sponsored programmes, but little in the way of emergency planning or resource mobilization for medicines, services, care pathways or funding for NCDs, which rarely have donor support. This posed a particular challenge for especially at-risk populations, such as people with type 1 diabetes, and some interviewees expressed distress over a perceived lack of a needs-based prioritization and an integrated emergency response.



Quote 4.6: non-governmental organization

"It's my view that it's the role of the WHO in the next crisis to be sure that the funder [donor] has not just organized a programme for emergency for [only] the programme of the big funder...It's a problem of the field that it's not a patient-centred intervention and programme."

Quote 4.7 non-governmental organization

"There is no funding like [redacted large donor agency]. In countries, prioritization of programmes is prioritization from the funder... There were no emergency meetings on the provision of insulin or anything like that, but [instead they were] around the prioritized programmes: maternal health, HIV, tuberculosis, malaria, because all the meetings were done by the partner!"

"During the crisis moment, the emergency is defined by the partner and not defined by the reality of the epidemiology in the field."

4.10.5. Increasing safety stock of priority medicines

Ideal safety stock levels increase proportionately with the variability and risk in a given system. In recent years, there has been an increasing trend towards leaner supply lines and safety stocks. Supply chains with less safety stock and higher ordering frequencies offer a number of advantages, including lower costs for warehousing, flexibility to quickly shift to lower-cost products, increased responsiveness to changes in demand and lower risk of product expiry as a result of surplus purchasing. These advantages became disadvantages in the context of the pandemic: supply chains scrambled to secure additional warehousing were more exposed to global delays and delivery disruptions, and did not have secure long-term contracts for in-demand supplies. Although there are inadequate data across countries to make any systematic assertion, countries with more substantial levels of safety stock were shielded from the initial supply disruptions.



Quote 4.8: academic researcher

"This issue of larger buffer stocks goes exactly antithetical to what I had been telling friends and colleagues, to keep the system lean and stagger your deliveries instead of getting all your supplies in one or two deliveries a year. The same collaborators are saying hey! We got the whole supply in one go in February and we're good, and those who took your advice to stagger deliveries and get them more periodically were off... We need to think carefully in saying higher buffer stocks can avoid disruptions unconditionally – we need to caveat to say that in some countries it helped, but there is still risk."

Although one interviewee (Quote 4.8) expressed regret in advocacy for supply chains with low levels of safety stock, another (Quote 4.9) acknowledged the challenge posed by the pandemic but expressed concern towards an overcorrection to norms of higher levels of safety stocks and proposals for local manufacturing, arguing that the additional stock needed to protect systems in emergencies was not worth the costs over time. In the absence of increased investment, budget tied to increasing safety stocks reduces flexibility to increase spending as needs arise.



Quote 4.9: international aid / donor

"My worry is that there are two buzz-phrases going round – first that we need to keep more inventory, and second, that we need to shorten supply chains with more local manufacturers. We are rushing to them. Both are fraught. I'd like to think that the community can think more creatively about ways to be more agile, and not set us up for year after year keeping large stock when not needed and local manufacturing where not economically viable."

Some countries maintain strategic stockpiles of medicines. Although in theory such stockpiles provide national buffers for essential medicines, they are only effective when maintained and kept ready for emergencies. Handfield et al. (27) described the failures of the United States Strategic National Stockpile (SNS), including a lack of inventory visibility systems such as barcode or QR code tracking to provide demand visibility and monitoring of the expiration dates of inventory. A January 2020 audit of the SNS found that inventories of PPE were depleted during the 2009 H1N1 pandemic and never replenished. The SNS was depleted of most materials by late March 2020 (27).

4.10.6. Reducing barriers to chronic care prescriptions access

A number of legal and regulatory extensions were granted to pharmacists, including the granting of temporary authority to renew chronic treatment prescriptions, as well as allowing pharmacists to fill pro actor and pro familia prescriptions (37). Prescription validity was extended in some cases. Consultations by telephone, SMS or WhatsApp were also provided.

One interviewee described how shifts in programmes to person-centred care can also have a secondary effect in promoting resilience in an emergency situation (Quote 4.10). Patients often prefer to receive bundled (multi-month) prescriptions; these same delivery models had the added benefit of giving patients a safety stock, allowing some flexibility as options were

assessed during the most difficult and volatile early weeks of the pandemic. Multi-month dispensing (MMD) is most notably implemented in HIV ART. MMD is an aspect of differentiated service delivery that provides patients with either 3 or 6 months of medication, removing the need for monthly clinic visits. From a patient's perspective, MMD has been shown to reduce the cost of travel, reduce patient burden and limit the hours of work or school lost. It also improves treatment adherence and viral suppression (187).

In response to COVID-19, as of June 2020, 16 of the 21 countries supporting the United States President's Emergency Plan for AIDS Relief (PEPFAR) reviewed adapted MMD policy or promoted an intensified scale-up of MMD; MMD coverage for all patients on ART increased from 49% in the fourth quarter of 2019 pre-COVID-19 to 72% in the second quarter of 2020 during the pandemic (188).

The India Hypertension Control Initiative introduced MMD and decentralized community distribution of hypertension medicines in April 2020 in Kerala, Madhya Pradesh, Maharashtra, Punjab and Telangana. Hypertension patients, who had previously received monthly prescriptions, received up to 3-month prescriptions if their blood pressure was under control. Prescribing was moved from the primary health care level and above to community-level distribution. An evaluation of the programme estimated that 38% of patients had received medicine refills through community-level health and wellness centres during the lockdown (189).



Quote 4.10: non-governmental organization

"In our NCD programmes over the 2–3 years, we have been trying to look and see what we can learn from the HIV world in terms of providing person centred, differentiated service delivery especially providing multi-month refills. What we saw for HIV is that approaches of 3-6 month prescribing for stable patients actually gives you some leeway in your system when an emergency hits."

The additional difficulties faced by people in accessing prescriptions – for example, concerns about safety in attending crowded waiting rooms or a lack of transport during lockdown periods – may have pushed people to rely on unsafe sources, such as unregistered internet pharmacies. Effective and timely regulation of unregistered pharmacies, as well as a public communications strategy outlining potential harms, can mitigate these risks.

Difficulties in accessing pharmacies also led to wastage. For example, regular human insulin is available from local public pharmacies in Brazil, but insulin analogues must be accessed through specialty services that require most people to travel further. Interviewees reported that, as a result, a

large stock of insulin analogues had to be destroyed because it had passed its expiry date.

4.10.7. Improving demand responsiveness

Nearly every interviewee reported that by March 2020 they had shifted from monthly or biweekly planning cycles to weekly or daily, to allow more rapid decision-making for a better response to changing circumstances. Forecasting was complicated by shifts in demand, as there was a decrease in some people seeking care or delaying some prescriptions, and an increase in other prescriptions as people sought to ensure they had adequate supplies at home.



Quote 4.11: non-governmental organization

“Your resilient supply chain comes partly from your ability to forecast. The M&E [monitoring and evaluation] situation right now for NCDs is not supporting that. The M&E is so weak in terms of ability to forecast.”

In countries with high levels of donor funding, procurement systems may be siloed between donor-funded procurement and public sector procurement, and the two are often not interoperable. Donor work on supply chains almost exclusively focuses on products used for communicable diseases, although there has been some movement in recent years to increase investments in broader health system strengthening activities that would indirectly affect NCD product supply chains. Donors may implement independent systems for

various reasons that may include quality assurance, anti-diversion or to comply with the donor country's regulations or legislation. However, siloed systems may have hindered the emergency response by contributing to administrative burden and inefficient distribution of capacity. In the context of a border closure or the shortage of a given medicine, visibility of the quantity of product available in a single siloed procurement stream is of much less utility than a national-level picture of available stock.



Quote 4.12: multilateral agency

"The verticalization of communicable versus noncommunicable disease procurement has been a distortion in terms of how you access essential medicines. The question should [instead] be how do we procure (essential/EML) versus (non-essential/non-EML) medicines?"

There were also challenges in maintaining visibility of relative supply capacity across the public and private sectors. In some cases, there was increased intersectoral coordination. One such example is in South Africa, where the National Department of Health has for years operated a medicines dashboard for advance warning of stockouts. Before the pandemic, the private sector did not have a monitoring or convening mechanism to prevent and address shortages. During the pandemic, however, the public and private sectors coordinated to better understand the availability and distribution of total stock for COVID-19 commodities. Such intersectoral cooperation and an enabling regulatory environment, if applied to medicines more generally, may support visibility in future

emergencies. Forthcoming WHO NCD Service Integration Implementation Guidance further details considerations in developing strong procurement systems to support an integrated approach to health system strengthening.

In reflecting on the experience of supply chains in COVID-19, some interviewees felt very strongly that the future of supply chains for medicines was exclusively in the private sector. In this view, in implementation models for both public and private purchasers, the supply chain is largely outsourced to private wholesalers who are responsible for warehousing and delivery to the final destination. One interviewee (Quote 4.13) describes one articulation of this view.



Quote 4.13: international aid / donor

"Wholesalers are more nimble in terms of replenishing their own inventory. They serve a broader supply base. In practice, by holding large amounts of inventory in the public sector, when warehousing owned and operated by the government is high risk, management is poor and capacity is limited, we further entrench the government's role in this function."

In contrast, other participants described the experience of supply chains in the pandemic as demonstrating the need for greater public sector investment, and less reliance on the private sector.

In the context of future emergencies, many described a hybrid model as the route to resilience, in which a public supply chain model would have agreements in place

with the private sector to rapidly scale up warehousing and transporting capacity if needed. The mapping of public and private sector warehousing and transport capacity was a risk mitigation strategy mentioned in a number of interviews. For example, The Global Fund maps capacity and maintains agreements with back-up providers.

4.10.8. Shaping incentives to smooth demand

One of the more unexpected and interesting themes that surfaced in interviews was the supply chain effects of information and coordination problems, especially in the earliest and most disruptive stages of the pandemic. Foreseeing expected shortages, purchasers bought surplus stock. While there were genuine stock shortages and delays, it seems likely that the greatest disruptions can be attributed to overreactions in anticipation of potential shortages, which led to inefficient and inequitable distribution of surplus stores for some purchasers and stockouts for others.

The irrationality of the situation was self-evident to those working in logistics but, without any mechanism to limit bubbles,

markets became increasingly volatile. The situation of a so-called prisoner's dilemma emerged, in which stockouts would have been minimized and their effects distributed more broadly if purchasers had cooperated to purchase the minimum of what was needed.

Interviewees reported a variety of strategies to address this problem. One supply chain actor automatically flagged any orders that were larger than average and reviewed each on a case-by-case basis to decide whether surplus stock was needed. Some actors increased transparency by publishing lists of medicines with low supply, while others restricted that information to prevent stockpiling. One regulatory organization restricted medical institutes from purchasing more than 110% of the previous year's monthly average of medicines (33).



Quote 4.14: logistics

"People generally know that there's going to be a shortage. What you don't know is that you have a savvy supply chain manager overstating demand."

4.10.9. Increasing price and supply transparency

The lack of transparency in medicine pricing and availability data are well described (190), and actions to improve transparency across the value chain are included in World Health Assembly (WHA) resolutions 72.8 Improving the transparency of markets for medicines, vaccines, and other health products and 74.4 Reducing the burden of noncommunicable diseases through strengthening prevention and control of diabetes.

A number of health systems passed regulations to improve demand transparency, regulate purchasing and prevent stockpiling. Enríquez-Fernández & del Castillo-Rodríguez (22) described special powers and orders passed in Italy and Spain relating to information sharing

between manufacturers and regulators. On 23 March 2020, the Minister of Health, Consumer Affairs and Social Welfare issued Order SND/276/2020, which required marketing authorization holders to provide daily electronic updates of available stock, stock supplied in the last 24 hours, and forecasts of the quantities of batches expected to be received and released. South Africa issued regulations that prohibit excessive prices for certain essential goods under the Competition Act; prices in a State of National Disaster are defined as excessive if they are higher than prices in March 2020, unless higher costs of production can be demonstrated (191, 192). Brazil, Greece, Indonesia, Italy, Romania, South Africa and Thailand have pursued investigations into price increases of some in-demand COVID-19 products (91, 193–197). Competition authorities in Kenya issued a

remedial order to a supermarket chain for “unconscionably adjusted prices” of hand sanitizers in contravention of Competition Act No. 12 (197).

4.10.10. Reporting mechanisms for stockouts and shortages

National reporting mechanisms have been put in place in some countries to promote transparency, reduce the frequency of shortages and facilitate measures that can reduce the negative impact of shortages. The root causes and impact of shortages vary, and responses need to account for the specific context of the medicine in shortage.

A 2018 informal WHO survey found that the presence of reporting mechanisms remains mainly limited to high-income markets. Of the 80 reporting countries, 36 indicated that a mechanism existed; the majority of these were high-income countries from the WHO European Region or the WHO Region of the Americas. Of the five (out of six) WHO regions that responded, a range of 10–37% of countries had reporting mechanisms. A rapid evaluation of the mechanisms showed that only slightly more than half could be verified to have current data or information.

WHA69.25 *Addressing the problem of global shortages of medicines and vaccines* discussed the paucity of data and called for a global reporting mechanism (3). Since its adoption in 2016, WHO has surveyed countries and developed reporting mechanisms that allow for the aggregation of existing data. WHO also provides an option for countries that do not have reporting systems to provide information to WHO. The initial version found that countries without reporting mechanisms had limited capacity to identify and report shortages. The system was redeveloped to collect and analyse existing data and provide risk profiles to users of the system.

Either short- or long-term responses to shortages may be appropriate, depending on the analysis of the situation. A rapid understanding of the root cause and an analysis of product availability at the upper end of global or regional supply chains are critical. Solutions in the short term may include the use of clinically appropriate substitutions, while long-term solutions would include assessing the potential for increased and/or diversified production.



Head of the DHL team Stanly G. (left) and WHO/Dubai Operations Manager and Pharmacist Nevien Attalla (right) inspect medical equipment and medication at a WHO warehouse in Dubai. © WHO / Blink Media - Natalie Naccache

Summary: Procurement, importation, and last mile delivery

As with other sectors, the pharmaceutical sector was affected by the unprecedented supply chain interruptions in 2020 and 2021. However, a number of key features unique to pharmaceuticals exacerbated delays and shortages, for some products and markets.

Procurement:

Demand prediction and forecasting for medicines and health products were complicated by greater variability in materials and resources planning. Uncertainty stemmed from a) unexpected changes in medicine utilization, b) concerns about potential border closures, c) poor coordination across manufacturers, wholesalers, and purchasers amplified market distortions and inefficient allocation and d) longer lead times.

The overall financing environment was affected, with significant implications on procurement planning and operations. In some cases, regular health funds were reallocated to emergency use. Health systems that receive significant financing from user fees experienced unexpected contraction in revenue, as many people self-isolated or postponed elective care. Some manufacturers and wholesalers experienced declines in revenue. Interviewees reported a shift in norms and rules around payments contracts, with some manufacturers newly requiring full upfront payment, which was not always compatible with domestic legislation. In an emergency context where financial resources, domestic priorities and administrative capacity were strained by the demands of the COVID-19 response, some

interviewees reported that donor-funded programmes had unintended effects on which health products and risks across the supply chain were prioritized. Fragmentation across systems contributed to poor visibility and inefficiencies in risk management.

Importation:

Nearly all interviewees emphasized the rise in air and sea freight costs as one of the most significant disruptors in supply chains for medicines. Interviewees estimated that freight costs had increased to two to six times compared to pre-pandemic costs. The capacity, availability and predictability of air cargo routes were severely disrupted. Routes dependent on connecting flights and/or those with lower profit margins for carriers were particularly affected. Maritime transport was also disrupted as a result of port closures, crew-change restrictions, changes in documentation requirements, requirements for physical examinations of vessels and crew members, and quarantines.

At least 20 countries and customs territories had introduced export restrictions on medicines by April 2020. In addition to direct effects on some products, there were also indirect effects through increased uncertainty and volatility, as well as stockpiling of components by some actors. Countries already disadvantaged in global medicine markets, including low-income countries with fewer resources, landlocked countries dependent on air cargo and/or sea ports in other jurisdictions, small island states and countries subject to international trade sanctions were disproportionately affected by the

intersection of COVID-19 related border measures and interruptions in air cargo. Delays in customs clearance and increased transport unpredictability complicated the safe transport of temperature-sensitive medicines and other health products.

Last mile delivery:

Last mile delivery was adversely affected by unpredictability in upstream sourcing, as well as a challenging operating environment where normal services or methods of transport were unavailable. Patients were often faced with financial hardship, and reduced availability of transport, which further exacerbated the ability of health systems to ensure people maintained access to medicines.

Risk mitigation strategies instituted by countries across the supply chain included:

- Chartering emergency freight transport where no commercial transport was available
 - Implementation of demand controls to stabilize supply chains, risk assessments by product and patient population, and increasing security stocks of medicines, based on risk assessment findings
 - Increasing security stocks of medicines, aligned with risk assessments
 - Introduction of regulations to increase transparency, regulate purchasing and pricing, and prevent stockpiling
 - Legal and regulatory adaptations to expand multi-month prescribing and innovative delivery methods
 - Establishment of hybrid model agreements with the private sector to rapidly scale up warehousing and transporting capacity as needed
- Establishment of priority lanes or exceptions to expedite customs clearance for essential goods like medicines. (However, interviewees reported significant challenges in using these mechanisms because a) definitions of which goods were essential varied across countries, b) regulations were in some cases ambiguous or not communicated to relevant officials, and c) pharmaceutical manufacturing inputs were not always included.)
 - Risk assessments by product and patient population

Policy Considerations: Procurement, importation, and last mile delivery

Governments, procurers and other key stakeholders in the supply chain could collaborate in diversifying the supply base as well as implementing periodic risk assessments to identify upstream vulnerabilities. Analysis of alternative data sources such as supply chain data or private sector distribution data could provide insights into shortages. Where multi-source procurement is infeasible due to market size, purchasers could pool demand as necessary to ensure a diverse, more resilient supply base.

Governments should pre-emptively avoid customs delays for health products and key manufacturing inputs, by ensuring that priority lanes (so-called green lanes) or other measures are available for priority clearance of health products and essential manufacturing components;

offering pre-arrival processing of customs documentation; or allowing the deferment or suspension of customs duties, taxes, fees or charge. Introduction of regulations to increase transparency, regulate purchasing and pricing, and prevent stockpiling should be considered in emergency contexts. Regulatory adaptations to expand multi-month prescribing and enable innovative delivery methods should also be considered to address transport barriers and improve adherence. Finally, the introduction or strengthening of communication channels, among health authorities, manufacturers, and wholesalers to improve national stock visibility, anticipate shortages, and re-allocate scarce stock more equitably could improve access to medicines (NCD) in emergency situations.



WHO CO KAZ receives and distributes German-funded shipments in August 2021. The shipment included: 3.7 million medical masks. © WHO

5. AVAILABILITY AND AFFORDABILITY OF NCD MEDICINES

5.1. Background

The coronavirus disease (COVID-19) pandemic represents the first truly global and prolonged shock to global supply chains for the manufacture, procurement, delivery and distribution of medicines. Numerous pharmaceutical supply chains were affected in different ways and to varying extents. Many manufacturers were able to maintain core production functions, but encountered challenges in ensuring timely shipping because of the collapse in international freight transport and changes in market dynamics and demand, especially at the beginning of the pandemic in early 2020. While some health facilities experienced product shortages, others ended up with surplus stock.

Prices for some products rose, but the greater impact on affordability was caused by the loss in income experienced by many. The primary challenges in assessing the impact of the COVID-19 pandemic on shortages and stockouts of medicines for noncommunicable diseases (NCDs) are (i) there are very little data with which to establish a pre-pandemic baseline and (ii) it was only possible to collect limited data during the pandemic. The situation is made more complex by the fact that data on downstream shortages often do not provide enough information to establish the root cause, and shortages of medicines can occur at the global, national, subnational and facility level.

First, data from the 2019 and 2021 World Health Organization (WHO) Country Capacity Surveys provide an overview of changes in NCD medicine availability (**Section 5.2**). Shortages are then defined in **Section 5.3**. The framework of global- and national-level efforts for shortage monitoring and reporting systems is briefly described in **Section 5.4**, followed by a quantitative analysis of publicly available national shortages databases

in **Section 5.5**. Finally, the effects of the COVID-19 pandemic on affordability are reviewed in **Section 5.6**.

5.2. Baseline access: WHO Country Capacity Surveys

The WHO Country Capacity Surveys ask Member States to report whether the following NCD medicines are generally available (defined as being available in 50% or more of pharmacies in primary care facilities of the public health sector): angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aspirin, benzathine penicillin, beta blockers, bronchodilators, calcium channel blockers, insulin, metformin, nicotine replacement therapy, oral morphine, statins, steroid inhalers, sulphonylureas and thiazide diuretics. Although the global shock caused by the pandemic was unprecedented, the state of access to NCD medicines in low-income countries before the pandemic could also be classified as an emergency: in the 2019 NCD Country Capacity Survey, just 10% of low-income countries reported that the 11 key NCD essential medicines were generally available compared with 93% of high-income countries [\(94\)](#).

This survey was repeated in May–September 2021, well into the pandemic. All 194 Member States responded to both rounds of the survey [\(95\)](#). The disparities between income groups persisted during this period; some of the greatest inequities between low- and high-income countries were observed in the general availability of beta blockers, insulin, statins and steroid inhalers (Table 5.1). The most widely available medicines were metformin, aspirin and thiazide diuretics (generally available in 90%, 87% and 84% of countries, respectively), and the least widely available were steroid inhalers, oral morphine and nicotine replacement therapy

(generally available in 66%, 50% and 40% of countries, respectively). Within each income group, levels of access were similar from the pre-pandemic (2019) to most recent (May–September 2021) surveys: 93% of high-income countries reported having all 11 key

NCD essential medicines generally available, compared with 15% of low-income countries. Roughly one third of low-income countries only had four or fewer key NCD essential medicines generally available.



Quote 5.1: non-governmental organization

“I hesitate to talk about NCDs and emergencies because normal availability of basic NCDs drugs is so poor including insulin. I don't know how much worse things can get in the public sector during an emergency?”

In the context of the COVID-19 pandemic, the WHO Department of Noncommunicable Diseases expanded the Country Capacity Survey to gather information from countries on the impact of the pandemic on NCD-related resources and services. This Rapid Assessment did not require respondents to assess availability of individual medicines, but instead focused on disruptions to NCD service delivery more broadly. The initial Rapid Assessment collected data in

May–June 2020, with responses from 163 Member States. These questions were repeated a year later as part of the larger NCD Country Capacity Survey in 2021. While all 194 Member States responded to the 2021 survey, comparisons between the 2020 and 2021 data are restricted to those 163 Member States who responded to both the 2020 Rapid Assessment and the 2021 Country Capacity Survey.

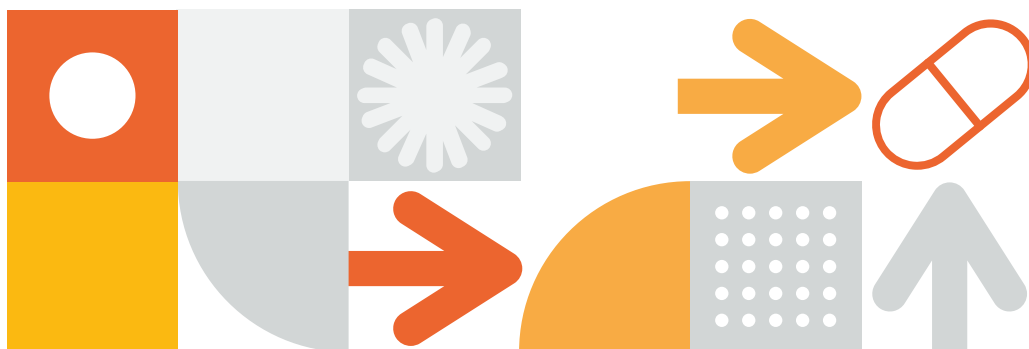


Table 5.1.

