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In a nutshell

Why does the world seem to suddenly be fighting over antibiotics? For one thing, production is increasingly concentrated in two countries - China and India. For another, an entire industry seems surprised by the rapid increase in demand for drugs after the decline during the Covid-19 pandemic. Our results suggest three broad policy recommendations. First, health policies should invest into improvements of the demand tracking, planning, and forecasting infrastructure. Health policies should focus on shortages of drugs for which substitutes are also unavailable. Second, the health system seeks to guarantee the sufficient provision of drugs at low prices. The international division of labour that has emerged seems to provide price efficiency, but supply security risks have become increasingly evident. This implies a refocusing of policies towards greater supply resilience. Third, the market structure should not only mitigate supply risks, but the market design should ideally internalise supply security risks, thereby rendering ad-hoc policy interventions obsolete.

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Executive Summary

Trends preceding the recent shortages

1. Supply disruption of medications in general, and antibiotics in particular, are not a new phenomenon. Since 2014, they have steadily increased in frequency and severity. In the vast majority of cases, it was possible to resolve these shortages by finding suitable substitutes and thereby reduce negative impacts on patients.
2. The Consumption of antibiotics declined in many European countries between 2011 and 2018. This is welcome as it reduces the build-up of antimicrobial resistance.
3. These trends in antibiotics demand coincided with structural transformations in the antibiotics production system. Overall, there is a clear trend of increasing geographic concentration of production. Production sites in China and India have benefitted from this trend.
4. The production concentration is more pronounced in upstream stages of the value chain (intermediaries and active pharmaceutical ingredients, APIs) rather than in downstream stages like unpackaged and packaged products. 76% of the manufacturing sites of intermediaries are located in China and India. 59% of API producers are situated in these countries.
5. The data suggests a tendency towards market segmentation in which firms in European and North American countries developed an increasing dependence on Chinese suppliers. Indian producers trade mostly with local neighbours in Asia, Oceania, and African countries.
6. When the pandemic hit, non-pharmacological interventions aimed at curbing the spread of SARS-CoV-2 also reduced the circulation of other pathogens. Consequently, both community and hospital demand and consumption of antibiotics dropped sharply during the pandemic (by approximately 20%).
7. Reducing contagion risks, hospitals restricted their services to non-COVID patients. Drug shortages in hospitals nearly halved during the pandemic compared to the frequency of shortages in 2018. The sudden appearance of shortages after the pandemic uncovered improvement potential in inventory management and demand forecasting.
8. The trend towards greater supply concentration has accelerated during the pandemic. Systemic trade risk indicators for China and India show sharp increases after 2018.

Currently observed shortages

9. In 2022, in an increasing number of countries, containment measures combatting the spread of SARS-CoV-2 ceased. As societies by and large “returned to normal” so did antibiotic consumption. Volatile demand and geographically concentrated production systems led to simultaneous shortages of antibiotics across many parts of the world.
10. Due to a higher production concentration in intermediaries and APIs, shocks affect these segments more strongly than packaged products. Hence, it becomes harder to find suitable substitutes when confronted with a shortage. In line with this observation, the estimated number of shortages that could be resolved by substitution halved in 2020. Negative impacts on patient care increased.

Policy considerations

11. There are short-term and long-term remedies. Short-term remedies include improvements in the data, planning and forecasting infrastructure. This will require additional investments. Supply chain disruptions can reflect market structure problems. Long-term policies address the market structure and the international division of labour.
12. Existing supply networks arise from market processes that reflect a competitive combination of qualities and prices. Deviating from market results comes at a cost which can be interpreted as an insurance premium that health agencies need to incur to avoid impacts on patients. Additional costs require appropriate financing. Ideally, a well-designed market should internalise the risk of disruption, e.g., through contracts between producers and buyers with appropriate incentive structures.
13. Antibiotics shortages need to be considered against the backdrop of the global risk of antimicrobial resistance. Ideally, policy remedies should address both issues.

Remedies

14. **Understand the scope of the problem is the basis for evidence-based policies.** Data availability is an issue. Efforts need to be undertaken to track and forecast drug shortages. The data collection should focus on shortages of drugs for which substitutes are also out of stock.
15. **Demand forecasting and stable supplier relationships.** Health authorities need to better understand the demand developments for antibiotics in the population. Evidence-driven demand planning could form the basis for building stable supply relationships, e.g., through multiyear contracts with producers that contain robust provisions in case of non-delivery.
16. **Capacity markets.** In case of emergencies, add-on production capacities that timely provide the drugs in question may address arising shortages from the outset.
17. **EU Single Market.** The European Union provides a powerful tool to mitigate supply risks across multiple players through the Single Market. Coordinated and more centralised EU inventories may help to reduce overall safety stock and thereby avoid inefficiencies.
18. **Bargaining power.** Countries, regions, or health agencies might consider deeper cooperation and pursue joint forecasting and joint procurement strategies. An intelligence system monitoring the market structure of suppliers and possibly anti-competitive behaviour should be installed.
19. **Diversification of supply.** Diversification requires internationally competitive producers. Hence, the debate about broadening the supplier base is embedded in a wider discussion about competitiveness and structural change.
20. **Subsidised procurement prices.** Polices may explore reimbursement models that delink development and production costs from unit sales.