Percentage (%) of countries (total n = 163) reporting medicine availability and risk-mitigation measures in Rapid Assessment (2020) and Country Capacity Survey (2021)

	Percentage (%)	
	2020	2021
Unavailability/stockout of medicines		
All	15	21
Low-income countries	26	39
Lower-middle-income countries	26	33
Upper-middle-income countries	10	19
High-income countries	4	4
Novel supply chain management and/or dispensing approaches		
All	34	39
Low-income countries	22	39
Lower-middle-income countries	30	37
Upper-middle-income countries	42	44
High-income countries	35	35
Novel prescribing approaches^a		
All	–	33
Low-income countries	–	13
Lower-middle-income countries	–	37
Upper-middle-income countries	–	38
High-income countries	–	35

^a No information on novel prescribing approaches was sought in the 2020 survey.

Among these 163 Member States, 15% reported unavailability/stockout of medicines in the 2020 round compared with almost 21% in 2021. The discrepancies by income group were stark: 26% of low- and lower-middle-income countries reported stockouts in 2020, compared with just 4% of high-income countries. A year later, the access gap by country income persisted with 39% of low- and 33% of lower-middle-income countries reporting recent stockouts, compared with just 4% of high-income countries. In 2020, roughly one third (34%) of countries reported that they were using novel supply chain management and/or dispensing approaches as a mitigation strategy to overcome service disruptions. This number grew to 39% of countries in the 2021 round of the survey. The 2021 round of the survey asked countries about the use of novel prescribing approaches as a mitigation strategy: one third (33%) of countries reported using this approach. Novel prescribing approaches were markedly under-utilized in low-income countries compared with

middle- and high-income countries, with just 13% of low-income countries using this approach compared with over one third of middle- and high-income countries. In 2021, there were greater differences between low-income and middle-/high-income countries in terms of novel prescribing approaches than for novel supply chain management.

5.3. Defining shortages

Definitions of shortages vary between different national medicines regulatory authorities. In response to a request by the Sixty-ninth World Health Assembly (WHA) on Addressing the global shortage of medicines and vaccines (WHA69.25), the Secretariat prepared a systematic review of available definitions used in the management of shortages and stockouts, and, through consultation with supply chain and programme management experts, developed a definition of shortages (Box 5.1 [\(3, 198\)](#)).

Box 5.1. Definition of shortages (EB140/19)

On the supply side: A shortage occurs when the supply of medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas.

On the demand side: A shortage will occur when demand exceeds supply at any point in the supply chain, and may ultimately create a stockout at the point of appropriate service delivery to the patient if the cause of the shortage cannot be resolved in a timely manner relative to the clinical needs of the patient.

Shortages are a complex challenge and may be the result of: interruptions in the availability of key starting materials (KSMs) or active pharmaceutical ingredients (APIs), or in the manufacture of finished pharmaceutical product (FPP); problems with forecasting; financial constraints at the patient and/or health system level; or challenges with supply chain management or logistics, especially in remote areas.

5.4. Shortage monitoring and reporting systems

Even before the COVID-19 pandemic, there existed increasing global concerns about shortages of medicines for a range of therapeutic areas, including in oncology, antibiotics and vaccines (199). The potential threat posed by a pandemic to the global medicine supply was emphasized in a July 2017 technical consultation hosted by the WHO Secretariat to review existing systems for reporting shortages. The consultation recommended the creation of a notification system for shortages, which would inform mitigation efforts in the case of a shock such as a pandemic. The report notes that "sudden increases in demand from an outbreak can create acute short-term shortages; however, if a production problem occurs at the same time, the problem could quickly become a stockout across multiple markets." EB138/41 notes that markets for paediatric formulations are especially prone to shortages (200).

In response to the global challenge of monitoring shortages, there have been a number of policy discussions concerning the improvement of monitoring and notification systems for shortages.

- WHA69.25 requested that the Director-General "develop an assessment of the magnitude and nature of the problem of shortages of medicines and vaccines", as well as "support Member States in addressing the global challenges of medicines and vaccines shortages by developing a global medicine shortage notification system that would include information to better detect and understand the causes of medicines shortages", with support and participation

from manufacturers, wholesalers, global and regional procurement agencies, and other stakeholders (3).

- The July 2017 WHO technical consultation on Notification systems for shortages and stockouts of medicines and vaccines noted that "a global reporting mechanism, as requested in Resolution WHA69.25, will be critical in understanding root causes and developing adapted solutions for the increasing global problem of shortages and stockouts of medicines and vaccines" (201).
- The 2018 report by the WHO Director-General for the 142nd session of the Executive Board recommended that WHO supports the development and implementation of national-level systems for collecting and monitoring price, availability, expenditure, usage, quality and safety data on medicines and vaccines (202).
- The WHO Road map for access to medicines, vaccines and other health products includes key activities to address shortages, including: the development of global tools for early detection of shortages and rapid notification systems; a framework of mitigation actions needed to prevent and respond to shortages; and market analysis for key strategic products and identification of access risks. Other activities include support mechanisms, such as regional/global virtual stockpiles and emergency health kits, for rapid mobilization in emergencies and crisis situations (203).
- In 2019 WHO launched a shortages portal to consolidate available information and provide a reporting mechanism for countries (3).

At the national level, a number of countries maintain monitoring and reporting mechanisms for medicines shortages. The actors managing these mechanisms vary between countries, and include national medicines regulatory agencies (NMRAs), pharmacist associations, procurement programmes, and hospital and pharmacy networks. A non-exhaustive list of examples includes: Australia (116), Belgium (204),

Canada (205), Croatia (206), Czechia (207), Denmark (208), Estonia (209), Finland (210), France (211), Germany (212), Greece (213), Ireland (214), Italy (215), Latvia (216), Lithuania (217), Norway (218), Romania (219), Slovakia (220), Slovenia (221), South Africa (222), Spain (223), Sweden (224) and the United States of America (117), as well as the European Medicines Agency (EMA) (225).

These databases vary significantly in the level of detail they provide on the cause of shortages. For example, the United States Food and Drug Administration (USFDA) database provides information on the cause of the shortage where this has been provided by the supplier on a voluntary basis. Databases from the European Medicines Agency generally provide more detailed information on the causes of shortages. In South Africa, the database also reports the

proposed action undertaken by the health system.

Further upstream (KSM, API), there is no global monitoring system or even systematically collected data on upstream shortages. Pharmaceutical manufacturers sometimes issue press releases on supply chain challenges on a voluntary basis, or may be obligated to report actual or expected shortages to national authorities in some jurisdictions. If the shortage of medicines is the result of upstream issues (e.g. a shortage of KSMs or APIs), this notification may often come too late for effective mitigation efforts. Some interviewees were concerned that these data were not used to prevent shortages as proactively as they might have hoped (Quote 5.2); others felt that their NMRA was generally responsive.



Quote 5.2: academic researcher

"Governments at least are monitoring [shortages], but I don't think this can be called regulation. It's just monitoring the dynamics of the market and asking companies."

Quote 5.3: academic researcher

"Whenever there is a shortage people need to find someone to blame. We never regulate that side. We only monitor. But it will fall to the management level— oh you didn't forecast properly, you didn't supply, but actually, it's really difficult to trace the cause."

Data on current or imminent shortages are essential for identifying shortages, preventing harm to patients, and tracking patterns of shortages over time to try to anticipate and prevent them. Nevertheless, shortages data are inherently reactive and less useful in anticipating longer-term market shifts and challenges. Although there has been limited movement towards collecting upstream data on KSM and API availability, other indicators can help regulatory authorities map markets and predict future challenges. In the context of COVID-19, governments and countries

used data on manufacturing volumes and capacity to plan orders across suppliers for COVID-19 therapeutics, diagnostics and vaccines. The limited global supply capacity for these products was not divided equitably (226), but this information was essential in planning manufacturing scale-up and vaccination roll-out timelines. Data on manufactured volumes and capacity can be used to map global production markets and identify and respond to upstream challenges that may later translate to downstream shortages.



Quote 5.4: academic researcher

“Reporting discontinuation and shortages can only allow reactive measures, reporting manufactured volumes gives the regulatory agency (and the WHO if it can be wider) the ability to analyse the market and proactively manage any upstream shortages. It may not fly easily but certainly an idea worth putting further and exploring for some key NCD products.”

Some countries have taken steps to gather this data, noting its importance in preventing shortages and promoting supply chain resilience. As an example, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) amended the United States Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j) to require each person (including repackers and relabellers) who registers under section 510 of the act with regards to a medicine must report annually “the amount of each medicine ... that was manufactured, prepared, propagated, compounded, or processed by such person for commercial distribution” (227, 228). This legislation has faced opposition by industry trade groups, including Biotechnology Innovation Organization (BIO) and Pharmaceutical Research and Manufacturers of America (PhRMA) (229).

5.5. Analysis of national shortages databases

Analysis of national shortages databases in Australia, Brazil, South Africa and the United States provides some insight into the distribution of causes of disruption and shortages across the supply chain. Shortages databases from these countries were used because they are publicly available and report the specific causes of shortage events (e.g. API availability, logistics, manufacturing, packing, regulatory delays, unanticipated demand increases and commercial decisions). Although the experiences of these countries cannot be generalized globally, they illustrate key points in the medicines supply chain that came under pressure during the pandemic.



WHO NCD kits delivery at Moheshkhali remote island in Bangladesh during COVID-19 pandemic (August 2020).
© WHO / Tatiana Almeida

5.5.1. Australia

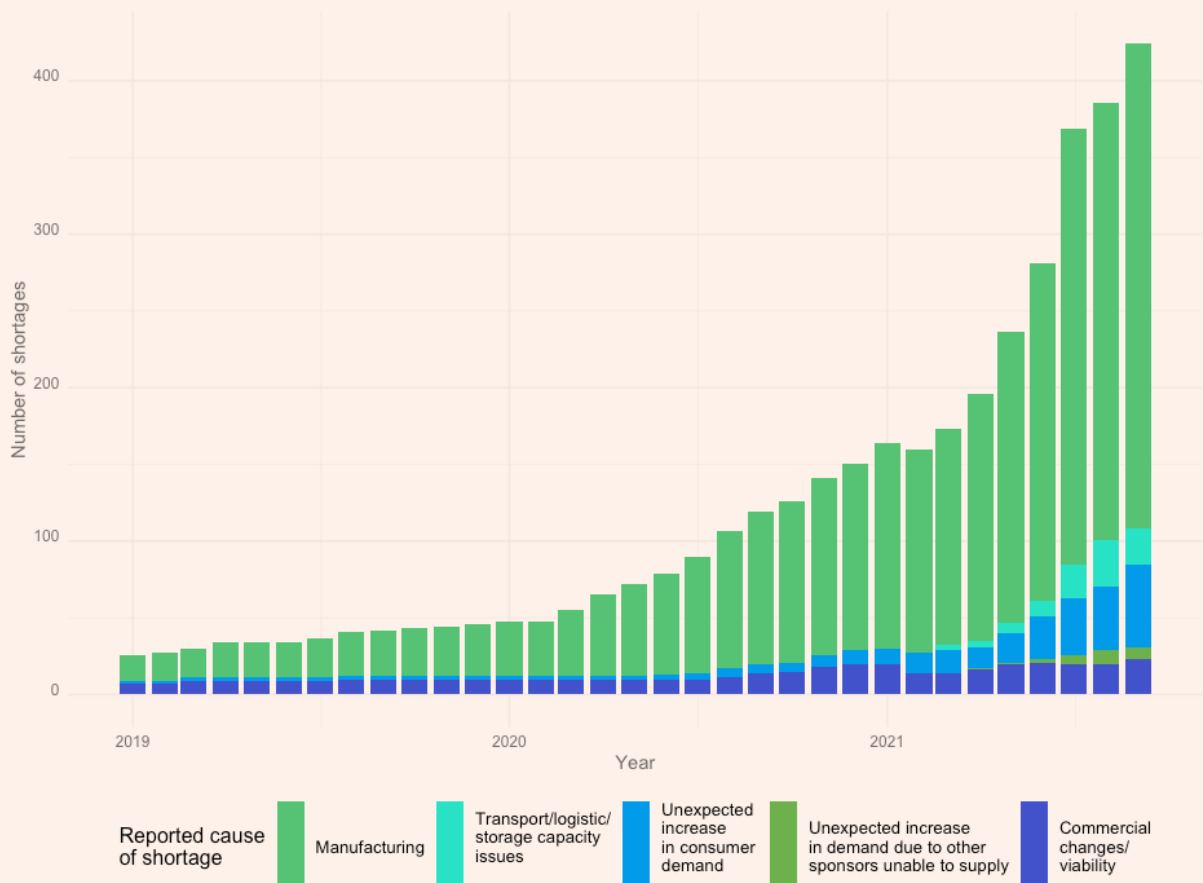
Pharmaceutical manufacturers in Australia are mandated to report shortages, including prescription and some over-the-counter medicines, to the Therapeutic Goods Administration (TGA). Shortages are defined "if at a particular time if at any time in the six months after that particular time, the supply of that medicine in Australia will not, or will not be likely to, meet the demand for the medicine for all of the patients in Australia who take, or who may need to take, the medicine" (230).

Anticipated, current and resolved shortages are published online (116). Records of all shortages from 1 January 2019 to 1 October 2021 were analysed by the reason reported

by the sponsor (i.e. supplier or manufacturer) for the shortage (Fig. 5.1). Each record corresponds to one formulation of a given medicine by the tendered supplier. See Annex 4 for details of the data source and analysis.

Before the COVID-19 pandemic, shortages within all reported reason categories remained constant, with the exception of manufacturing (which experienced a slight increase). There was a sharp increase in shortages as a result of manufacturing issues from February 2020. All other shortage categories remained relatively constant until slight increases beginning in August 2020, and then accelerated disruptions from February 2021.

Fig. 5.1. Shortages reported to Australia Therapeutic Goods Administration by root cause, January 2019–September 2021



Source: Australia Department of Health Therapeutic Goods Administration

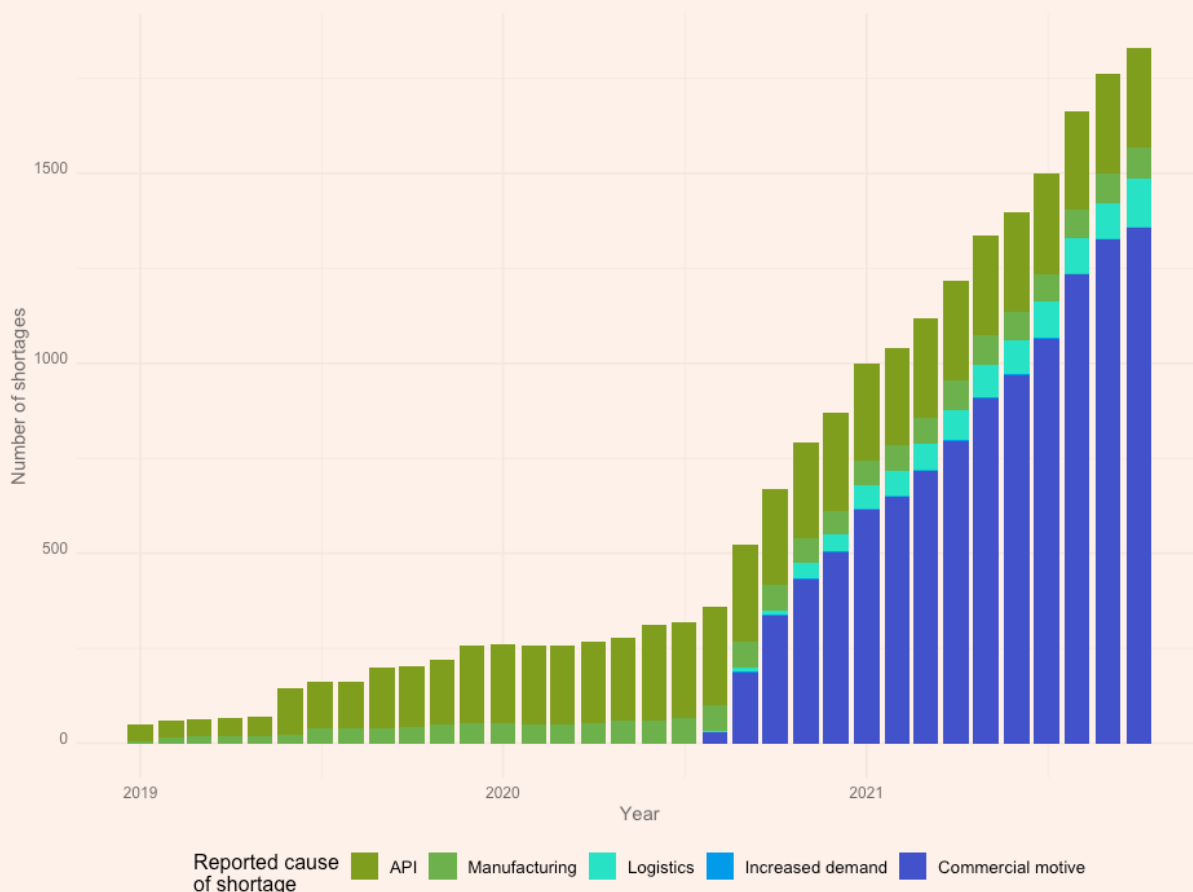
5.5.2. Brazil

Resolução da directoria colegiada nº 18/2014 obligates registration holders to notify the regulator (Agência Nacional de Vigilância Sanitária or ANVISA) should they temporarily or permanently discontinue manufacturing a product. Notification must occur at least 12 months in advance of discontinuation if a market shortage is anticipated. Should a discontinuation occur as a result of unforeseen circumstances, the registration holder is obligated to notify ANVISA within 72 hours (231). These notifications are published online, with reason for discontinuation. Records from this database from 1 January 2019 to 28

September 2021 were analysed by the reason reported by the manufacturer to ANVISA (Fig. 5.2). See Annex 4 for details of the data source and analysis.

There had already been a rise in shortages caused by problems with API availability in 2019 before the pandemic. This increasing trend continued until the second half of 2020, when it plateaued. Shortages caused by manufacturing remained relatively constant. Shortages coded as caused by “commercial motive” (i.e. suppliers departing the market) increased sharply in the second half of 2020. Finally, shortages caused by logistics remained near-zero until the second half of 2021, when they increased linearly.

Fig. 5.2. Notifications of interruptions to medicine manufacturing and importation reported to Agência Nacional de Vigilância Sanitária (ANVISA) Brazil, 2019–2021



Source: Brazil Agência Nacional de Vigilância Sanitária

5.5.3. South Africa

Pharmaceutical manufacturers in South Africa are not legally required to report medicine shortages to the South African Health Products Regulatory Authority (SAHPRA). However, since 2015 the National Department of Health has required as a condition of public tenders for medicines that pharmaceutical companies report any conditions that may delay or disrupt delivery (232). These data are not published in full, but the National Department of Health publishes so-called hot lists of medicines “where the interventions implemented may not have been able to avert a shortage and reflects those medicines which manufacturers have been unable to supply” (118).

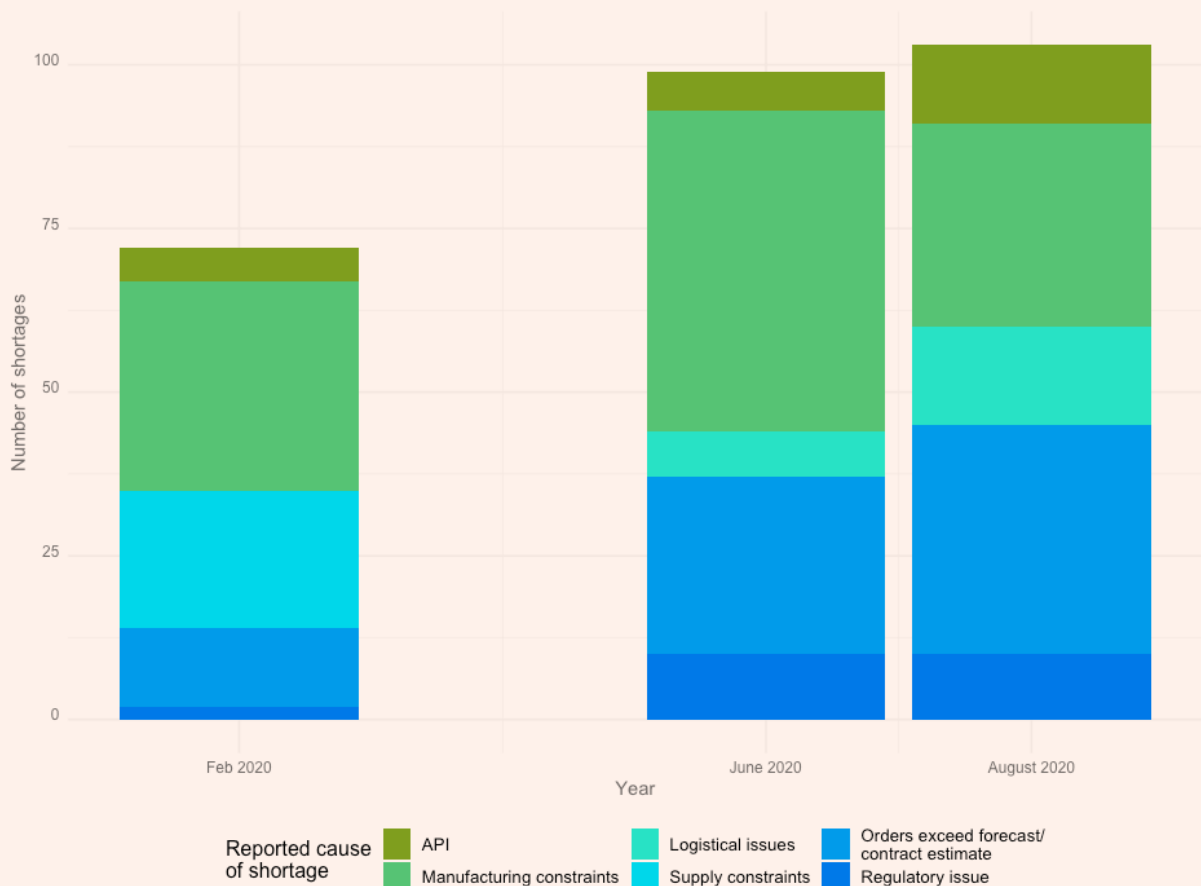
Records of all medicines on all available hot lists (February, June and August 2020) were analysed by reported root cause (Fig. 5.3).

See Annex 4 for details of the data source and analysis. Each record corresponds to one formulation of a given medicine by the tendered supplier.

Anticipated shortages increased for all root causes from February and June 2020. Anticipated shortages from manufacturing constraints decreased from June to August 2020, but increased for issues with forecasting, logistics and API availability. Anticipated shortages from regulatory issues remained constant from June to August 2020.

Limitations to this analysis include the restricted window of available data: challenges in the supply chain are well documented to have continued until the end of 2020 and 2021, especially as the COVID-19 Delta variant affected manufacturing from the third quarter of 2020. Hot-list data

Fig. 5.3. Anticipated shortages reported on South Africa National Department of Health hot lists by root cause, February, June and August 2020



Source: South Africa National Department of Health hot lists

describe medicines for which implemented interventions may not avert shortages. There may be confounding by changes in resources or available mitigation strategies available to stakeholders over time.

5.5.4. United States of America

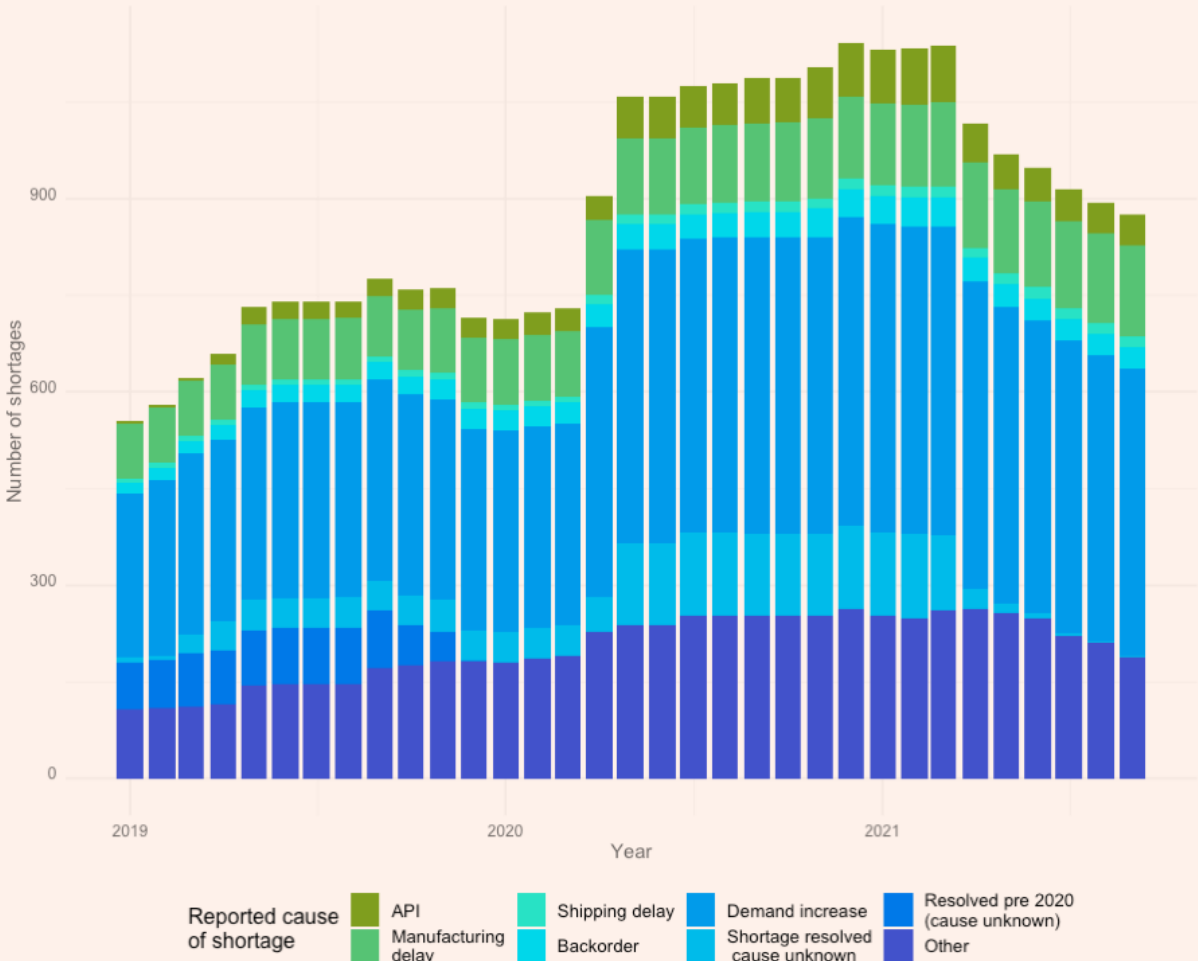
The USFDA maintains a database of current and resolved shortages; data are mostly sourced from manufacturer notifications, but any stakeholder can submit notice of a shortage (117). Records of all shortages from 1 January 2019 to 28 September 2021 were analysed by the reason reported by the manufacturer to the USFDA, where available

(Fig. 5.4). There are a number of challenges in analysing USFDA shortages data; see Annex 4 for details of the data source and analysis.

5.6. Affordability

The COVID-19 pandemic had severe economic and health consequences, and unemployment in both the formal and informal sectors increased (183). The reported increase in poverty during 2019–2020 is the largest on record since the World Bank began tracking poverty globally in a consistent manner (233) (Fig. 5.5).

Fig. 5.4. Drug shortages and reported causes reported to the United States Food and Drug Administration during 2019–2021



Source: United States Food and Drug Administration.

An estimated 90% of people in low- and middle-income countries use out-of-pocket payments to purchase medicines (234). Out-of-pocket payments for prescribed and over-the-counter medicines were already a major source of financial hardship before the health and economic shock of COVID-19 (235–248). Both, high and low-cost price of medicines that are not included in benefit packages and/or for which the user charge is not carefully designed can lead to catastrophic and impoverishing health spending, even in high income countries (249). In many regions, reducing gaps in the coverage of outpatient medicines was identified as critical in reducing the out-of-pocket health spending and resulting financial hardship (250). Identifying such gaps in health coverage and redesigning coverage policy

to address these gaps is critical for everyone but particularly important for most people with NCDs as treatment protocols often require taking medicines over a prolonged period, which also requires regular outpatient visits. Although investigating the relationship between a requirement for NCD care, catastrophic and impoverishing health spending is beyond the scope of this study, there is a robust literature on (i) costs of care, including for medicines, as a barrier to treatment (238, 245), (ii) catastrophic (243, 245, 246, 247) and impoverishing (235) expenditures experienced by people with NCDs and some evidence on distress financing strategies, such as borrowing or asset depletion, used by people with NCDs to find the means to get the treatment they need (244).

Fig. 5.5. World Bank nowcast of the global poverty rate at the poverty line of 1.90 United States dollars per day, 2015–2021 (233)

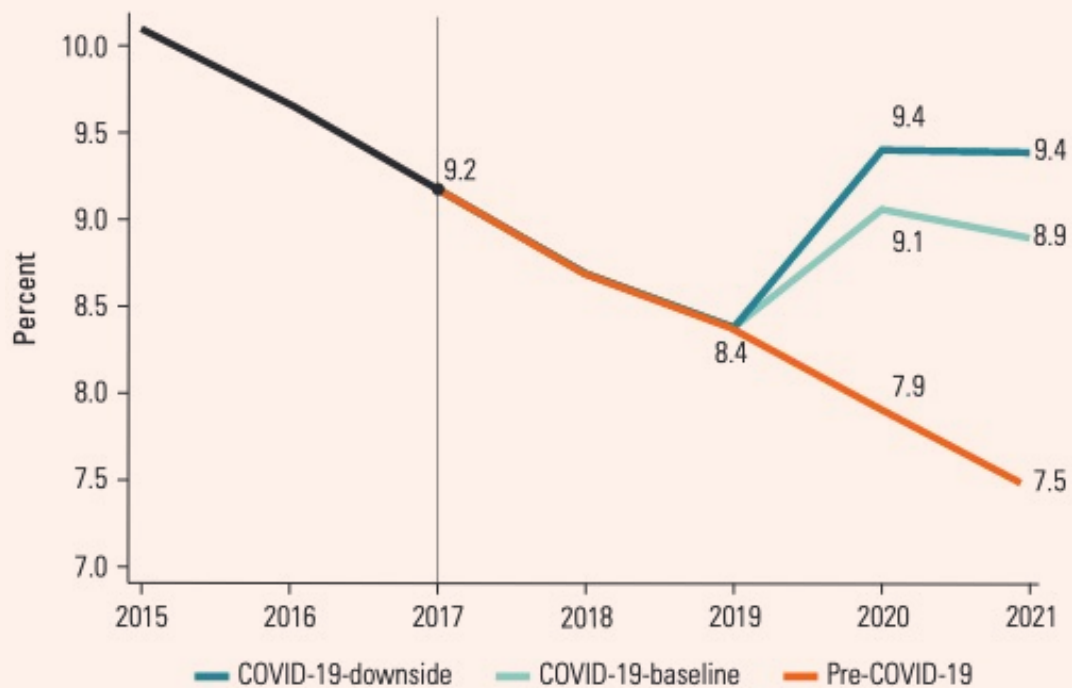


Fig. published in World Bank. 2020. Poverty and Shared Prosperity 2020: Reversals of Fortune. Washington, DC: World Bank. doi: 10.1596/978-1-4648-1602-4. License: Creative Commons Attribution CC BY 3.0 IGO

- **Non-disease-specific NCDs:** In their systematic review of the global impact of NCDs on households and impoverishment, Jaspers et al. found that the costs of NCD care are growing on all continents and in countries of all income levels, and are likely to be underestimated as many do not seek health care because of financial barriers.
- **Asthma:** In an analysis of 16 low- and middle-income countries, Niëns et al. found that between 0% (Jordan) and 67% (Mali) of the population would fall below a poverty line of 1.25 United States dollars (US\$) per day if they purchased the lowest-priced generic salbutamol.
- **Cancer:** Doshmangir et al. conducted a systematic review and meta-analysis of catastrophic health expenditures and their determinants in cancer patients. They found that, among 19 included studies, an average of 43.4% (95% confidence interval (CI): 36.7–50.1) of cancer patients experienced catastrophic health expenditures.
- **Cardiovascular disease:** Karan et al. reported that 33% of households affected by cardiovascular disease borrowed or sold assets to finance health care, and had 17% higher out-of-pocket health costs than unaffected households.
- **Chronic obstructive pulmonary disease:** In a study of patients enrolled with the Respiratory Ambulatory Care Service in western Sydney, Essue et al. found that 18% were unable to pay for medicines and 46% experienced catastrophic out-of-pocket spending.
- **Diabetes:** In an analysis of 16 low- and middle-income countries, Niëns et al. found that between 2% (Kyrgyzstan) and 71% (Nigeria) of the population would fall below a poverty line of US\$ 1.25 per day if they purchased the lowest-priced generic glibenclamide in the private sector. Gwatidzo & Williams reported how 17% of people with diabetes in China and 7% in India experienced catastrophic health expenditures on medicines.

- **Stroke:** In a study by Heeley et al., 71% of 3-month survivors of stroke in China experienced catastrophic out-of-pocket health expenditures. Among those without private health insurance, 62% fell below a poverty line of US\$ 1 per day.

The loss of employment and income associated with COVID-19 exacerbated already significant access challenges resulting from high prices, especially for poor and/or uninsured people, as well as those who need medicines still on patent. The most at-risk people, such as those with diabetes – who experience an 87% (pooled odds ratio: 1.87; 95% CI: 1.51–2.31) higher risk of death after testing positive for COVID-19 than COVID-19-positive patients without diabetes – likely experienced greater negative income shocks as a result of longer and more intensive shielding (248). For those relying on work-associated health insurance, unemployment brought an abrupt loss of coverage.

Many interviewees mentioned the intersecting challenges of high prices and the negative shock on household income from COVID-19. Even where medicines were free within the health system at the point of use, accessing them incurred transport costs.





Quote 5.5: non-governmental organization

"The public sector has no payments for medicines. However, each visit to the hospital is [redacted amount/currency]... On the one hand you're not paying for your treatment, but you are paying to go to your treatment... The fact of the matter is patients still have to access the treatment centres, [need money for transport], then what happens if they can't, that happened for COVID-19, they would go to hospital for treatment only to be turned away and come back. That is the kind of out-of-pocket expenses that in the public sector you have to deal with, you have to sit there without food for the whole day."

Quote 5.6: non-governmental organization

"A lot of people have lost their income. Women especially... they would be working as a [domestic worker], but now, the employer is at home, and doesn't require the domestic worker anymore... The country started with a COVID-19 support grant... Even worse, you could only apply for that if you had a valid ID [identification card]. Many people have lost their IDs and are displaced because they don't have ID documents. To get an ID you need to pay... and then you wait."

Summary: Availability and affordability of NCD medicines

Existing barriers in accessing medicines experienced by people with NCDs were in many cases exacerbated in 2020–2021. The findings of WHO Country Capacity Surveys highlight continuing access disparities by country income, with low- and lower-middle-income countries having more limited access to essential NCD medicines than upper-middle and high-income countries.

There is no global monitoring mechanism for shortages of active pharmaceutical ingredients (APIs), nor are there institutional mechanisms through which countries can coordinate to respond to and mitigate such shortages as they arise. National shortage databases in Australia, Brazil, South Africa and the United States were analysed to identify NCD-related APIs that were affected. These countries were selected because data are publicly available and include the

specific causes of shortage events (e.g. API availability, logistics, manufacturing, packing, regulatory delays, unanticipated demand increases and commercial decisions). While not globally representative, the included countries represent large, competitive markets; if these markets experienced upstream challenges in API markets, it is likely that the underlying cause also contributed to shortages in other countries.

The scoping review identified no longitudinal studies of factors affecting medicines availability before and after the pandemic across a representative sample. However, a number of smaller studies focussed on specific patient populations, providing insight into the experiences of people with cardiovascular disease, diabetes, cancer, chronic respiratory disease, pain, mental illness and those needing palliative care. Key themes included:

- **Affordability:** Studies showed an increase in the number of patients reporting financial stress in accessing medicines, either as a result of lost income and employment or an increase in medicine prices.
- **Availability:** Studies across all disease categories reported decreased availability of medicines. Where possible, health services adapted treatment protocols. Health providers also adapted prescribing behaviour to try to maintain supply stability, for example, by encouraging providers to write prescriptions for single-month supplies instead of multi-month prescriptions for medicines known to be in scarce supply. The literature mostly focused on patient experiences and did not explore the causes of the stockouts.
- **Transport:** Another theme identified was a breakdown in transportation, both for patients and for components of the medicines supply chain. While health facilities mostly remained open during national lockdown periods, public and private transport operated with reduced schedules and routes. Increased financial pressures made already difficult journeys more burdensome for patients. At the national and international level, the reductions in commercial airline services led to a disruption in supply of some components and products.
- **Inequity:** National level availability data from Country Capacity Surveys further highlights inequities in access to key products between high-income countries the rest of the world.

Policy Considerations: Availability and affordability of NCD medicines

Governments should work towards improving access to quality medicines and health products, including for NCD, to populations in need without financial hardship. WHO should also continue to provide technical

assistance to help manufacturers seeking WHO prequalification comply with international regulatory norms and standards for priority health products for improved availability of NCD medicines.



6. ACCESS TO NCD MEDICINES BY DISEASE CATEGORY

6.1. Background

This chapter covers the four main types of NCDs that represent the greatest morbidity and mortality (i.e. cardiovascular disease, diabetes, cancer and chronic respiratory disease), and includes data on access to medicines used for pain and palliative care, mental health and other NCDs where available.

As well as a qualitative analysis of the grey literature and interview responses, this chapter uses information gathered from (i) the scoping review of the academic literature; (ii) quantitative data from Country Capacity Surveys before (2019) and during (2021) the coronavirus disease (COVID-19) pandemic; and (iii) quantitative data from medicines shortages databases in Australia, Brazil, South Africa and the United States of America.

The scoping review identified 47 studies reporting on access to NCD medicines during the COVID-19 pandemic: 14 papers had no disease focus, but were inclusive of NCDs; three reported on NCDs in general; four reported on cardiovascular disease; four reported on diabetes; three reported on chronic respiratory disease; eight reported on cancer; three reported on mental health; and 14 reported on other NCDs. Garcia-Azorin et al. (24), Shimels et al. (44) and Singh et al. (45) reported on two, two and five separate disease categories, respectively. No papers reported on access to medicines for palliative care during the pandemic. Where possible, information on shortages obtained from interviews was corroborated through other sources, including through published statements by manufacturers and trade associations, other press materials and statements from affected patient groups.



Mustafa Bashe, logistics assistant at the WHO warehouse, pulls an oxygen concentrator from the warehouse inventory for delivery to a local hospital on 19 January 2021 in Hargeisa. © WHO / Blink Media - Mustafa Saeed

Country Capacity Surveys conducted in 2019 and 2021 asked Member States to report whether key essential medicines were generally available, defined as being available in 50% or more of pharmacies in primary care facilities of the public health sector (further details of the survey are available in **Section 5.2 on Baseline access: WHO Country Capacity Surveys**). There are some limitations to these data: although all Member States responded to the survey, not all questions were answered, and slight fluctuations should not be interpreted as clear evidence of improvement or worsening of access. The data have not been validated.

At present, there is no global upstream monitoring, reporting and mitigation mechanism for shortages of active pharmaceutical ingredients (APIs). Some APIs are manufactured by only one or two producers, and are therefore vulnerable to (i) shocks and emergencies, such as pandemics or natural disasters; and (ii) business decisions, where a firm may stop manufacturing a medicine. Even when notice is given of an interruption, downstream shortages may occur in the months it takes for a new entrant to establish manufacturing facilities and secure regulatory approval to enter the market.

A number of countries require or request that manufacturers report anticipated shortages, and publish databases of shortages by medicine, firm, formulation and cause. Data on shortages from Australia, Brazil, South Africa and the United States were analysed to identify NCD-related APIs that were reported to national authorities as being affected by a shortage (see Chapter 2 on Methods). The included countries represent large, competitive markets; if these markets experienced upstream challenges in API markets, it is likely that the underlying mechanism also contributed to shortages in other countries. See also **Section 2.6 (Quantitative analysis of medicines shortages databases)** and **Annex 4 (National shortages databases analysis)** for more details of the data source and cleaning protocol. NCD medicines for which a problem in the supply of API was reported as the cause of shortages are reported, with overlapping shortages in multiple countries

highlighted **through Venn diagrams, in Sections 6.2–6.7**.

The medicines shortages data reported in this chapter have a number of limitations. First, the data are generally submitted by manufacturers, and not routinely verified by national medicines regulatory authorities. Second, it is unclear whether API shortages were localized to a specific firm or reflected a wider global or regional disruption. Third, there is no counterfactual global supply chain, and it is therefore not possible to conclusively establish whether the shortages were truly caused by the COVID-19 pandemic alone. Further information gathering for medicines of concern should be conducted to establish contextualized case histories of each shortage, and further data are needed to establish whether shortages attributed to the availability of APIs extend beyond the included countries.

6.2. Cardiovascular disease

Cardiovascular disease (CVD) includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism. It is the leading cause of mortality globally: an estimated 18 million deaths were attributable to CVD in 2019, of which 85% were the result of myocardial infarction or stroke. 38% of the 17 million premature deaths, i.e. in those aged < 70 years) were caused by CVDs (251). Treatment of hypertension is key in preventing myocardial infarction and stroke, and is a risk factor of concern because of the increased number of people with either undiagnosed hypertension or diagnosed but untreated hypertension (251). The number of people aged 30–70 years with hypertension doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019 (252). There exist stark disparities by income and region; globally, less than one quarter of people with hypertension were estimated to have controlled hypertension in 2019, but control rates were below 10% in some countries in north and sub-Saharan Africa, central and south Asia, eastern Europe and Oceania (252).

6.2.1. Scoping review of published literature

The published academic literature comprises self-reported surveys among people with CVD, reporting their access to and utilization of medicines. The scoping review identified four papers with outcomes relating to how the COVID-19 pandemic affected access to medicines for cardiovascular disease.

A study in India found that access to CVD medicines was disrupted by the COVID-19 pandemic, partly as a result of increased financial constraints. Singh et al. (45) evaluated the health, psychosocial and economic impacts of the COVID-19 pandemic on people with chronic conditions in India, including a structured questionnaire conducted by telephone (n = 1734) and in-depth interviews (n = 40). Participants were already enrolled in the pre-existing cohort studies Centre for Cardio-metabolic Risk Reduction in South Asia (CARRS) and India-UDAY, and were receiving treatment for chronic disease. A total of 15.3% of respondents with cardiovascular disease and 20.3% with hypertension reported that they “experienced difficulties in accessing medicines due to COVID-19 situation”, which could include a variety of factors such as availability, increased transport barriers and movement restrictions. A total of 10.9% of respondents with cardiovascular disease and 16.6% with hypertension stated that financial difficulties were the cause of challenges in accessing medicines.

A study in France found that adherence to medications was minimally affected, at least in the earliest stages of the COVID-19 pandemic. Cransac-Miet et al. (19) evaluated the impact of the COVID-19 lockdown on adherence for people with chronic coronary syndromes in France. A random sample of patients (n = 205) from an existing cohort (RICO: Observatoire des infarctus de Côte d’Or) were interviewed 4 weeks after the implementation of the first national lockdown. Only 3% of respondents reported medicine discontinuation, although this study was limited by reliance on self-reporting.

Shimels et al. (44) assessed the magnitude and drivers of medication adherence among

people with diabetes and hypertension in Ethiopia. Survey respondents were selected from adults (n = 409) visiting public health facilities during 1–30 August 2020 in Addis Ababa, Ethiopia who had been using antihypertensive or antidiabetic medicines for more than 6 months. A total of 40% of respondents reported that the COVID-19 pandemic had negative impacts on the availability of medications, and a similar proportion (39%) reported increased prices of, and even unaffordable, medications. These findings are perhaps confounded by the ongoing conflict in Ethiopia, which may have affected the health system and supply chains, although this is not discussed by Shimels et al. (44).

Few studies in the scoping review address the effects of transport barriers on access to medicines for CVD during the pandemic. Schwartz et al. (43) evaluated the impact of the pandemic-related lockdown in Uganda on access to medicines for both HIV and hypertension. The study was conducted among people who attend the largest HIV clinic in Uganda as part of a prospective cohort study of integrated care delivery. The clinic also provides hypertension care, and prescribes amlodipine, hydrochlorothiazide and valsartan at no charge. Health facilities remained open during the national lockdown in Uganda (25 March–30 June 2020), but the ban on motor vehicle transport made it difficult for patients to travel to the clinic to collect medicines. Among those patients who missed appointments, 49–66% self-reported by telephone or at their next visit that they had sought care at other health facilities. However, among those that sought care elsewhere, 92–100% were dispensed HIV but not hypertension medicines.

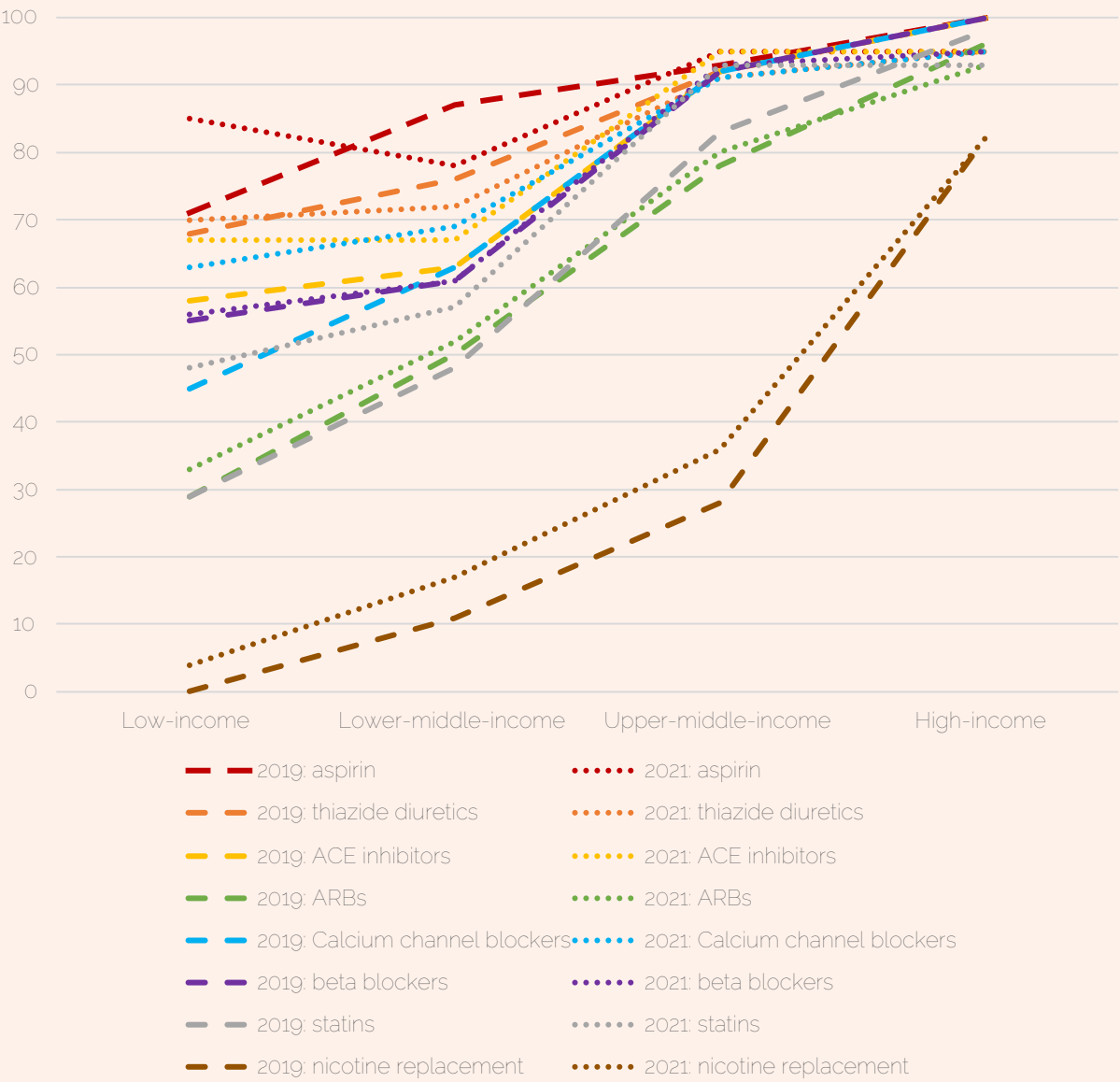
6.2.2. Medicine availability in 2019 and 2021

Data from WHO 2019 and 2021 Country Capacity Surveys on the availability of CVD medicines highlight disparities by both WHO region and World Bank income level (Table 6.1; Fig. 6.1). From 2019 to 2021, growth in access to all medicines for CVDs was observed in low-income countries. Levels of access to most CVD medicines remained

relatively constant for lower-middle- and upper-middle-income countries, with the exception of nicotine replacement and statins for which a significant relative increase was observed (55% and 19% for nicotine replacement and statins, respectively, in lower-middle-income countries; and 29% and 12% for nicotine replacement and statins, respectively, in upper-middle-income countries). The largest relative increase in countries reporting general availability was

observed for statins in low-income countries, with a 66% relative increase (from 29% in 2019 to 48% in 2021). The largest relative decrease in countries reporting general availability was observed for aspirin in lower-middle-income countries, with a 10% relative decrease (from 87% in 2019 to 78% in 2021).

Fig. 6.1. Equity curve of percentage of countries where medicines for cardiovascular diseases were generally available across World Bank income categories, by drug and from 2019 to 2021



Source: WHO Country Capacity Surveys, 2019 and 2021

Table 6.1.

Percentage of countries in which medicines for cardiovascular disease were generally available according to WHO 2019 and 2021 Country Capacity Surveys, by WHO region and World Bank income group, and relative percentage change from 2019 to 2021

WHO region/ World Bank income group	Angiotensin II receptor blockers		Angiotensin- converting enzyme inhibitors		Aspirin		Beta blockers		Calcium channel blockers		Nicotine replace- ment		Statins		Thiazide diuretics									
	2019	2021	2019	2021	2019	2021	2019	2021	2019	2021	2019	2021	2019	2021	2019	2021								
African Region	36	45	+25	66	68	+3	79	83	+5	57	57	0	64	64	+12	6	9	+50	36	49	+36	77	81	+5
Region of the Americas	77	74	-4	91	89	-2	94	91	-3	86	91	+6	89	89	0	23	23	0	83	86	+4	91	89	-2
South-East Asia Region	73	91	+25	73	100	+37	91	100	+10	91	91	0	64	91	+42	9	36	+300	73	91	+25	82	91	+11
European Region	92	91	-1	94	92	-2	100	92	-8	96	92	-4	94	92	-2	75	77	+3	91	91	0	98	92	-6
Eastern Mediterranean Region	76	57	-25	86	76	-12	86	86	0	90	76	-16	90	81	-10	29	38	+31	81	76	-6	86	67	-22
Western Pacific Region	63	67	+6	74	81	+9	89	85	-4	74	74	0	78	81	+4	41	44	+7	67	81	+21	78	78	0
Low-income	29	33	+14	58	67	+16	71	85	+20	55	56	+2	45	63	+40	0	4	NA	29	48	+66	68	70	+3
Lower-middle-income	50	52	+4	63	67	+6	87	78	-10	61	61	0	63	69	+10	11	17	+55	48	57	+19	76	72	-5
Upper-middle-income	78	80	+3	92	95	+3	93	95	+2	92	93	+1	92	91	-1	28	36	+29	83	93	+12	92	91	-1
High-income	96	93	-3	100	95	-5	100	95	-5	100	95	-5	100	95	-5	82	82	0	98	93	-5	100	95	-5
Overall	69	70	+1	82	83	+1	90	89	-1	81	79	-2	80	82	+3	36	40	+11	71	77	+8	87	84	-3

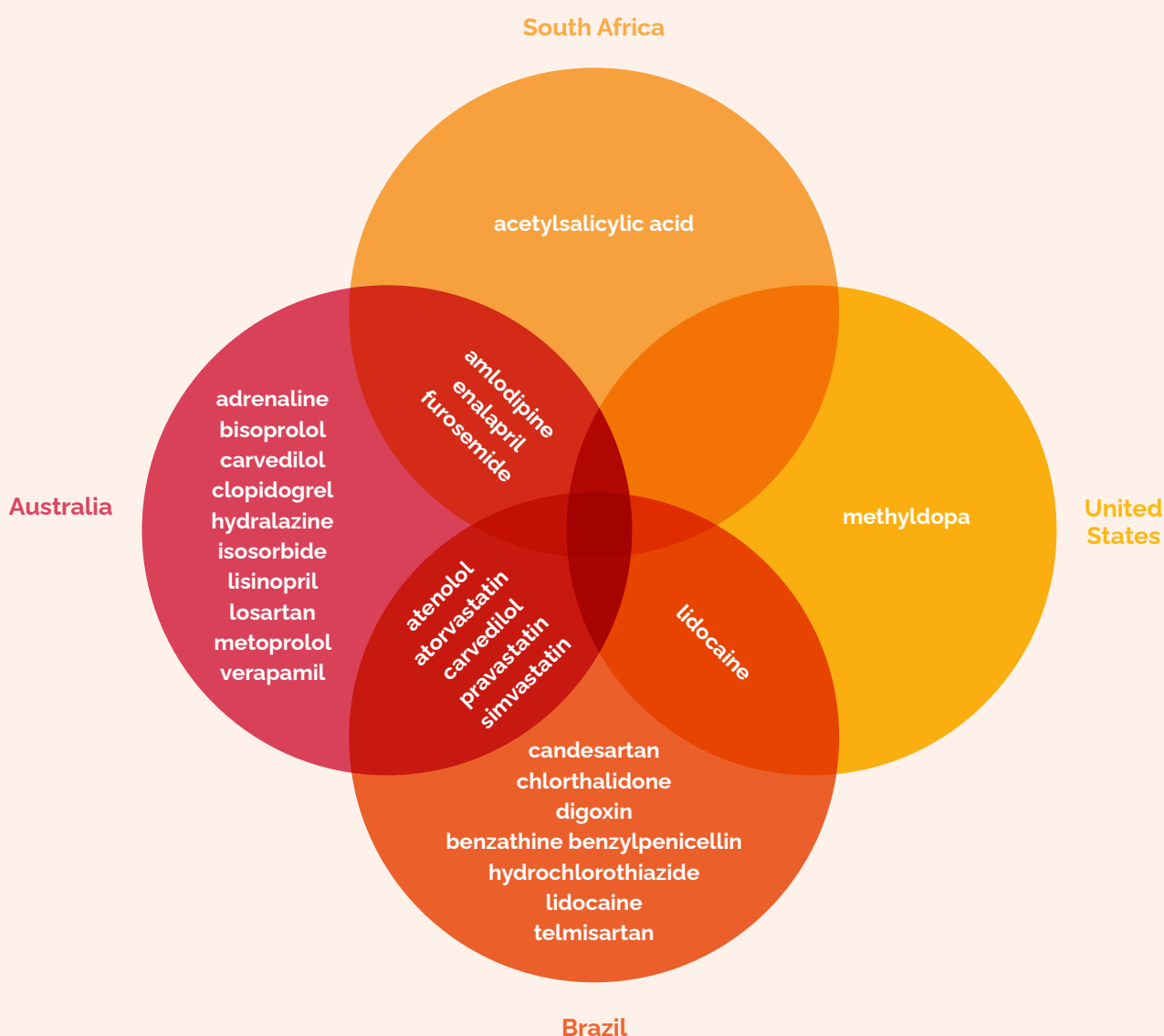
NA: not applicable.

6.2.3. CVD medicines shortages for which API supply was reported as the problem

This analysis includes those medicines in section 12 (Cardiovascular medicines) of the 22nd WHO Model List of Essential Medicines (6). See Sections 2.6 and 6.1, as well as Annex 4, for more information on methods and data sources. South Africa and Australia both

reported problems in the supply of APIs as the cause of shortages of amlodipine, enalapril and furosemide. In Australia and Brazil, shortages of atenolol, atorvastatin, carvedilol, pravastatin and simvastatin were reported as being the result of API shortages. The United States and Brazil reported problems in the supply of API as the cause of shortages of lidocaine (Fig. 6.2).

Fig. 6.2. Cardiovascular disease medicines for which API shortages were reported as the cause of medicine shortages in Australia, Brazil, South Africa and the United States



Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, South Africa National Department of Health Affordable Medicines Directorate and United States Food and Drug Administration.



Diabetic adolescent Elenilda Jesus dos Santos, age 17, injects herself with insulin at CEDEBA - Centro de Referência Estadual para Assistência ao Diabetes e Endocrinologia (Center for Diabetes Assistance and Endocrinology). © WHO / Panos / Eduardo Martino

6.3. Diabetes

There were an estimated 1.5 million deaths resulting directly from diabetes in 2019 [\(253\)](#). The number of people with diabetes quadrupled from 1980 (108 million) to 2014 (422 million) [\(254\)](#). People with diabetes are at a higher risk of severe symptoms and death as a result of contracting COVID-19, and substantial pre-2020 barriers to insulin access were amplified by the pandemic. Baseline availability of insulin prior to the COVID-19 pandemic was low and highly inequitable by income. It is estimated that of the 63 million people with type 2 diabetes who need insulin, only half of these people can access it [\(253\)](#). Although there is no global estimate for morbidity and mortality resulting from lack of insulin access, it is

well documented that high insulin costs have led to rationing, catastrophic health expenditures, increased morbidity and, in some cases, death.

High and rising insulin costs are a key barrier to access that was further exacerbated by the economic shocks of the COVID-19 pandemic. Insulin is not especially costly to manufacture; the cost of production of a 1000-unit phial has been estimated at 2.28–3.37 United States dollars (US\$) [\(256\)](#). For a number of reasons, insulin prices today span a wide range and are unaffordable to many people in low- and middle-income countries, and those globally without health coverage. Inequity in pricing is observed at a national level, with middle-income countries in some cases paying significantly

more than high-income countries. Tuvalu (gross domestic product (GDP) per capita: US\$ 4143) pays US\$ 43.51 per 10 mL vial of human insulin, while the United Kingdom (GDP per capita: US\$ 40 285) pays US\$ 9.75 and Pakistan (GDP per capita: US\$ 1194) pays US\$ 2.24 (256, 257). Prices for insulin aspart, insulin glargine and insulin lispro are significantly higher.

In discussions of prioritization of continuity of NCD medicine access, interviewees with procurement responsibilities described insulin as their top concern and priority. From a supply chain perspective, insulin is one of the most high-risk products because of the cold chain requirements. One interviewee reported that a cargo shipment of insulin had to be destroyed as a result of pandemic-related delays in unloading a cargo plane. In terms of global production, Major insulin manufacturers released public statements on the stability of upstream insulin manufacturing (258-260). Although stable upstream global insulin production is critical, downstream challenges, which include lost income and employment (as well as employment-derived health insurance) as a result of the COVID-19 pandemic, also need to be highlighted. In a global survey (n = 1064) across 64 countries, 63.2% of respondents reported disrupted insulin supplies and 25.3% reported increased insulin prices related to the COVID-19 pandemic (261).

Many health providers implemented temporary measures to decrease barriers, including extending prescription date validity, multi-month prescribing and virtual consultations; see **Section 4.10.6 (Reducing barriers to chronic care prescriptions access)** for more information about these measures.

6.3.1. Scoping review of published literature

The published academic literature comprises self-reported surveys of people with diabetes. The scoping review identified four papers reporting on the effect of the COVID-19 pandemic on access to diabetes medicines, with outcomes related to drivers of access (financial difficulties, food insecurity) as well as medicine shortages and stockouts.

Shimels et al. (44) assessed the magnitude and drivers of medication adherence among people with diabetes and hypertension in Ethiopia. Survey respondents were selected from adults (n = 409) visiting public health facilities during 1–30 August 2020 in Addis Ababa, Ethiopia who had been on antihypertensive or antidiabetic medicines for more than 6 months. A total of 40% of respondents reported that the COVID-19 pandemic had negative impacts on the availability of medications, and a similar proportion (39%) reported unaffordable or increased prices of medications.

A study in India found that access to diabetes medicines was disrupted by the COVID-19 pandemic, partly the result of increased financial constraints. Singh et al. (45) evaluated the health, psychosocial and economic impacts of the COVID-19 pandemic on people with chronic conditions in India, including a structured questionnaire conducted by telephone (n = 1734) as well as in-depth interviews (n = 40). Participants were already enrolled in the pre-existing cohort studies CARRS and India-UDAY and were receiving treatment for chronic disease. A total of 18% of participants with diabetes reported that they "experienced difficulties in accessing medicines due to COVID-19 situation" as a result of a variety of factors such as availability, increased transport barriers and movement restrictions. Compared with people with other chronic diseases (CVD, hypertension, chronic kidney disease, chronic obstructive pulmonary disease (COPD)) enrolled in the study, respondents with diabetes were most likely to report difficulties in accessing medicines as a result of financial difficulties (16.7%).

A national survey conducted in China found a significant difference between people with and without diabetes in terms of medicine and food shortages. Yan et al. (50) conducted a survey on perceived risk, behaviour changes and health-related outcomes. A total of 9016 participants, including 585 with diabetes, were recruited through convenience and snowball sampling during 25 April–11 May 2020. Of respondents with diabetes, 59.7% reported experiencing medicine shortages compared with 28.4% of people without diabetes. A similar proportion (59.8%) of people with diabetes reported

that they also experienced food shortages, compared with 25.0% of people without diabetes.

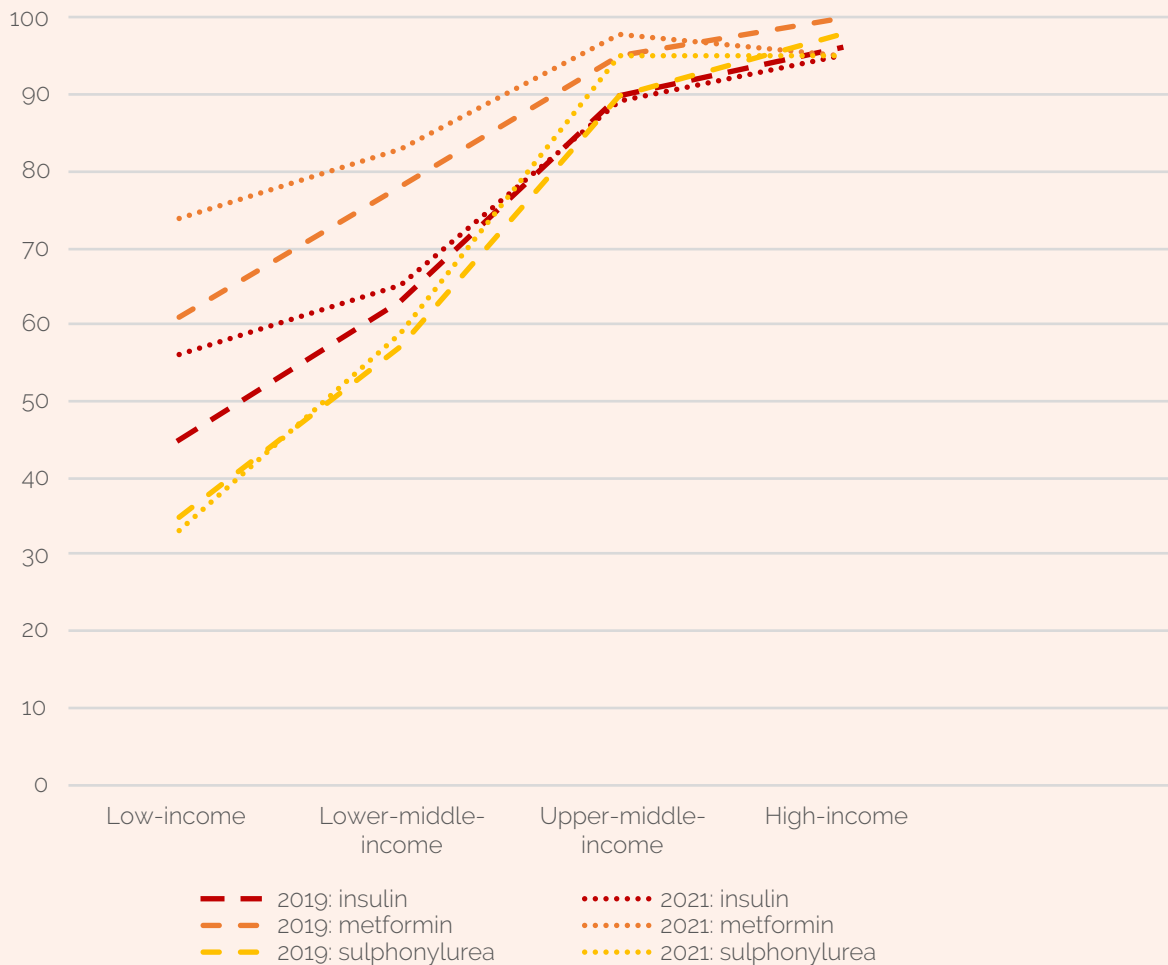
In Singapore, a web survey assessing the impact of COVID-19 and partial lockdown on access to care, self-management and psychological well-being among people with diabetes found little interruption to respondents' access to diabetes medicines. Yeoh et al. (51) recruited patients (n = 201) from two public hospitals in Singapore and via social media, posters and referral from a diabetes voluntary welfare association during June–October 2020. Nearly all respondents reported that they were able to access medications and diabetes equipment (94%)

and supplies (97%) during the pandemic lockdown.

6.3.2. Medicine availability in 2019 and 2021

Data from WHO 2019 and 2021 Country Capacity Surveys on the availability of diabetes medicines highlight disparities by both WHO region and World Bank income level (Table 6.2; Fig. 6.3). By WHO region, the relative change in availability of diabetes medicines is observed to range from -17% (Eastern Mediterranean Region) to +28% (South-East Asia Region).

Fig. 6.3. Equity curve of percentage of countries where medicines for diabetes were generally available across World Bank income categories, by drug and from 2019 to 2021



Source: WHO Country Capacity Surveys, 2019 and 2021

Table 6.2.

Percentage of countries where medicines for diabetes were generally available according to WHO 2019 and 2021 Country Capacity Surveys, by WHO region and World Bank income group, and relative percentage change from 2019 to 2021

WHO region/World Bank income group	Insulin			Metformin			Sulphonylureas		
	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change
African Region	60	68	+13	70	81	+16	51	49	-4
Region of the Americas	83	91	+10	94	100	+6	91	97	+7
South-East Asia Region	45	55	+22	91	100	+10	64	82	+28
European Region	94	89	-5	94	92	-2	92	89	-3
Eastern Mediterranean Region	86	71	-17	90	86	-4	71	67	-6
Western Pacific Region	81	81	0	89	85	-4	74	78	+5
Low-income	45	56	+24	61	74	+21	35	33	-6
Lower-middle-income	63	65	+3	78	83	+6	57	59	+4
Upper-middle-income	90	89	-1	95	98	+3	90	95	+6
High-income	96	95	-1	100	95	-5	98	95	-3
Overall	78	79	1	87	90	3	76	76	0

NA: not applicable.

A large relative increase (24%) was observed in the availability of insulin from 2019 to 2021 in low-income countries. Although this is a promising increase, only 56% of low-income countries reported insulin being generally available in 2021 compared with 95% of high-income countries. A similar change in the general availability of metformin in low-income countries was observed, with a relative increase of 21%. However, less than three quarters of low-income countries reported metformin as being generally available in 2021, compared with 98% of upper-middle-income and 95% of high-income countries. In contrast, a decline of 6% in the percentage of low-income countries reporting sulphonylureas as being generally available was observed. The availability of insulin, metformin and sulphonylureas remained relatively constant throughout this period in lower-middle-income, upper-middle-income and high-income countries.

6.3.3. Diabetes medicines shortages for which API supply was reported as the problem

This analysis includes those medicines in section 18.5 (Diabetes medicines) of the 22nd WHO Model List of Essential Medicines (6). See Sections 2.6 and 6.1, as well as Annex 4, for more information on methods and data sources. Australia, Brazil and South Africa reported problems in the supply of APIs as the cause of shortages of metformin (Fig. 6.4).

6.4. Cancer

Cancer care was among the most affected health services during the pandemic, as many hospitals delayed screening tests and converted wards to serve COVID-19 patients. There were 10 million deaths from cancer in 2020, with 7 out of 10 occurring in low- and middle-income countries (262). The most common cancers in 2020 were breast (2.26 million cases), lung (2.21 million cases), colon and rectum (1.93 million cases), prostate (1.41 million cases), skin (non-melanoma, 1.2 million cases) and stomach (1.09 million cases) (260). The WHO International Agency for Research on Cancer (IARC) has projected that new cancer cases will grow from 19.3 million in 2020 to 30.2 million by 2040 (263).

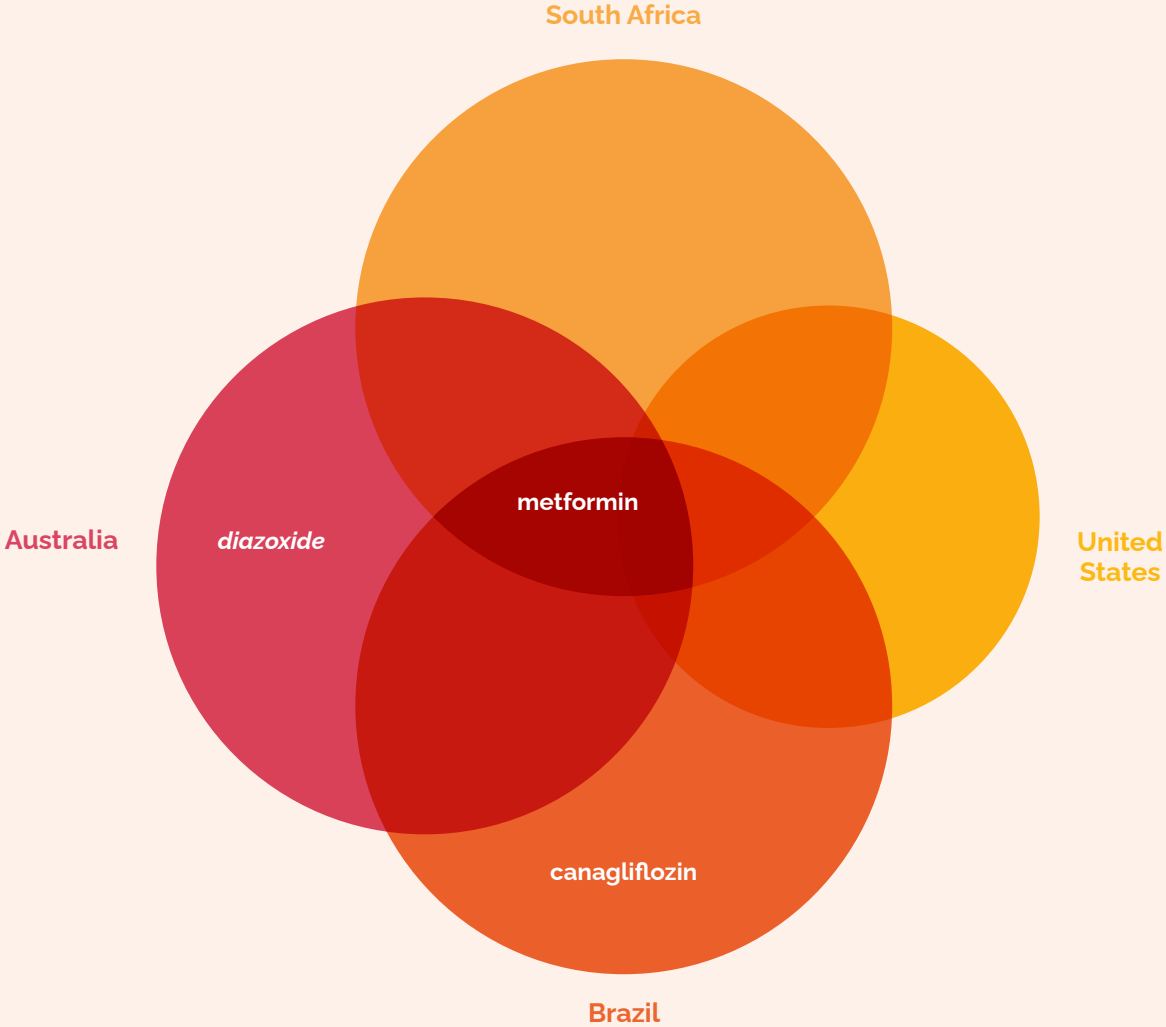
There is significant inequity in access to cancer treatment, with low-income patients and patients in low-income countries having lower inclusion rates of cancer medicines on national essential medicines lists (NEMs), higher costs relative to GDP in procurement and higher burdens of out-of-pocket costs for patients.

Cancer medicines are among the most expensive on the WHO Model List of Essential Medicines (EML) (6). In 2021, the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines noted that the "prohibitively high price – multiples of median annual household incomes" of a number of medicines associated with "large, clinically relevant benefits and favourable safety profiles" delayed or prevented the Committee from recommending their inclusion. While these findings applied to a range of medicines, the Expert Committee specifically noted a number of medicines with cancer indications that had "potential for future inclusion", including cyclin-dependent kinase (CDK) 4/6 inhibitors, daratumumab, osimertinib, PD-1/PD-L1 immune checkpoint inhibitors and zanubrutinib. The Expert Committee recommended the establishment of a standing WHO EML Working Group to "provide advice to WHO on policies and rules to make highly priced essential medicines more affordable and accessible" (264).

At the national level, the procurement price of medicines may not correlate with country income or cancer incidence. In a study of 949 procurement transactions across 29 countries in Africa, the Caribbean and Latin America, Cuomo et al. (265) found that countries in Africa appeared to pay more than countries in Latin America for a package of essential care medicines. For example, Costa Rica paid US\$ 2.00 for 100 tablets of dexamethasone in the same year that Namibia paid US\$ 7.96 (265).

There are also disparities by country income at the level of medicine inclusion in NEMs. Bazargani et al. (266) conducted a study of oncology medicine selection on NEMs in low- and middle-income countries; low-income countries reported a median of 11 cancer medicines on NEMs, lower-middle-income countries reported 18 and upper-middle-income countries reported 26.

Fig. 6.4. Diabetes medicines for which API shortages were reported as the cause of medicine shortages in Australia, Brazil, South Africa and the United States



Note: italicized medicines indicate medicines on the complementary list. Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, South Africa National Department of Health Affordable Medicines Directorate and United States Food and Drug Administration.

6.4.1. Scoping review of published literature

The scoping review identified eight papers with outcomes relating to how access to medicines for cancer was affected by the pandemic. The published academic literature comprises reviews of interruptions in cancer care, surveys of oncology providers reporting interruptions in care and one survey of breast cancer patients reporting increased barriers to care during lockdown.

At the facility level, the International Research Network on COVID-19 Impact on Cancer Care (Jazieh et al. (29)) conducted a web-based survey evaluating the

impact of the pandemic on cancer care worldwide. Among 356 centres from 54 countries who responded to the survey between 21 April and 8 May 2020, 44% in low-income countries reported that a lack of medications had led to interruptions in usual care, compared with 14% of centres in middle-income countries and 4% of high-income countries. Nnaji & Moodley (38) reviewed current evidence and contextual perspectives of the impact of the COVID-19 pandemic on the management of cancer diagnosis, treatment and research in health systems in Africa. They found that pre-existing health system and cancer management gaps were exacerbated by the

pandemic, including inadequate oncology and other vital resources. A systematic review of delays and disruptions in cancer health care as a result of the COVID-19 pandemic was published by Riera et al. (40), who found that up to 79% of facilities faced interruptions as a result of supply chain issues. Of the 62 studies identified, three reported medicine shortages and stockouts, and five reported supply shortages.

At the patient level, Wadasadawala et al. (48) found that breast cancer patients in Mumbai experienced a significant loss in income after the lockdown, and many reported shortages of money, food and medicines. In a telephone survey (n = 138) of non-metastatic breast patients already seeking treatment at a tertiary cancer centre in Mumbai, many patients reported a shortage of money (81%), food (32%) and medicine (28%). Average monthly expenditure was defined as "the expenditure of the patients and consumption [of] the accompanying person(s) at the place of treatment and it does not include expenditure of other household members at their permanent residence". The average monthly expenditure increased by 32% during lockdown from 24 March 2020 (the pre-pandemic period) onwards. At the same time, the mean monthly household income of breast cancer patients decreased by 74%. The median household income was 0 during lockdown.

Supply chain disruptions interrupted access to care for cancer patients. Lombe et al. (34) described the impact of COVID-19 on the management of cervical cancer patients in Zambia, the most common cancer in that country. Zambia imports radioactive isotopes for brachytherapy, but the suspension of commercial airlines services led to a disruption in supply; as a result, 28 patients were not able to complete radiotherapy within the recommended treatment period. Treatment providers promoted mitigation strategies to maintain the pace of treatment, including adjusting work schedules and shifts to accommodate longer treatment times.

Three studies focused on the specific impacts of the pandemic on paediatric oncology. Saab et al. (41) conducted a survey of 34 centres in 19 countries, namely: Algeria; Armenia; Bahrain; Georgia; Iran (Islamic Republic of); Iraq; Jordan; Kuwait;

Lebanon; Morocco; Nepal; Oman; Pakistan; occupied Palestinian territory, including east Jerusalem; Saudi Arabia; Sudan; Syrian Arab Republic; Türkiye; and Yemen. Respondents reported medicine shortages in 80%, 50% and 23% of centres in high-income, upper-middle-income, and low- and lower-middle-income countries, respectively. Traoré et al. (46) conducted a survey during 1–15 May 2020 of 25 paediatric oncology centres in 15 African countries (Algeria, Benin, Burkina Faso, Central African Republic, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Guinea, Madagascar, Mali, Mauritania, Morocco, Senegal, Togo and Tunisia). A total of 54% of respondents reported that COVID-19 had negatively affected cancer management for the six priority paediatric cancers of the WHO Global Initiative for Childhood Cancer. Drivers of these impacts included medicines shortages and a reduction of parental financial means, although disaggregated survey data were not reported for these items. Paediatric haemoncologists in Latin America reported that they had to modify chemotherapy treatments early in the pandemic because of medicine shortages. In a web-based survey distributed through the Latin American Society of Pediatric Oncology (SLAOP) e-mail list and St. Jude Global regional partners, 35.76% of respondents reported that they had to modify chemotherapy treatments because of a lack of medicines (47).

6.4.2. Medicine availability in 2019 and 2021

According to the 2019 Country Capacity Survey, chemotherapy is generally available in fewer than 30% of low-income countries and 65% of lower-middle-income countries (94). More than 80% of children diagnosed with cancer in high-income countries will be cured, compared with less than 30% in low- and middle-income countries (267).

Country Capacity Surveys do not include data on specific cancer medicines. Nicotine replacement, which acts to reduce risk factors for cancer, is reported on in the sections on cardiovascular disease (Section 6.2), chronic respiratory disease (Section 6.5) and mental health (Section 6.7).

6.4.3. Immunomodulators and antineoplastic shortages for which API supply was reported as the problem

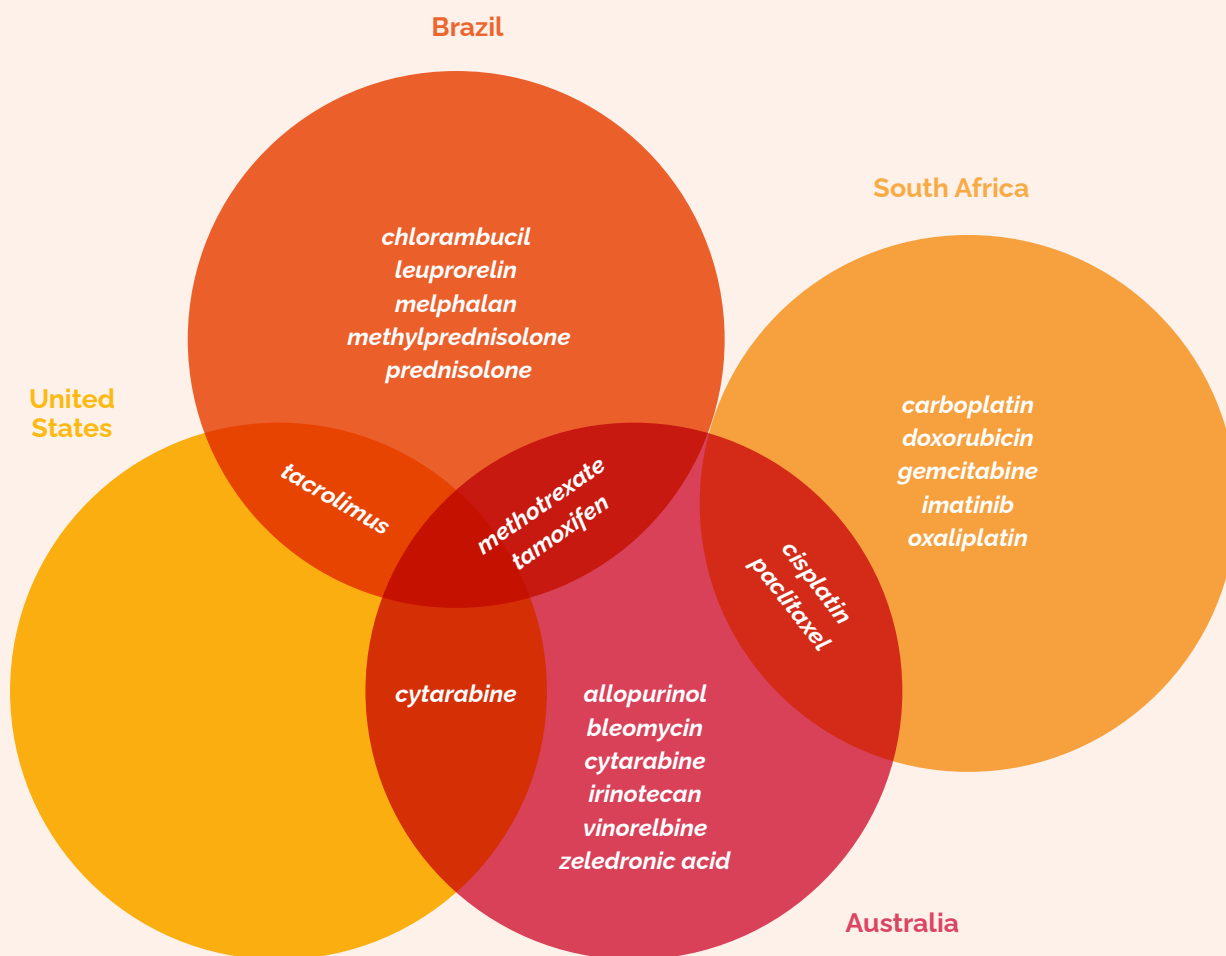
This analysis includes those medicines in section 8 (Immunomodulators and antineoplastics) of the 22nd WHO Model List of Essential Medicines (6). See Sections 2.6 and 6.1, as well as Annex 4, for more information on methods and data sources. Both Australia and Brazil reported problems in the supply of APIs as the cause of shortages of methotrexate and tamoxifen. In Australia and South Africa, API shortages were reported as the cause of shortages of

cisplatin and paclitaxel. Both Australia and the United States reported problems in the supply of APIs as the cause of shortages of cytarabine. Finally, in Brazil and the United States API shortages were reported as the cause of shortages of tacrolimus (Fig. 6.5).

6.5. Chronic respiratory disease

COPD and asthma have the highest disease burden among chronic respiratory diseases. Of the 3.23 million deaths caused by COPD in 2019 globally, 80% occurred in low- and middle-income countries (268). Asthma

Fig. 6.5. Immunomodulators and antineoplastic medicines for which API shortages were reported as the cause of medicine shortages in Australia, Brazil, South Africa and the United States



Note: italicized medicines indicate medicines on the complementary list. Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, South Africa National Department of Health Affordable Medicines Directorate and United States Food and Drug Administration.



COVID-19 vaccinations in Thailand © WHO / Ploy Phutpheng

affects 262 million people globally, and caused 455 000 deaths in 2019 [\(269\)](#).

Increased demand for bronchodilators used in the routine care of patients with chronic respiratory diseases was reported by hospitals for the treatment of patients with COVID-19. One major inhaler manufacturer reported delays in the supply of materials and increased demand for its 100 µg (or mcg) pressurized metered dose inhalers, and issued an alert that it would be unable to guarantee supply [\(270\)](#). The British Thoracic Society reported that demand for inhalers increased by 400% during the pandemic [\(271\)](#), and requested that health care professionals (i) write prescriptions for 1 month rather than for several months and (ii) encourage patients not to stockpile until supply pressures were resolved [\(272\)](#).

A major manufacturer of albuterol, reported that it was increasing production in response to increased demand [\(273\)](#). Teva Pharmaceuticals reported that it was producing albuterol at maximum capacity to meet "historic" demand, "likely as a result of the current COVID-19 pandemic" [\(273\)](#). As described in **Chapter 3 on Manufacturing**, there was a sharp increase in salbutamol API costs in March 2020, a potential result of the increased demand for use by COVID-19 patients.

6.5.1. Scoping review of published literature

The scoping review identified three papers on how access and adherence to medicines for chronic respiratory diseases was affected by the COVID-19 pandemic; all identified studies were self-reported surveys among

people with COPD, reporting their access to and utilization of medicines during lockdown.

A study in India found that access to COPD medicines was disrupted by the COVID-19 pandemic, partly because of increased financial constraints. Singh et al. (45) evaluated the health, psychosocial and economic impacts of the COVID-19 pandemic on people with chronic conditions in India, including a structured questionnaire conducted by telephone (n = 1734) as well as in-depth interviews (n = 40). Participants were already enrolled in the pre-existing cohort studies CARRS and India-UDAY and were receiving treatment for chronic disease. A total of 11% of respondents with COPD reported difficulties in accessing medicines during the COVID-19 pandemic, citing financial difficulties as the cause.

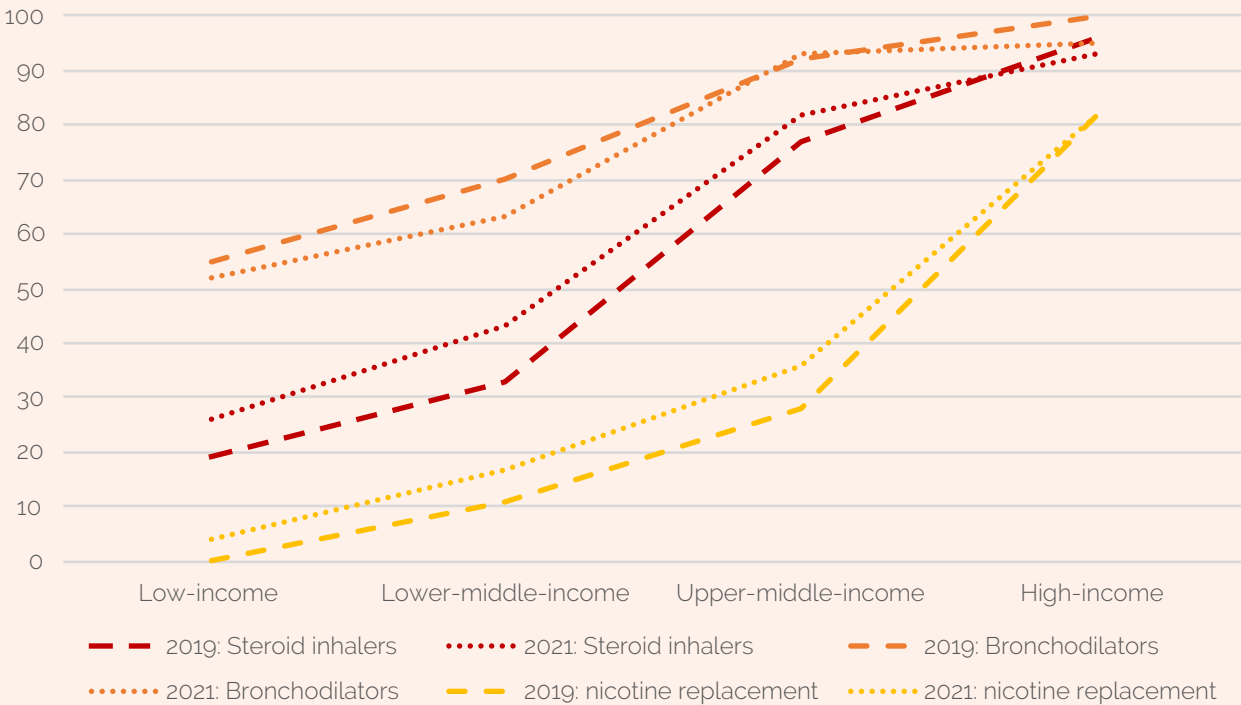
Two surveys assessed medication adherence for patients with COPD in China. Liang et al. (32) conducted a telephone survey (n = 153) of people seeking care for

COPD in Beijing during January–April 2020. A total of 75.2% of patients reported that they maintained treatment by April 2020. Of those interviewed, 13.3% were worried about access to a sufficient supply of maintenance medicine, and 6.5% reduced their dosage or stopped taking medication. Zhang et al. (52) conducted a telephone survey (n = 191) of people seeking care for COPD, and found that medication adherence during the COVID-19 pandemic was similar to pre-pandemic levels. Drivers for poor adherence include out-of-stock medicines (4.5%) and price concerns (4.5%).

6.5.2. Medicine availability in 2019 and 2021

Data from WHO 2019 and 2021 Country Capacity Surveys on the availability of chronic respiratory disease medicines highlight disparities by both WHO region and World Bank income level (Table 6.3; Fig. 6.6).

Fig. 6.6. Equity curve of percentage of countries where medicines for chronic respiratory disease were generally available across World Bank income categories, by drug and from 2019 to 2021



Source: WHO Country Capacity Surveys, 2019 and 2021

Table 6.3.

Percentage of countries in which medicines for chronic respiratory disease were generally available according to WHO 2019 and 2021 Country Capacity Surveys, by WHO region and World Bank income group, and relative percentage change from 2019 to 2021

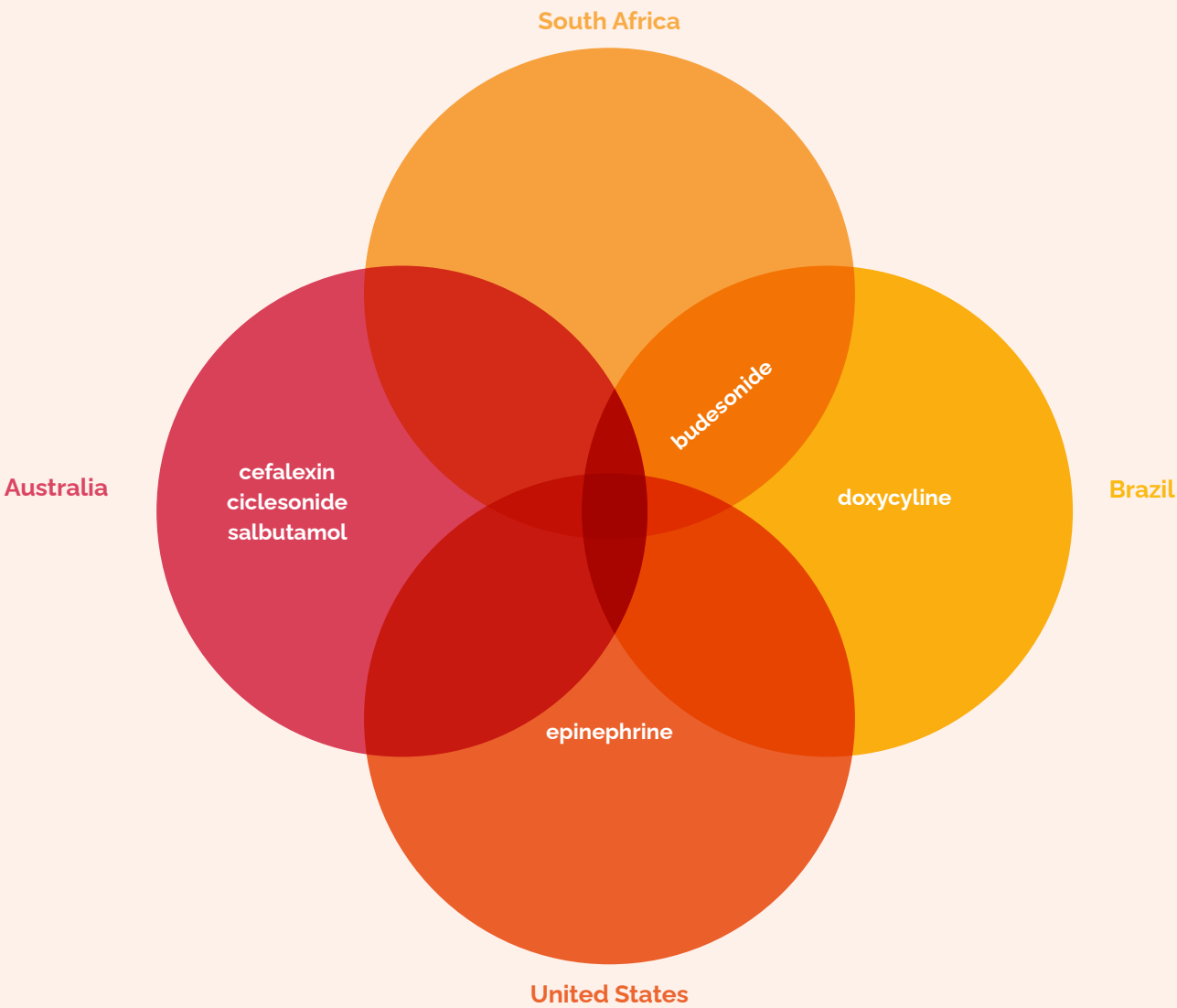
WHO region/World Bank income group	Bronchodilators			Nicotine replacement			Steroid inhalers		
	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change
African Region	64	60	-6	6	9	+50	23	30	+30
Region of the Americas	91	89	-2	23	23	0	77	77	0
South-East Asia Region	73	82	+12	9	36	+300	36	64	+78
European Region	96	92	-4	75	77	+3	89	89	0
Eastern Mediterranean Region	90	81	-10	29	38	+31	71	76	+7
Western Pacific Region	78	74	-5	41	44	+7	67	67	0
Low-income	55	52	-5	0	4	NA	19	26	+37
Lower-middle-income	70	63	-10	11	17	+55	33	43	+30
Upper-middle-income	92	93	+1	28	36	+29	77	82	+6
High-income	100	95	-5	82	82	0	96	93	-3
Overall	83	79	-5	36	40	+11	63	66	+5

NA: not applicable.

Levels of availability of bronchodilators and steroid inhalers in upper-middle-income and high-income countries were largely stable from 2019 to 2021. In contrast, the percentage of lower-middle-income countries reporting general availability of bronchodilators demonstrated a relative decrease of -10%. The percentage of countries reporting general availability of nicotine replacement increased in all regions and across all income categories, with the largest relative increase observed in the South-East Asia Region

(300%). Although the relative percentage increase was high for low-income and lower-middle-income countries in reporting general availability of steroid inhalers (a relative percentage increase during 2019–2021 of 37% and 30% for low-income and lower-middle-income countries, respectively), general availability remained low in low-income countries (26%) and lower-middle-income countries (43%) compared with upper-middle-income countries (82%) and high-income countries (93%) in 2021.

Fig. 6.7. Chronic respiratory disease medicines for which API shortages were reported as the cause of medicine shortages in Australia, Brazil, South Africa and the United States



Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, South Africa National Department of Health Affordable Medicines Directorate and United States Food and Drug Administration.

6.5.3. Chronic respiratory disease medicines shortages for which API supply was reported as the problem

This analysis includes those medicines in section 25 (Medicines acting on the respiratory tract) of the 22nd WHO Model List of Essential Medicines (6). See Sections 2.6 and 6.1, as well as Annex 4, for more information on methods and data sources. Both Brazil and South Africa reported problems with the supply of APIs as the cause of shortages of budesonide (Fig. 6.7).

6.6. Pain and palliative care

As many as 80% of the world's population do not have access to controlled medicines (274). The increase in medical ventilation patients as a result of the COVID-19 pandemic led to an increased demand for analgesics and sedatives, many of

which are also used in palliative care (275). WHO identified four global-level shortages of controlled substances with increased demand resulting from their use in intensive care units for treatment of severe cases of COVID-19. However, the same medicines are also needed in regular palliative care, management of pain, surgical care, anaesthesia, and mental health and neurological conditions (275).

Shortages of palliative care medicines were reported in Canada (276), France (277), India (278), Kenya (279), South Africa (279), Uganda (279), the United Kingdom (280) and the United States (281). Shortages were likely more widespread, and almost certainly observed in many other countries. A major manufacturer of propofol reported that the company "observed an unprecedented surge in demand for propofol beyond historical demand which [limited its] ability to fully satisfy customer orders in the short-term"



Abdul Salam Ansari collect his medicine for diabetes at government initiated Kamala Raman Nagar dispensary. It has Tuesday & Friday dedicated for diabetes check up. © WHO / Panos / Atul Loke

(282). Interviewees described shortages and difficulties in procuring oral morphine. One procurer had anticipated using a United Kingdom supplier, but was prevented from doing so because of an export ban on necessary medicines enacted by the United Kingdom government (283). Where first-line anaesthesia medicines were not available, second- or third-line medications were used, with clinical effects on monitoring and maintenance. For example, doctors in the United States reported using a combination of hydromorphone, ketamine and midazolam because fentanyl and propofol were not available (281).

The International Drug Control Conventions allow competent national authorities to export controlled medicines without corresponding import authorizations and/or estimates during acute emergencies. The United Nations Office on Drugs and Crime (UNODC) and WHO issued a joint statement recommending that

countries ease COVID-19-related transport restrictions for controlled medicine, as well as consider local production where possible (273).

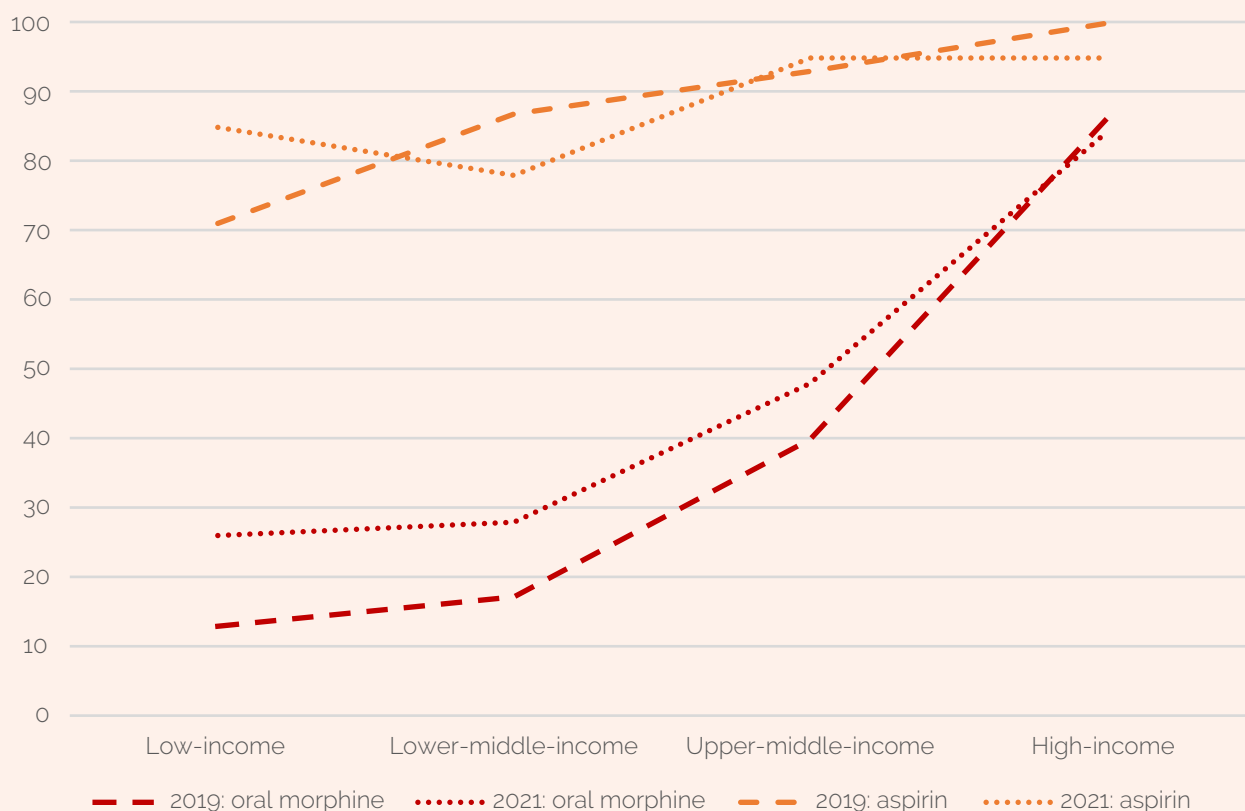
6.6.1. Scoping review of published literature

The scoping review did not identify any published literature on how the COVID-19 pandemic affected access to medicines for pain and palliative care.

6.6.2. Medicine availability in 2019 and 2021

Data from WHO 2019 and 2021 Country Capacity Surveys on the availability of pain and palliative care medicines highlight disparities by both WHO region and World Bank income level (Table 6.4; Fig. 6.8).

Fig. 6.8. Equity curve of percentage of countries where medicines for pain and palliative care were generally available across World Bank income categories, by drug and from 2019 to 2021



Source: WHO Country Capacity Surveys, 2019 and 2021

Table 6.4.

Percentage of countries in which medicines for pain and palliative care were generally available according to WHO 2019 and 2021 Country Capacity Surveys, by WHO region and World Bank income group, and relative percentage change from 2019 to 2021

WHO region/ World Bank income group	Aspirin			Oral morphine		
	2019	2021	Relative change	2019	2021	Relative change
African Region	79	83	+5	21	26	+24
Region of the Americas	94	91	-3	49	51	+4
South-East Asia Region	91	100	+10	18	36	+100
European Region	100	92	-8	70	81	+16
Eastern Mediterranean Region	86	86	0	24	29	+21
Western Pacific Region	89	85	-4	52	52	0
Low-income	71	85	+20	13	26	+100
Lower-middle-income	87	78	-10	17	28	+65
Upper-middle-income	93	95	+2	40	48	+20
High-income	100	95	-5	86	84	-2
Overall	90	89	-1	44	50	+14

Across all WHO regions, the change in availability of aspirin and oral morphine ranged from -8% (European Region) to +100% (South-East Asia Region). From 2019 to 2021, there was a 20% relative increase in the percentage of low-income countries reporting aspirin as generally available. Aspirin remained more widely available than oral morphine, with 85% of low-income

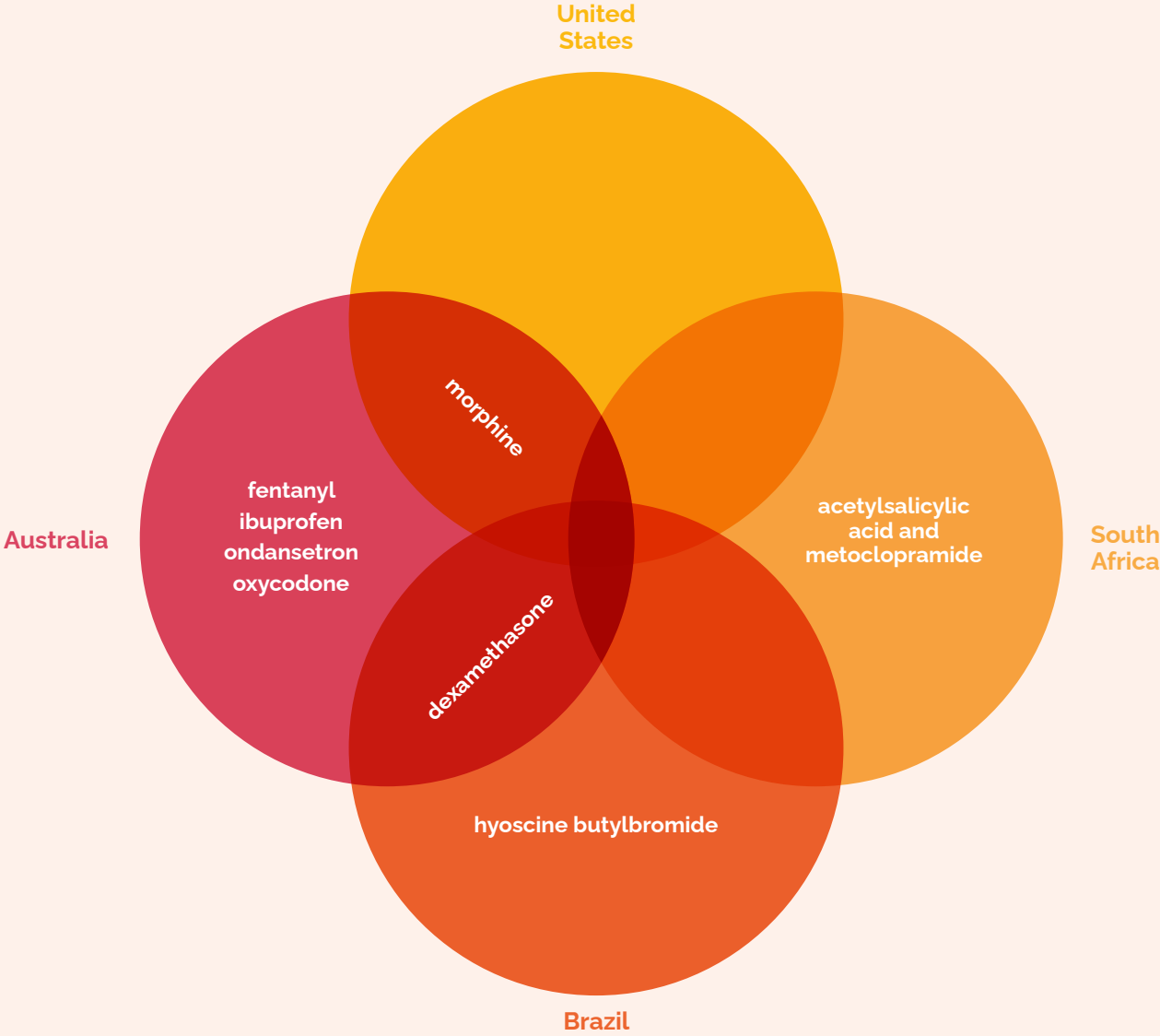
countries reporting aspirin as generally available in 2021 compared with only 26% for oral morphine. There were large relative increases in the percentage of low-income countries (+100%) and lower-middle-income countries (+65%) reporting oral morphine as generally available from 2019 to 2021. However, there exist wide disparities by income group in terms of general availability:

only 26% of low-income and 28% of lower-middle-income countries reported oral morphine as generally available in 2021, compared with 84% in high-income countries.

6.6.3. Pain and palliative care medicines shortages for which API supply was reported as the problem

This analysis includes those medicines in section 2 (Medicines for pain and palliative care) of the 22nd WHO Model List of Essential Medicines (6). See Sections 2.6 and 6.1, as well as Annex 4, for more information on methods and data sources. Both Australia and Brazil reported problems in the supply of APIs as the cause of shortages of dexamethasone. In Australia and the United States, API shortages were reported as the cause of shortages of oral morphine (Fig. 6.g).

Fig. 6.9. Pain and palliative care medicines for which API shortages were reported as the cause of medicine shortages in Australia, Brazil, South Africa and the United States



Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, South Africa National Department of Health Affordable Medicines Directorate and United States Food and Drug Administration.

6.7. Mental health

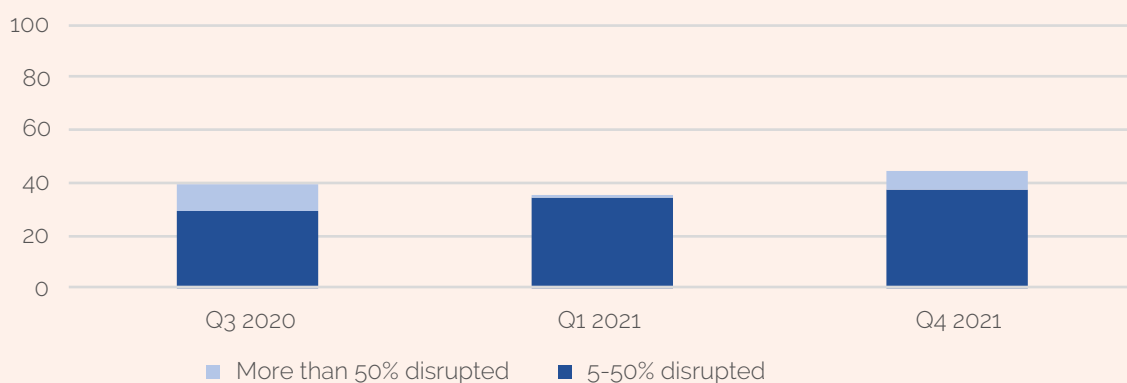
Although not generally classed within the umbrella of NCDs, a brief summary of challenges relating to medicines for mental, neurological and substance use (MNS) disorders is included. The WHO *Comprehensive mental health action plan 2013–2030* notes that NCDs are often associated with mental disorders and co-exist with other medical and social factors, as noted in World Health Assembly (WHA) resolution 65.4 *The global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level*, and recommends that the implementation plan for NCDs complement that for mental health (284, 285).

The term mental health conditions includes MNS disorders. Depression is the most prevalent mental disorder and was estimated to affect 280 million people globally in 2019 (284); depression and anxiety are estimated to cost the global economy US\$ 1 trillion annually (287). Other mental health disorders with relatively high prevalence include dementia (55 million cases) (288), bipolar

disorders (40 million cases in 2019) (289), schizophrenia (24 million cases in 2019) (289) and developmental disorders (unknown prevalence) (290). An estimated 700 000 people died due to suicide in 2019 (291). Despite a high burden and high associated costs, limited resources are available for mental health. Globally, only about 2% of national health budgets is spent on mental health, and an estimated 76–85% of people with mental health conditions in low- and middle-income countries do not receive treatment (75).

The COVID-19 pandemic had significant effects on the provision of mental health care. Isolation, economic distress, bereavement and anxiety contributed to psychological stress; young people, older adults, people living in conflict settings, first responders and frontline workers were particularly affected. Existing challenges were exacerbated by the pandemic; the 148th session of the WHO Executive Board (EB148(3)) *Promoting mental health preparedness and response for public health emergencies* emphasized the importance of equity and whole-of-society approaches to mental health care, urging member states to make an “extra effort

Fig. 6.10. Comparison of availability of psychotropic medicines for mental, neurological and substance use disorders in countries that responded to all three survey rounds in Q3 2020, Q1 2021 and Q4 2021 (see text for definitions) (290).



Source: Third round of the WHO global pulse survey on continuity of essential health services during the COVID-19 pandemic.

to reach people at high risk and those in vulnerable situations, leveraging innovative technologies, including remote mental health services through promoting equitable access to telehealth and other essential and cost-effective technologies, when feasible, in the context of the COVID-19 pandemic and beyond" (292).

Among countries responding to the WHO Mental Health Atlas survey (293), 39% had pharmacological interventions available at more than 75% of primary care centres; 21% had psychosocial interventions available. There are also significant access gaps in neurological care: 34% of 110 countries responding to the WHO Neurology Atlas survey reported that levodopa/carbidopa for Parkinson's disease was available at all times at the primary care level (294). No low-income country reported levodopa/carbidopa availability at the primary care level, in contrast to 77% of high-income countries (294).

WHO conducted a pulse survey of mental health focal points at ministries of health in "Q3 2020" (defined in the report as the 6-month period preceding the month of survey completion), "Q1 2021" (May–September 2021) and "Q4 2021" (the 3-month period preceding survey completion) (Fig. 6.10) (295). Of Member States who responded to all rounds of the survey, levels of availability of psychotropic medicines remained relatively constant throughout the survey period, with 39% reporting disruptions in the first round (Q3 2020), 36% in the second round (Q1 2021) and 39% in the third round (Q4 2021). Of the 130 Member States who responded to an MNS-specific survey conducted during June–August 2020, more than half reported that overdose prevention and management programmes were at least partially disrupted. Opioid agonist maintenance treatment (OAT) was disrupted for more than 50% of patients in 18% of Member States, and disrupted for 5–50% of patients in 32% of Member States responding to the survey. For patients using medicines including clozapine and lithium, regular monitoring is necessary to prevent dangerous contraindications. Further, 40% of Member States responding to the survey reported that laboratory services at mental health facilities were disrupted during the COVID-19 pandemic (296).

6.7.1. Scoping review of published literature

The scoping review identified three papers with outcomes relating to the effect of the COVID-19 pandemic on access to medicines for mental health.

Dunlop et al. (21) reviewed barriers experienced by patients receiving OAT in the context of the COVID-19 pandemic. Most OAT programmes require patients to receive daily dosing; interruptions because of lockdowns and other movement restrictions led to interruptions in access. The authors recommended increasing access to takeaway methadone and buprenorphine, and the expansion of takeaway naloxone supplies.

A systematic review of service disruptions for neurological disorders by García-Azorin et al. (24) found that 16.7% (40/140) of studies meeting inclusion criteria reported unavailability or stockout of essential medicines, medical diagnostics or other health products at health facilities during the COVID-19 pandemic.

Focusing on care in Gabon, Marehin et al. (36) reviewed the literature on care for hospitalized psychiatric patients, with added inputs from practitioners. They found that the economic effects of COVID-19 affected the affordability of needed medicines.

6.7.2. Medicine availability in 2019 and 2021

Data from WHO 2019 and 2021 Country Capacity Surveys for mental health medicines availability are reported in Table 6.5. The data in the NCD survey did not include most medicines used for mental disorders, but did include nicotine replacement therapy, which is indicated on the 22nd WHO Model List of Essential Medicines (6) under section 24.5 (Medicines for disorders due to psychoactive substance use).

Table 6.5.

Percentage of countries in which medicines for mental health were generally available according to WHO 2019 and 2021 Country Capacity Surveys, by WHO region and World Bank income group, and relative percentage change from 2019 to 2021

WHO region/ World Bank income group	Nicotine replacement		
	2019	2021	Relative change
African Region	6	9	+50
Regions of the Americas	23	23	0
South-East Asia Region	9	36	+300
European Region	75	77	+3
Eastern Mediterranean Region	29	38	+31
Western Pacific Region	41	44	+7
Low-income	0	4	NA
Lower-middle-income	11	17	+55
Upper-middle-income	28	36	+29
High-income	82	82	0
Overall	36	40	+11

NA: not applicable.

From 2019 to 2021 there were large relative increases in the percentage of low- and middle-income countries reporting nicotine replacement therapy as generally available. However, there exist wide disparities by

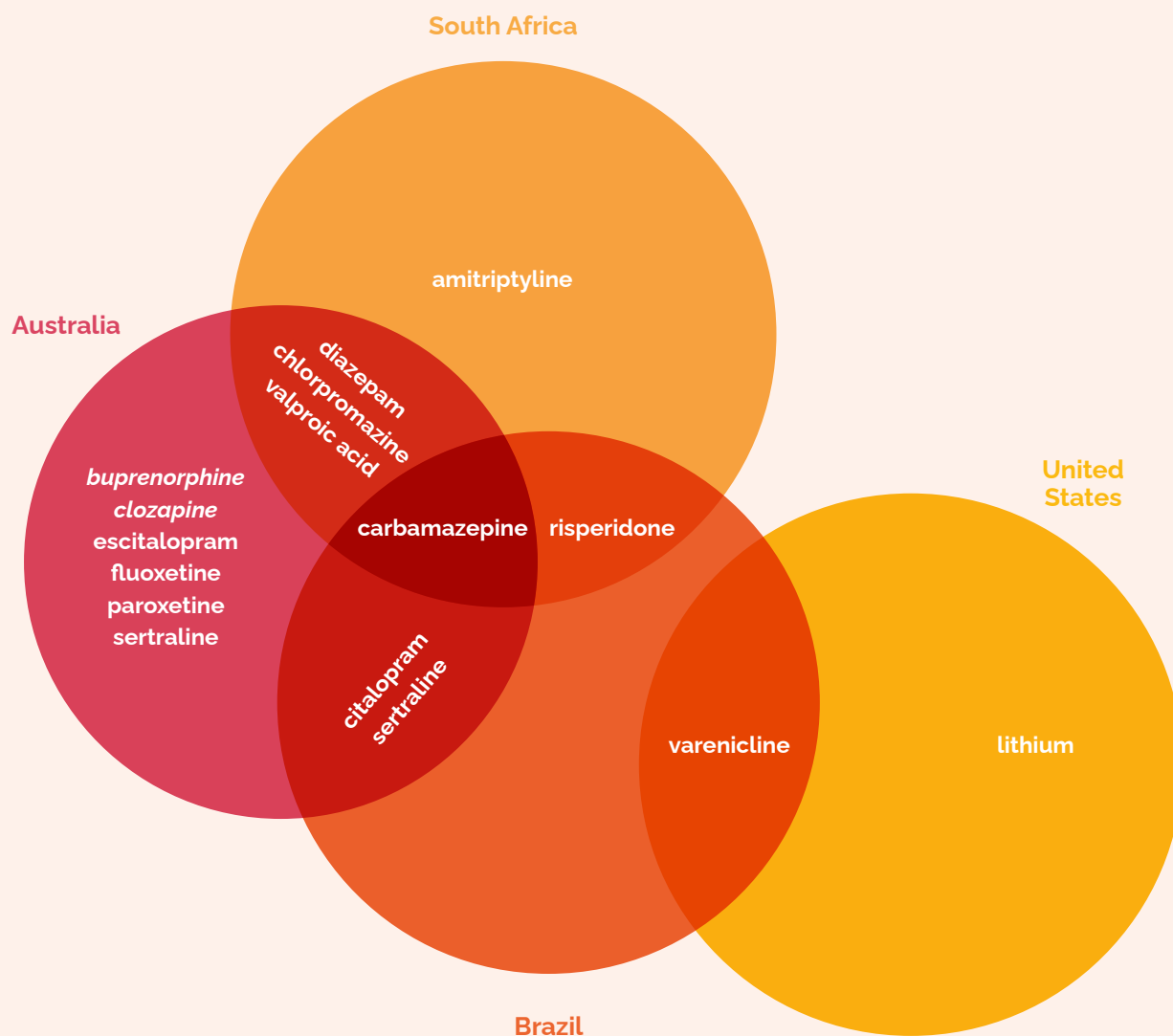
income group: 4% of low-income and 17% of lower-middle-income countries reported nicotine replacement therapy as generally available in 2021, compared with 82% of high-income countries.

6.7.3. Mental and behavioural disorder medicines shortages for which API supply was reported as the problem

This analysis includes those medicines in section 24 (Medicines for mental and behavioural disorders) of the 22nd WHO Model List of Essential Medicines (6). See Sections 2.6 and 6.1, as well as Annex 4, for more information on methods and data sources. Australia, Brazil and South Africa all

reported problems in the supply of API as the cause of shortages of carbamazepine. In both Australia and South Africa, shortages of APIs were reported as the cause of shortages of chlorpromazine, diazepam and valproic acid. South Africa and Brazil both reported problems in the supply of APIs as the cause of shortages of risperidone. Finally, in the United States and Brazil, API shortages were reported as the cause of shortages of varenicline (Fig. 6.11).

Fig. 6.11. Medicines for mental and behavioural disorders for which API shortages were reported as the cause of medicine shortages in Australia, Brazil, South Africa and the United States



Note: italicized medicines indicate medicines on the complementary list. Source: Australia Department of Health Therapeutic Goods Administration, Brazil Agência Nacional de Vigilância Sanitária, South Africa National Department of Health Affordable Medicines Directorate and United States Food and Drug Administration.

Summary: Access to NCD medicines by disease category

Cardiovascular disease: Country Capacity Survey data suggest that levels of access to medicines for cardiovascular diseases remained relatively constant for lower-middle- and upper-middle-income countries, apart from nicotine replacement therapy and statins, for which a significant relative increase was observed. Limited published literature (n=4) found mixed results for changes in access.

Diabetes: High and rising insulin costs are a key barrier to access and were further exacerbated by the economic shocks of the COVID-19 pandemic. The published academic literature comprises self-reported surveys of people with diabetes. In most identified studies (n=4), barriers to diabetes medicine access increased due to lost income, increased prices, decreased availability, and/or transport barriers. Country Capacity Survey data suggest that the availability of insulin, metformin and sulphonylureas remained relatively constant throughout this period in lower-middle-income, upper-middle-income and high-income countries.

Cancer: Country Capacity Survey data does not measure access to specific cancer medicines. The published academic literature identified in the scoping review (n=8) comprises reviews of interruptions in cancer care, surveys of oncology providers reporting interruptions in care and one survey of breast cancer patients reporting increased barriers to care during lockdown. Most studies identified increased access barriers, both as the result of stock availability and lost income.

Chronic respiratory diseases: Country Capacity Survey data suggest that levels of availability of bronchodilators and steroid inhalers in upper-middle-income and high-income countries were largely stable from 2019 to 2021. In contrast, the percentage of lower-middle-income countries reporting general availability of bronchodilators saw a relative decrease of 10%. Increased demand for bronchodilators used in the routine care of patients with chronic respiratory diseases was reported by hospitals for the treatment of patients with COVID-19. At least three manufacturers reported that delays in manufacturing components and/or increased demand for products had led to supply disruptions. The scoping review identified just two studies, both self-reported surveys among people with COPD, reporting their access to and utilization of medicines during lockdown. Results on effects on access diverged.

Pain and palliative care: The increase in medical ventilation patients as a result of the COVID-19 pandemic led to an increased demand for analgesics and sedatives, many of which are also used in palliative care. Shortages of palliative care medicines were reported in a number of countries. One manufacturer reported unprecedented increases in demand affecting supply, and some clinical guidelines were updated to provide alternative prescribing options, in the event of shortages.

Mental, neurological and substance use: There was little data on medicine availability for specific MNS products. Of the 130 Member States who responded to an MNS-specific survey conducted during June–August 2020, more than half reported that overdose prevention and management programmes were at least partially disrupted. Opioid agonist maintenance treatment (OAT) was disrupted for more than 50% of patients in 18% of Member States, and disrupted for 5–50% of patients in 32% of Member States responding to the survey.

7. CONCLUSION AND PATHWAYS TO IMPROVE NCD MEDICINE ACCESS DURING THE COVID-19 PANDEMIC AND BEYOND:

The modern, globalized supply chain of medicines for non-communicable diseases (NCDs) has not previously been subjected to a health crisis at the scale of the coronavirus disease (COVID-19) pandemic. Although a few short-term interventions were established to respond to immediate pandemic needs, a longer-term strategy to strengthen access and delivery mechanisms during emergencies and mitigate future outbreaks needs to be developed, with particular focus on ensuring uninterrupted and sustainable provision for medicines and products needed to diagnose and treat chronic diseases.

It is difficult to make concrete predictions about future pandemics or how to circumvent them. The unpredictable nature of emergent infections means that effects on medicine access could vary extensively; it is possible that a future pandemic could lead to a complete shutdown of manufacturing or more widespread border controls than seen in response to COVID-19. Nevertheless, it is clear that many of the actions needed to strengthen the resilience of medicine supply chains in the context of pandemics and emergencies overlap with those needed to create health systems that are responsive, equitable and accountable.



A medical officer from government initiated Kamala Raman Nagar dispensary gives monthly diabetes medicine to the patient. It has Tuesday & Friday dedicated for diabetes check up. © WHO / Panos / Atul Loke

7.1. Health system strengthening to improve access to NCD medicines

7.1.1. Promote monitoring and transparency across the supply chain

Challenge: Risk mitigation planning requires robust data to identify vulnerable products and vulnerable points in the supply chain. WHA resolution 72.8 Improving the transparency of markets for medicines, vaccines, and other health products recognised the need to progressively enhance the publicly available information on inputs across the value chain of health products. Compared to other segments in the medicine supply chain, there is very little publicly available data on upstream manufacturing, and no systematic data collected to identify monosource API production or assess global capacity for key manufacturing inputs. Stakeholders may consider policies that address gaps in the overall pharmaceutical information ecology to provide a foundation for resilient production of essential medicines, as well as for the prediction and prevention of shortages.

Strengthening established practices

- Governments could require manufacturers to submit detailed information on critical infrastructure, supply sources and manufacturing capacity, as a condition of market approval.
- Governments could require mandatory reporting of any anticipated interruptions to supply and/or increases in demand, including the cause of interruptions and expected duration.
- Governments could require manufacturers to give at least 18 months' notice for discontinuations of products for commercial reasons so that supply continuity and mitigation plans can be implemented.

Future directions

- Governments could require manufacturers to develop regular production risk evaluation and management plans.
- Governments could collaborate with manufacturers in assessing manufacturing volumes for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), in order to better understand the supply capacity.
- Global actors could propose reporting standards and data indicators for health product shortages, to enable comparability and upstream visibility of global production and supply.



On 19 October 2022, Medina and her 12-month-old son Siso are seen by Jemal Endris, a health officer who is part of the Eltomale Site Mobile Health and Nutrition Team in Chifra, Afar. © WHO / Martha Tadesse

7.1.2. Manufacturing and supply security

Challenge: Multisource procurement provides the greatest supply stability. However, there are tradeoffs between the decreased risk associated with more decentralized and geographically diverse production versus the potential economies of scale allowed by centralized production. These challenges are particularly acute for medicines with small markets, which may require other innovative approaches to balance supply security with affordability.

Strengthening established practices

- More efficient manufacturing techniques, such as continuous pharmaceutical manufacturing, should be encouraged.
- Local manufacturing should be further explored, taking into account the balance between the need to diversify supply (including for API) to improve global resilience and efficiencies and cost considerations.

Future directions

- Global actors and governments could explore further mechanisms to improve access, especially for medicines with chronic supply challenges. Potential mechanisms to promote supply security and improve access may include pooled procurement, public manufacturing, subscription models and market-shaping interventions.

7.1.3. Procurement and supply security

Challenge: While many manufacturers conduct risk assessments on supply networks, health systems do not generally have this information available when making procurement decisions.

Strengthening established practices

- Purchasers could encourage manufacturers to diversify their supply base and provide periodic risk assessments to identify upstream vulnerabilities as a condition of contracting and procurement. They could also structure procurement criteria in a way that gives manufacturers with diversified supply bases and robust risk mitigation plans preference in tender awards. Similarly, a percentage of a tender can be reserved, as appropriate and in line within contract evaluation and qualifying criteria, for local bidders to strengthen local manufacturing.

Future directions

- Purchasers could consider the development of a grading system for supply chain stability and manufacturing system resilience, which could help in awarding tenders.
- Small markets may not be able to offer sufficient demand volumes to ensure multi-source and/or geographically diverse tenders. Purchasers could therefore pool demand where necessary to ensure multi-source procurement.
- Pharmacopeial standards should be harmonized as far as possible, in order to minimize barriers.



The De Martini COVID-19 isolation center in the Banaadir region of Somalia is supported by WHO. © WHO / Ismail Taxta

7.1.4. Support patient-centred medicine delivery models

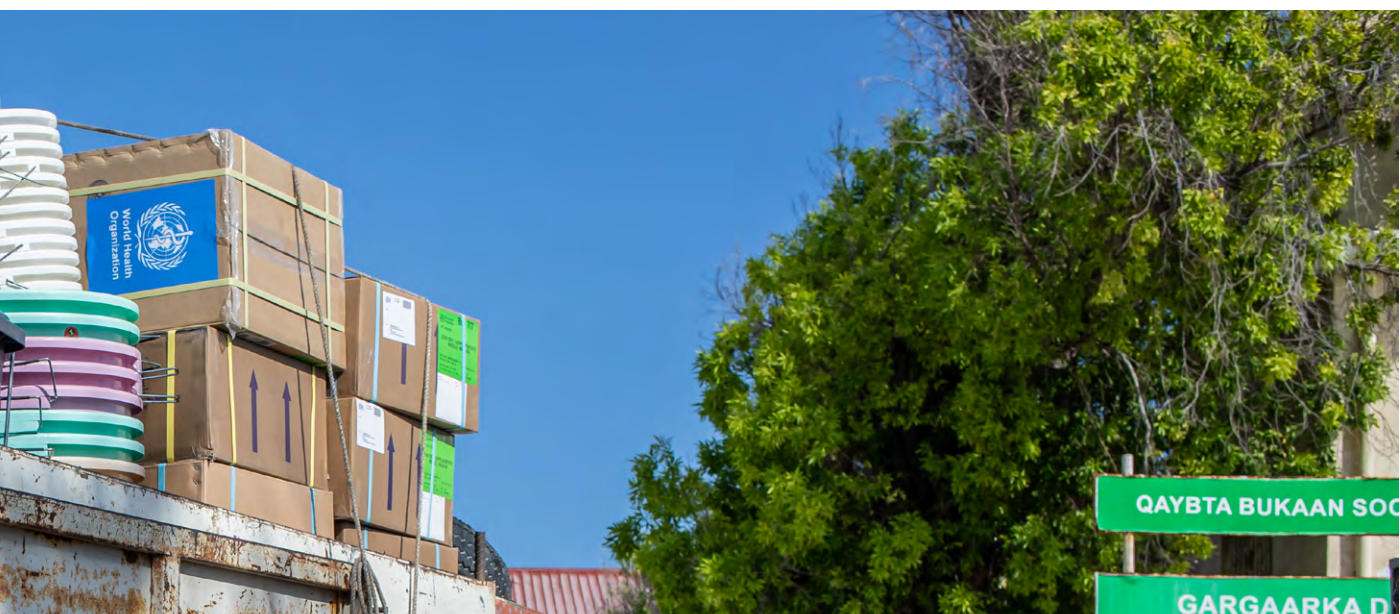
Challenge: Patients face challenges in using medicines consistently and as prescribed. These challenges are exacerbated where it is costly or time-consuming to obtain medicines, especially for long-term care for chronic diseases.

Strengthening established practices

- For patients receiving long-term medications, countries should consider multi-month dispensing, as well as strengthening and scaling-up alternative delivery mechanisms and decentralized distribution models (e.g. by post or delivery to a neighbourhood delivery location, private pharmacy, local clinic or post office, or distribution managed by community health workers). This could improve health outcomes and supply resilience, as patients have a larger stock at home.

Future directions

- Other decentralized medicine distribution systems could be piloted and explored with regards to safety, effectiveness and cost-effectiveness (e.g. automated dispensing units such as electronic lockers and pharmacy dispensing units).
- Buyers should implement demand verification to correct inflated demand, and prevent stockpiling and shortages in case of emergency.



7.1.5. Expand and strengthen the medicine shortage notification systems

Challenge: Data on current or imminent shortages are essential for preventing harm to patients, and for interventions that anticipate and prevent them. At the global level, there are no standardized data collection frameworks, which makes data aggregation and comparison challenging. Similarly, national level surveillance of medicines availability is complicated where procurements occurs through different systems (e.g. public, private and donor-financed), which are not always interoperable. There are opportunities for global and national actors to coordinate in improving the monitoring of shortages, as well as anticipating and prevent shortages.

Strengthening established practices

- World Health Assembly (WHA) resolution 69.25 and the World Health Organization (WHO) Road map for access to medicines, vaccines and other health products (2019–2023) includes plans to develop global tools for reporting shortages and stockouts, a framework of mitigation actions needed to prevent and respond to shortages, and ongoing market analysis for strategic products with access risks.
- Global actors could consider expanding or supporting a complementary data source to collect data on the number of API suppliers for medicines on the WHO Model List of Essential Medicines. These data could be used to better understand market shifts, gaps and upstream drivers of future shortages.

Future directions

- Capacity-building initiatives should include support to countries to track and respond to shortages, particularly those that have a root cause at the manufacturing level.
- Global actors could investigate portal expansions that use alternative data sources to predict shortages, especially to support countries with limited capacity to detect and report. Analysis of alternative data sources such as supply chain data or private sector distribution data could provide insights into shortages that would otherwise go unreported.
- Global actors could develop a framework of definitions for shortages so that reports have standardized information that can be better aggregated and analysed.
- With this improved data, global actors could consider working with national medicines regulatory authorities and stakeholders to develop a priority list of medicines with one or a few API suppliers and/or a history of chronic shortages that would be vulnerable to disruption. These data could inform governments as they consider market interventions.
- Donors and other actors undertaking procurement should align their labelling (barcode) systems with those used by partner health systems, and health systems should consider aligning with harmonized global standards, incorporating the recommendations of the WHO policy paper on the traceability of medical products [\(297\)](#).

7.1.6. Governance and financing

Challenge: COVID-19 exacerbated an already challenging financing environment for NCDs. In many countries, investments in NCD care are not proportional to disease burden and need. Alongside increasing investment in NCD prevention and treatment, and improving the efficiency and targeting of existing resources, health systems must put health equity at the heart of resource prioritization and allocation decisions. This requires better understanding and monitoring the social determinants of NCDs and working with other sectors to improve access to healthcare and social services.

Strengthening established practices

- Health actors should give special consideration to particularly vulnerable populations including, for example, groups that are highly dependent on uninterrupted access to medicines (e.g. people living with insulin-dependent diabetes), marginalized populations and those with reduced access to healthcare.
- When and where health products are scarce, ensure that they are distributed in an equitable way, at both national and international dimensions. This requires allocating resources primarily based on health needs.

Future directions

- Global actors, national authorities and community organizations should work to address infodemics of misinformation that can cause panic buying and stockpiling.
- Governments should consider novel financing mechanisms for emergency response.



7.2. Emergency response planning for NCD medicine resilience

Pandemics are only one cause of health emergencies; health emergencies can also be caused by natural disasters or humanitarian crises resulting from war. While the preceding policy ideas and applications broadly relate to making supply chains more resilient to global shocks, the following are provided with emergency scenarios in mind.

7.2.1. Global support and coordination

Challenge: The COVID-19 pandemic has highlighted the interdependence in both the global supply chain for medicines and emergency response financing. This interdependence can pose challenges, but also offers opportunities.

Strengthening established practices

- Donors should allow rapid and flexible reprogramming of funds to address emergencies while maintaining core health supply chain functions.
- As part of emergency response planning, simulation exercises of hypothetical future pandemics with different characteristics could be used to help define roles and responsibilities of various actors and identify supply chain vulnerabilities.
- Financial support must be mobilized to countries facing logistical challenges (e.g. landlocked countries and small island states) to ensure supply chain continuity in emergencies.

Future directions

- International actors should evaluate the feasibility of establishing global or regional stockpiles of key products.
- Organizations providing emergency health funding should include mechanisms for health systems to rapidly access interest-free bridge funding to use for health product procurement while waiting for regular financing to renew or for additional funding to be secured.



7.2.2. Regulatory flexibility and discretion

Challenge: By the time a shortage is identified, there is often a narrow window for action. In the context of an emergency, there may be fewer options available, and regulators may consider adapting approval processes in order to maintain safety and quality while responding to specific, prioritized needs pragmatically and rapidly.

Strengthening established practices

- Regulators could establish and develop abridged and agile regulatory pathways to prioritize and fast track the review of products that are of critical importance.
- Regulators could consider accepting applications for extensions of pharmaceutical expiry dates, as supported by scientific data. Delays along every stage of the supply chain contribute to shorter windows of use for key drugs.
- Regulators could consider reliance mechanisms in their regulatory approaches by relying on health products approved by regulatory systems operating at an advanced level of performance (for example, WHO-Listed Authorities).
- WHO should continue to provide technical assistance to help manufacturers seeking WHO prequalification comply with international regulatory norms and standards for priority health products.
- WHO should continue to provide capacity building and technical support to NMRA to further strengthen their regulatory system aligned with Good Regulatory Practices and utilizing reliance in their regulatory approaches.
- Competition authorities should consider applying discretion and flexibility in evaluating collaborations undertaken by pharmaceutical companies, wholesalers and pharmacies to prevent shortages.

Future directions

- Regulators could consider flexibilities aligned with Good Regulatory Practices and Principles in some regulatory/administrative requirements during emergencies, for example, by waiving language requirements for packaging inserts or by allowing different packaging formats (e.g. those that use less packaging and are appropriate for use in secondary care settings). WHO should continue to develop innovative prequalification pathways aiming at increasing the number of applicants for prequalification and ultimately of prequalified products. For example, developing an active pharmaceutical ingredient master file (APIMF)-like pathway for human insulin could facilitate further geographic expansion of production sites, diversification of supply, contribute to supply chain resilience and security, and improve affordability [\(301\)](#).
- As part of pandemic preparedness, manufacturers could build capacity to quickly repurpose and scale up production of quality-assured priority products for health emergency responses.

7.2.3. Minimize barriers to trade in health products and key manufacturing inputs

Challenge: Import and export restrictions during COVID-19 disrupted global supply chains. Measures implemented to protect essential goods such as medicines did not always work as intended, with significant friction and delays reported by interviewed stakeholders.

Strengthening established practices

- Governments should pre-emptively avoid customs delays for health products and key manufacturing inputs, by:
 - ensuring that priority lanes (so-called green lanes) are available for priority clearance of health products and essential manufacturing components;
 - offering pre-arrival processing of customs documentation; or
 - allowing the deferment or suspension of customs duties, taxes, fees or charges.

Future directions

- Governments should consider classifying health product manufacturing and distribution as an essential activity, and include provisions in emergency legislation ensuring that workers are permitted to travel to relevant manufacturing and distribution sites.
- Governments could establish advance agreements with neighbouring countries to establish contingency plans for the transport of goods in the case of emergencies, with prioritization and safeguards for health products and essential manufacturing components.
- Governments should collaborate with logistics and shipping providers to design contingency delivery and distribution plans in the case of suspension or non-viability of regular commercial travel and shipping routes.

7.3. Areas for further research

- Further research should be undertaken on the stability conditions or shelf life of health products that are often considered to have particular storage or transport requirements, such as insulin.
- Health actors and research funders should support the development of techniques to extend pharmaceutical shelf life or enhance thermostability.
- Emergencies and other contexts where refrigeration is not available, affordable or reliable because of irregular electricity supply can result in disruptions of normal storage conditions. Further research should be undertaken to investigate the clinical implications of using medicines stored at higher or lower temperatures than those specified by the manufacturer. These data should be used to make clinical recommendations and improve patient care in emergency contexts. One medicine for which this is being studied is insulin. Further research should be undertaken on the root causes of shortages, empowered by greater data sharing and monitoring.
- In risk evaluations and audits of procurement sources, national authorities should give special focus and prioritization to health products that are the most essential from a clinical perspective.
- Further research should be undertaken on the unique challenges faced by vulnerable populations in accessing medicines.
- Academic and technical partners should support the development of open-source supply chain management software initiatives integrating all procured products, as well as supporting the development of open-source software with the ability to simulate emergency scenarios. Further information gathering for medicines of concern should be conducted to establish contextualized case histories of each shortage, and further data are needed to establish whether shortages attributed to API extend beyond the included countries.

- A 2017 study by the WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products found that an estimated 1 in 10 medical products circulating in low- and middle-income countries is either substandard or falsified (298). Further research should be undertaken to understand the incentives shaping markets for substandard and falsified medical product and evaluate the effectiveness of policy responses aimed at strengthening technical capacity and monitoring oversight of regulators. Two key areas of focus could be dynamics specific to emergency situations and the role of global, e-commerce platforms (299).

7.4 Conclusion

The global burden of NCD mortality continues to rise and is projected to reach more than 100 million deaths annually by 2025 (300). Integrated, people-centred service delivery approaches anchored in strengthened primary health care and broader health systems are required for sustainable improvement towards achieving the Universal Health Coverage, WHO Global NCD Action Plan and the health-related Sustainable Development Goal targets. The NCD Global Action Plan Implementation Roadmap 2023-2030 provides a further opportunity and raises the priority accorded to the prevention and control of NCDs in global, regional and national agendas through strengthened international cooperation and advocacy. Insufficient global action on NCDs, combined with the COVID-19 pandemic, may lead to the Sustainable Development Goal (SDG) targets 3.4 and 3.8 not being met, and progress made over decades has been rolled back. Currently, only 14 countries are on track to achieve SDG target 3.4 - to reduce by one-third the premature mortality of NCDs through prevention and treatment and promote mental health and well-being by 2030.

Significant strides have been made in adapting country strategies and policies to respond to challenges in NCD medicines access and management requirements, both

before and during the COVID-19 pandemic. Although there were significant challenges and stresses that led to pauses in planned improvements and reforms within health systems, there were also opportunities to experiment with new models of delivery to address both structural and emergent barriers. These lessons learned from COVID-19 and related health emergencies should be incorporated into future plans to ensure more resilient and strengthened access to NCD medicines and health products.

Globally, more is spent on medicines for noncommunicable diseases (NCDs) than any other therapeutic class (96). Despite the significant resources spent on purchasing medicines, the robust, systematically collected data that would be needed to monitor and respond to disruptions in NCD supply chains is scarce. Essential questions – for example, how many medicines are directly or indirectly available from a single source; how many countries experienced a shortage of a given formulation; are there consistent patterns for shortages for certain molecules, formulation types, or classes of drugs – cannot be answered with existing data.

A key finding of this report is the urgent need for transparency and improvement to the overall pharmaceutical information ecology as a foundation for pandemic planning and response: if we are unable to identify weaknesses in the global NCD supply chain, we cannot hope to mend them. Measures to promote monitoring and transparency are needed across the full NCD supply chain: upstream, governments could collaborate with manufacturers to conduct molecule and product-specific risk assessments, as well as report annual manufacturing volumes to assess supply capacity. Risk assessment of raw material sources could be broadened to include mapping critical

infrastructure. Downstream, standardized reporting standards and data indicators for NCD health product shortages could enable comparability and upstream visibility of global production and supply to facilitate improved coordination. Qualitative and quantitative patient-centred research can measure and identify social determinants of medicines access, and provide an evidence base for overcoming them. Transparency and coordination across stakeholders in developing pandemic response plans could mitigate information asymmetries and coordination problems, as well as build the trust and communication essential to an effective emergency response. Improving the evidence base and building systems to generate real-time supply chain data is only one side of the equation: political will, multisectoral coordination, stakeholder involvement and investment in health systems are essential to ensuring that once identified, access gaps are addressed.

In this report, we have aimed to describe and analyse how the COVID-19 pandemic affected supply chains of medicines for NCDs, identify key vulnerabilities and bottlenecks and propose key themes and a framework for future policy development. We hope this report will prove useful in discussions about the actions needed to respond to this pandemic, as well as to prepare for public health crises in the future.

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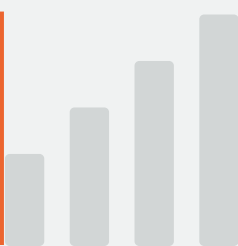
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ANNEX



ANNEX 1. SCOPING REVIEW

Fig. A1.1. Relevant concepts for developing the scoping review search algorithm

COVID-19	Medicines	Noncommunicable diseases		Access
Pandemic	Drug	NCD	COPD	Supply
Epidemic	Pharmaceutical	Chronic disease	Chronic respiratory disease	Stockout
COVID-19	Medicine	Asthma	Heart failure	Shortage
Coronavirus		Cancer	Analgesic	Interruption
		Lymphoma	Psychiatric	Bottleneck
		Diabetes	Mental health	Risk mitigation
		Hypertension	Immunomodulator	Resilience
		Palliative	Antineoplastic	Logistics
		Cancer	Antithrombotic	Health system strengthening
		Cardiovascular	Anti-inflammatory	Access to medicines
		Heart disease	Cytotoxic	Risk mitigation
		Angina	Oncology	Availability
		Arrhythmia	Hypoglycaemia	Affordability
		Blood pressure		Dispensing
		Heart failure		Pharmacy
		Heart disease		Procurement
			Utilization	
			Price and/or cost	
			Manufacturing	
			API	
			Key starting material	

Search query

PubMed: (pandemic* OR epidemic* OR COVID-19 OR coronavirus) AND (drug*[tiab] OR medicine*[tiab] OR pharmaceutical*[tiab]) AND (NCD* OR non-communicable disease* OR asthma OR cancer OR lymphoma OR diabetes OR hypertension OR palliative OR cardiovascular OR heart disease OR angina or arrhythmia OR blood pressure OR COPD OR chronic obstructive pulmonary disease OR chronic respiratory disease OR chronic disease* OR heart failure OR stroke OR analgesic OR psychiatric OR mental health OR immunomodulator* OR antineoplastic* OR anti-neoplastic* OR antithromb* OR anti-thromb* OR thrombolytic OR anti-inflammatory OR cytotoxic OR oncolog* and hypoglyc* AND (supply OR stockout* OR stock out OR shortage* OR interruption* OR bottleneck* OR risk mitigation OR resilience OR logistic* OR health system strengthening OR access to medicines OR risk mitigation OR (medicine* AND availab*) OR (medicine* AND affordab*)) OR utilization OR utilization OR price OR cost OR manufacturing or API or key starting material) AND Delivery of Health Care[MeSH Terms] AND ("2020/01/01"[Date - Completion] : "2021/06/01"[Date - Completion])

Web of Science: (((ALL=(pandemic OR epidemic OR COVID-19 OR coronavirus)) AND ALL=(drug OR medicine OR pharmaceutical)) AND ALL=(NCD OR non-communicable disease OR asthma OR cancer OR lymphoma

OR diabetes OR hypertension OR palliative OR cardiovascular OR heart disease OR angina or arrhythmia OR blood pressure OR COPD OR chronic obstructive pulmonary disease OR chronic respiratory disease OR chronic disease OR heart failure OR stroke OR analgesic OR psychiatric OR mental health OR immunomodulator OR antineoplastic OR anti-neoplastic OR antithrombotic OR thrombolytic OR anti-inflammatory OR cytotoxic OR oncology OR oncologic OR hypoglycemia OR hypoglycaemia)) AND ALL=(supply OR stockout OR stock out OR shortage OR interruption OR bottleneck OR risk mitigation OR resilience OR logistics OR health system strengthening OR access to medicines OR risk mitigation OR medicine availability OR medicine affordability OR utilization OR utilisation OR price OR cost OR manufacturing or API or key starting material). Dates 1 January 2020- 6 June 2021. Web of Science categories: Economics or Social Sciences Interdisciplinary or Cardiac cardiovascular systems or rheumatology or social sciences biomedical or tropical medicine or primary health care or health policy services or respiratory system or pharmacology pharmacy or multidisciplinary sciences or oncology or health care sciences services. Exclude editorial materials, letters, meeting abstracts, data papers, corrections, and proceedings papers. Include articles, review articles, and early access.

Table A1.1.
Summary of data extraction and charting protocol

Field	Notes
Brief study design and methods	
City/country/region	
Primary, secondary or incidental outcomes on access to NCD medicines	<ul style="list-style-type: none"> • Primary: The study was designed to capture direct and indirect effects of COVID-19 on access to NCD medicines. • Secondary: The study was not designed to capture direct and indirect effects of COVID-19 on NCD medicines but has a related aim and reports at least one outcome relating to NCD medicine manufacturing, freight/shipping, procurement/forecasting/purchasing, stock availability/supply chain, prescribing and patient access (availability, affordability, utilization). • Incidental: The study does not have a related aim, but nevertheless incidentally includes some data on direct or indirect effects of COVID-19 on access to NCD medicines.
Disease focus	<ul style="list-style-type: none"> • No disease focus • NCDs • Cardiovascular disease • Diabetes • Chronic respiratory disease • Cancer • Palliative care • Mental health • Other
Pathway of effect	<ul style="list-style-type: none"> • Manufacturing • Freight/shipping • Procurement, forecasting and purchasing at the central level • Stock availability/supply chain • Prescribing • Patient access: availability, affordability and utilization
Reported outcomes relating to NCD medicine access	

ANNEX 2. QUESTIONNAIRE FOR EXTERNAL INTERVIEWS

A number of prospective interviewees did not respond or were unable to schedule an interview, including industry (3), international aid/donors (7), logistics (2), multilaterals (1) and non-governmental organizations (NGOs) (1). Interviews were held by MB, as well as by BE in most cases. Interviews lasted around an hour and were conducted by videoconference. Interviews were not recorded but detailed notes were taken by MB, with follow-up by e-mail for clarifications.

Questionnaire

As global and local supply chains for health products are continued to be affected by the global coronavirus pandemic it is important to assess the in-depth challenges low- and middle-income countries face and therefore find appropriate risk mitigation solutions to ensure continued access to essential NCD medicines, diagnostics and other technologies and maintain essential NCD services.

Risk mitigation

- 1) In light of COVID-19 and emergency settings, what risk mitigation strategies have you put in place to avert stockouts or to prevent barriers to access for your product lines?
- 2) In your experience, what key steps might better prepare supply chains for emergencies (resilience strategies)?
- 3) Where do you see the biggest opportunities for medicine integration of communicable and noncommunicable disease efforts?
- 4) What guidance and normative work do you believe countries will benefit from to prepare for future emergencies or pandemics?

- 5) Do you have any literature that would be useful in terms of recommendations or country experiences that could be provided to member states to inform strategies to promote supply chain resilience for future disruptions to medicine access?

Production and manufacturing

- 1) Are you aware of any interruptions or delays in active pharmaceutical ingredient (API) production or sourcing that have affected operations?
- 2) Are you aware of any interruptions or delays in finished pharmaceutical product (FPP) production or sourcing that have affected operations?
- 3) If so, what strategies have been put in place to address production challenges?

Procurement and importation

- 1) Have you experienced substantial changes in freight charges this year or needed to change shipping mode? (i.e., ocean, air, road transport)
- 2) Have lead times for medicine purchases that are imported and/locally produced changed?
- 3) Have you or partners delayed purchasing or procurement of products? Have you or partners procured less volume than previous years?
- 4) Have there been new challenges, delays, or barriers in clearing medicines through customs?
- 5) Have national rules on confinement of freight affected your supply chain?
- 6) Have prices for medicines increased from the previous year?

- 7) If you use a tender system, has the emergency led to any changes to standard medicines contracts or unexpected challenges?
- 8) How have currency fluctuations affected procurement?
- 9) Do you foresee any challenges around budgeting and purchasing as a result of COVID-19?

Distribution

- 1) Have there been additional freight challenges in transporting medicines from national to subnational facilities? (or global and regional that you are aware of)
- 2) Have any strategies been put into place to modify standard dispensing? (for example, differentiated delivery models or exceptional multi-month dispensing)

Other: general

- 1) What are any other a) acute b) systemic and c) intersectional risks that you think are important to highlight in understanding access to medicines throughout the pandemic or emergencies?

Other: donor-specific

- 1) Are you supporting MOH programmes or budget lines for NCD or supply chain activities? Which areas of work are being supported?
 - a. Capacity building, specific training on preparedness and response?
 - b. Direct interventions or support to operations?
 - c. Has funding been shifted as a result of COVID-19?

Other: private sector-specific

- 1) Have export/import disruption affected access to raw materials?
- 2) Have human resource interruptions and restrictions on work affected production?



To ensure maintenance of essential health services, in particular Mental Health services, Ministry of Health supported by WHO continued to provide psychotropic medications to patients at home during COVID-19 pandemic taking into consideration patient privacy and safety measures. © WHO

ANNEX 3. WHO 2019 AND 2021 COUNTRY CAPACITY SURVEY RESULTS

Table A3.1.

Percentage of countries in which NCD medicines were generally available, by WHO region and World Bank income group, and relative percentage change from 2019 to 2021

WHO Region/World Bank income group	Angiotensin II receptor blockers			Angiotensin-converting enzymes inhibitor			Aspirin			Benzathine penicillin injection			Beta blockers		
	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change
African Region	36	45	+25	66	68	+3	79	83	+5	81	77	-5	57	57	0
Region of the Americas	77	74	-4	91	89	-2	94	91	-3	89	89	0	86	91	+6
South-East Asia Region	73	91	+25	73	100	+37	91	100	10	82	64	-22	91	91	0
European Region	92	91	-1	94	92	-2	100	92	-8	92	89	-3	96	92	-4
Eastern Mediterranean Region	76	57	-25	86	76	-12	86	86	0	67	67	0	90	76	-16
Western Pacific Region	63	67	+6	74	81	+9	89	85	-4	78	70	-10	74	74	0
Low-income	29	33	+14	58	67	+16	71	85	+20	68	70	+3	55	56	+2
Lower-middle-income	50	52	+4	63	67	+6	87	78	-10	76	72	-5	61	61	0
Upper-middle-income	78	80	+3	92	95	+3	93	95	+2	85	84	-1	92	93	+1
High-income	96	93	-3	100	95	-5	100	95	-5	96	86	-10	100	95	-5
Overall	69	70	+1	82	83	+1	90	89	-1	84	79	-6	81	79	-2

WHO Region/World Bank income group	Bronchodilators			Calcium channel blockers			Insulin			Metformin			Nicotine replacement		
	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change
African Region	64	60	-6	57	64	+12	60	68	+13	70	81	+16	6	9	+50
Region of the Americas	91	89	-2	89	89	0	83	91	+10	94	100	+6	23	23	0
South-East Asia Region	73	82	12	64	91	+42	45	55	+22	91	100	+10	9	36	+300
European Region	96	92	-4	94	92	-2	94	89	-5	94	92	-2	75	77	+3
Eastern Mediterranean Region	90	81	-10	90	81	-10	86	71	-17	90	86	-4	29	38	+31
Western Pacific Region	78	74	-5	78	81	+4	81	81	0	89	85	-4	41	44	+7
Low-income	55	52	-5	45	63	+40	45	56	+24	61	74	+21	0	4	NA
Lower-middle-income	70	63	-10	63	69	+10	63	65	+3	78	83	+6	11	17	+55
Upper-middle-income	92	93	+1	92	91	-1	90	89	-1	95	98	+3	28	36	+29
High-income	100	95	-5	100	95	-5	96	95	-1	100	95	-5	82	82	0
Overall	83	79	-5	80	82	+3	78	79	+1	87	90	+3	36	40	+11

WHO Region/World Bank income group	Oral morphine			Statins			Steroid inhalers			Sulphonylureas			Thiazide diuretics		
	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change	2019	2021	Relative change
African Region	21	26	+24	36	49	+36	23	30	+30	51	49	-4	77	81	+5
Region of the Americas	49	51	+4	83	86	+4	77	77	0	91	97	+7	91	89	-2
South-East Asia Region	18	36	+100	73	91	+25	36	64	+78	64	82	+28	82	91	+11
European Region	70	81	+16	91	91	0	89	89	0	92	89	-3	98	92	-6
Eastern Mediterranean Region	24	29	+21	81	76	-6	71	76	+7	71	67	-6	86	67	-22
Western Pacific Region	52	52	0	67	81	+21	67	67	0	74	78	+5	78	78	0
Low-income	13	26	+100	29	48	+66	19	26	+37	35	33	-6	68	70	+3
Lower-middle-income	17	28	+65	48	57	+19	33	43	+30	57	59	+4	76	72	-5
Upper-middle-income	40	48	+20	83	93	+12	77	82	+6	90	95	+6	92	91	-1
High-income	86	84	-2	98	93	-5	96	93	-3	98	95	-3	100	95	-5
Overall	44	50	+14	71	77	+8	63	66	+5	76	76	0	87	84	-3

ANNEX 4. NATIONAL SHORTAGES DATABASES ANALYSIS

A4.1. Australia

Pharmaceutical manufacturers in Australia are mandated to report shortages, including prescription and some over-the-counter medicines, to the Therapeutic Goods Administration (TGA). Shortages are defined as "if at a particular time if at any time in the six months after that particular time, the supply of that medicine in Australia will not, or will not be likely to, meet the demand for the medicine for all of the patients in Australia who take, or who may need to take, the medicine" ⁽¹⁾.

Anticipated, current and resolved shortages are published online ⁽²⁾. There were 912 total records in the database, with a range of anticipated shortage start dates of 1 October 2008–7 January 2023. A total of 228 records were excluded from the analysis because they describe discontinued products instead of shortages. There were 684 records of current, anticipated or resolved shortages (Table A4.1). Each record corresponds to one formulation of a given medicine by the sponsor (manufacturer or supplier registered with TGA).

Table A4.1.

Number of shortages reported by reason, 1 October 2008–1 October 2021

Root cause	No.
Manufacturing	493
Unexpected increase in consumer demand	73
Transport/logistic issues/storage capacity issues	45
Commercial changes/commercial viability	39
Other	17
Unexpected increase in demand due to other sponsors unable to supply	12
Product recall	4
Seasonal depletion of stock	1
Total	684

The database includes supply impact start date and end date. Using this duration data, the number of shortages on the first of every month from January 2019 to October 2021 was calculated.

A4.2. Brazil

Brazil has a decentralized health system, with medicines procured at the federal, state and/or municipal level. During the pandemic, the National Council of Health Secretaries (CONASS) conducted a number of activities to address shortages, including treatment guidelines. The Resolução da diretoria colegiada nº 18/2014 obligates registration holders to notify the regulator (Agência Nacional de Vigilância Sanitária; ANVISA) should they temporarily or permanently discontinue manufacturing a product. Notification must occur at least 12 months in advance of discontinuation if a market shortage is anticipated. Should a discontinuation occur as a result of unforeseen circumstances, the registration holder is obliged to notify ANVISA within 72 hours (3). These notifications are published online, with reason for discontinuation.

Records were analysed from this database from 1 January 2019 to 28 September 2021 according to the reason reported by the manufacturer to ANVISA (see Section 5.4.2). Anticipated, current and resolved shortages are published online (4). There were 8360 total records in the database, with a range of petition from registration holder to regulatory from May 2018 to 7 January 2023. The reasons given for discontinuations are provided in Table A4.2, with the definitions of each cause code provided in Table A4.3.

Table A4.2.
Number of shortages reported by reason

Reported cause	Notes	No.
Manufacturing	Manufacturing process Manufacturing process; manufacturing process, manufacturing site; Manufacturing site; Commercial motivation; manufacturing site; manufacturing process; manufacturing site	620
Logistics	Manufacturing process; Commercial motivation; logistical issues Logistical issues	346
Commercial motivation	Commercial motivation; Commercial motivation	6049
API*	Active pharmaceutical ingredient	1319
Increased demand	Increased demand	14
Blank		12
Total		8360

* API: active pharmaceutical ingredient.

Table A4.3.

Definition of classifications of reasons, per Resolução da Diretoria Colegiada (RDC)* nº 18/2014

Reported cause	Description
Logistical matters	The company holding the registration informed that it had logistical issues, such as: increase in demand, problems in the release of the imported and/or manufactured products, compromised sales with the public sector, among others. This category also includes cases of transfer of ownership or of brand names.
Commercial motivation	The company holding the registration informed that it was no longer interested in marketing the medicine.
Manufacturing site	The company holding the registration informed the adjustment, inclusion or alteration of the manufacturing site or of the site of a specific stage of manufacturing, whether at the laboratory's own discretion or as determined by the regulatory agency.
Manufacturing process	The company holding the registration informed that changes were to be made at any stage in the manufacture of the medicine, whether at the laboratory's own discretion or as a result of a regulator's order, such as: change of equipment, change of excipient, change of raw material supplier, change of packaging or labelling, change in conservation or expiry date, change in the production process, among others.
API**	The company holding the registration informed that it is experiencing difficulties in acquiring the active ingredient due to a change of supplier, importation issues, logistical issues, among others.

*RDCs are regulatory norms issued by the Brazilian regulatory agency to ensure good practice through the implementation of standards for the quality of products and services.

**API: active pharmaceutical ingredient.

A4.3. South Africa

Data are publicly available and were downloaded from the South Africa Department of Health website (5). "Hot lists" describe medicines "where the interventions implemented may not have been able to avert a shortage and reflects those medicines which manufacturers have been unable to supply" (5). All available hot lists (February, June and August 2020) were analysed. Data across months were generally comparable, although some codes used slightly different language. See analysis notes for manual recodes.

The following codes were included in the analysis: API issue, logistical issues, manufacturing constraints, orders exceed forecast/contract estimate, packing delays and regulatory issues. Root causes by month are summarized in Table A4.4, with definitions in Table A4.5.

Table A4.4.

Number of anticipated shortages reported on hot lists by root cause, February, June and August 2020

Root cause	February	June	August
API issue	5	6	12
Cash-flow challenges	1		
Inconsistent uptake	1		
Item recalled	1		
Logistical issues		7	15
Manufacturing constraints	32	49	31
No supply constraints			12
Orders exceed forecast/contract estimate	12	27	35
Packing delays	3		
Product discontinued		1	
Product not launched yet			1
Product recall		1	
Regulatory issue	2	10	10
Supply constraints	21		
Suspension of contract		1	1
Grand total	78	102	117

API: active pharmaceutical ingredient.

For clarity, reported issues with few instances are not included in Fig. 5.3. The following reported categories (instances) were removed: cash-flow challenges (1), inconsistent uptake (1), item recalled (1), packing delays (3), product discontinued (1), product not launched yet (1), product recall (1) and suspension of contract (2). "Supply constraints" that were otherwise unspecified as well as "no supply constraints" that were only reported in August were also removed, as they only appear in one month's data and could not be matched to other categories.

Table A4.5.
South Africa data codes with descriptions

Root cause	Definition from National Department of Health website (where available)	Analysis notes
API	Active Pharmaceutical Ingredient <ul style="list-style-type: none"> • The manufacturer of the API has closed down. • The API manufacturer is experiencing a global shortage of raw materials (intermediates and/or key starting materials). • The API quality is lower than the acceptable standard (batch/batches of API failed the quality control tests). 	February reported "API"; recoded as "API issue" to be comparable with June and August
Discontinuation	The medicine will no longer be manufactured <ul style="list-style-type: none"> • The manufacturer has ceased production of the medicine. 	
Forecast	The prediction/estimation of the volumes <ul style="list-style-type: none"> • Unexpected high usage/uptake of the medicine by the demander. • Low usage/uptake of the medicine by the demander resulting in short-dated stock and stock expiry. 	February and June reported "high uptake"; recoded to "orders exceed forecast/contract estimate" to be comparable with August
Manufacturing constraints	NA	February reported "manufacturing capacity" and "manufacturing constraints" [sic]; recoded to "manufacturing constraints" to be comparable with February, June and August data
Supplier capacity	The contracted supplier does not have the capacity to meet the demand.	

Root cause	Definition from National Department of Health website (where available)	Analysis notes
GMP	<p>Good manufacturing practices</p> <ul style="list-style-type: none"> The manufacturing plant is deemed non-compliant or no longer meets the GMP standards as required by SAHPRA (South African Health Regulatory Authority). 	
Regulatory	<p>Concerns the control around the production, distribution and use of the medicine</p> <ul style="list-style-type: none"> The submission of amendments to the dossier that require approval from SAHPRA, including a change/addition of an API source and/or manufacturing site. The importation of a registered medicine in terms of Section 3.6 of the Medicines and Related Substances Act. The application of a Section 2.1 authorization, in terms of the Medicines and Related Substances Act, for the acquisition of unregistered medicines for human use in South Africa that are of vital importance for public health. Manufactured products requiring additional quality checks by SAHPRA. The transfer of ownership of dossiers that results in a change of marketing authorisation. Delays in the issuing of the permits for imported medicines. Country-specific legislation changes that can impact on the supply of the medicines (e.g. legislation to reduce pollution in countries of manufacture negatively impacting production and supply). 	<p>February reported "SAHPRA approval required"; recoded to "regulatory issue" to be comparable with June and August</p>
Short-term supply constraint	<ul style="list-style-type: none"> The release of the medicine from the local/international supplier has been delayed due to operational challenges (e.g. machine breakdown, labour unrest, theft, post importation testing, etc.). Sourcing of products from alternative local suppliers with registered products using quotations. 	

API: active pharmaceutical ingredient; NA: not applicable; SAHRA: South African Health Regulatory Authority.

A4.4. United States of America

The United States Food and Drug Administration (USFDA) maintains a database of current and resolved shortages; data are mostly sourced from manufacturer notifications, but any stakeholder can submit notice of a shortage [\(6\)](#).

There are a number of challenges in analysing this data. Most significantly, historical records in the database are not maintained for research purposes. Updates on products are added to the database but, in contrast to the databases of Australia and Brazil, there are no duration data. This presents a number of challenges in longitudinal analysis. As an example, a shortage may be reported as “reverified” and “resolved”, which means that the USFDA has reverified that a past shortage that was resolved in the past is still resolved. In request for historical data, the USFDA advised the use of Wayback Machine, a digital archive of the World Wide Web that provides snapshots of websites that the Wayback Machine “crawls”. All available snapshots were downloaded, including 29 December 2019, 2 April 2020, 12 June 2020, 24 August 2020, 17 January 2021, 18 March 2021 and 12 May 2021, along with the current file downloaded on 28 September 2021. All “resolved” records were manually linked using this historic data to determine the original cause and estimated shortage start date, which was assumed to be the date when the shortage was first reported in the database. Shortages resolved before the earliest available snapshot on 29 December 2019 were therefore not always able to be linked to a cause. The same record over time would sometimes change. Where there existed a conflict of information, the latest entry was used. More commonly, information was removed when the shortage was resolved; in this instance, the most detailed information available was merged and included across snapshots. In many cases, the cause of the shortage was described in one of several additional columns for notes, but not as a category. In these cases, information from the notes was coded to correspond to the most relevant category.

These limitations are known of in the literature. A separate database is maintained by the American Society of Health-System Pharmacists (ASHP), with some comparative advantages including more frequent updates and shortage reports that reflect the status at the health care provider level [\(7\)](#). ASHP includes all medicines (including those unapproved) reported by healthcare providers, while the USFDA only reports medically necessary drugs, defined as those that prevent serious disease or medical condition [\(8\)](#). ASHP does not make this data available for download, although it is searchable in batches of 10, and drug shortage bulletins are protected under copyright. The USFDA database was chosen because the data were available and accessible, and the scope of shortages included approved medicines.

There were 1971 total records from 22 February 2012 to 28 September 2021. The following records were excluded from analysis: records of discontinued products, with no other information specifying a shortage (539); records of updated product codes (2); records with no start date (69); and records of products where availability in all snapshots is listed as available and no (or another) reason given.

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