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1 Introduction

Reports of medication shortages have increased since 2022. Health authorities in Australia[1], Canada[2], USA[3], China[4], Japan[5] and multiple countries across Europe[6] have struggled with continued shortages of potentially life-saving medications, such as antibiotics. To respond to these global shortages in an evidence-based way, it is necessary to understand their underlying reasons. Two frequently cited culprits include a concentration of drug manufacturing sites in a handful of countries, such as China and India, as well as unexpected demand due to a post-pandemic resurgence of infectious diseases. Across the globe, countries phased out non-pharmaceutical interventions that not only prevented the spread of SARS-CoV-2 but also of many other pathogens. However, it has become evident that the situation is more complex. Even countries with ample domestic manufacturing capacities experienced drug shortages, raising doubts about whether (re)establishing local production facilities alone can solve the problem. In addition, empirical evidence suggests that shortages emerged as a result of the rebound of demand after its decrease during the pandemic. [7] This raises questions about whether the current shortages are an extraordinary phenomenon. If not, then the current crisis is not a "major event" that requires specific mitigation measures, as concluded by European authorities, but rather long-term, structural policies to strengthen the EU's resilience related to drug supply. [8]

The aim of this ASCII study is to disentangle the various threads related to the global drug shortage crisis, particularly focusing on antibiotics. We aim to shed light on the extent of this crisis and to what degree different demand- and supply-side factors have contributed to the situation. We will conduct an in-depth data analysis of the global antibiotic trade network and production system, enabling us to derive indicators for the vulnerability of the antibiotics supply in over 100 countries regarding production disruptions in any other country. Additionally, we will discuss how global interdependencies have evolved over the last decade. Ultimately, we will conclude by discussing policy-relevant implications for response measures to increase the security of drug supply.

1.1 Are the current shortages exceptional?

In the ten years preceding the pandemic, many countries experienced shortages in antibiotics. According to a series of surveys conducted by the European Association of Hospital Pharmacists (EAHP) and the European Centre for Disease Prevention and Control,[9] 57% of hospital pharmacists (i.e., 237 out of 418) experienced antibiotics shortages in 2014. In 2018, this number rose to 77% (i.e., 1032 out of 1348). Enter COVID-19, hospitals have limited their services to non-COVID patients[10] while non-pharmaceutical interventions like social distancing and the wearing of face masks reduced the circulation of other pathogens. This led to less demand for antibiotics (e.g., 33.5% less antibiotic prescriptions in Wales[11], 34% less in

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[1] See https://www.tga.gov.au/safety/shortages/information-about-specific-shortages/about-antibiotics-shortage-2022-2023 (accessed on 21 March 2023).

[2] See https://www.cbc.ca/news/canada/calgary/antibiotic-shortage-alberta-1.6741395 (accessed on 21 March 2023).

[3] See https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm (accessed on 21 March 2023).

[4] Editorial: Where are the drugs? The scarcity of medications in the Western Pacific. The Lance Regional Health – Western Pacific 2023, 31: 100728.

[5] See https://www.japantimes.co.jp/news/2023/01/11/national/restricting-bulk-drug-purchases/ (accessed on 21 March 2023).

[6] See https://www.politico.eu/article/health-care-pharma-why-is-europe-running-out-of-medicines-and-whats-being-done-about-it/ (accessed on 21 March 2023).

[7]Milijikovic N, Polidori P, Kohl S. Managing antibiotic shortages: lessons from EAHP and ECDC survey. European Journal of Hospital Pharmacy 2021, 29(2).

[8] See https://www.ema.europa.eu/en/news/ema-update-shortages-antibiotics-eu (accessed on 21 March 2023).

[9] Milijkovic N, Polidori P, Kohl S. Managing antibiotic shortages: lessons from EAHP and ECDC survey. European Journal of Hospital Pharmacy 2021, 29(2).

[10] Vinci DL, Polidori P, Milijkovic N, Batista A, Amann S, Markidari D, Kohl S. Lessons learnt from the COVID-19 pandemic: result of EAHP survey on the future crisis preparedness of hospital pharmacies. European Journal of Hospital Pharmacy 2022, 29(5): 242-47.

[11] Wasag DR, Cannings-John R, Hughes K, Ahmed H. Antibiotic dispensing during the COVID-19 pandemic: analysis of Welsh primary care dispensing data. Family Practice 2022, 39(3): 420-25.

Scotland[12], 27% less in UK[13]). Consequently, in 2020 only 37% of hospital pharmacists reported antibiotics shortages (down from 63% in 2019). These trends were also observable in Canada, where the overall number of drug shortages also increased from 2017 up until the pandemic during which it dropped sharply.[14] However, since March 2022, drug shortages started to increase. Many countries only started to rigorously track drug shortages with the beginning of the pandemic. Hence, policy makers in many countries do not know exactly where their pre-pandemic baseline lies.

1.2 Short term responses to the current shortages

Drug shortages typically refer to products with a specific formulation, dosage, and package size. Their emergence instantly puts health practitioners under pressure, who seek to continue their services to avoid adverse impacts on patients.

Shortages can be resolved in several ways, such as

- Substituting a drug with the same active ingredients but with a different package size.
- Substituting a drug with another active ingredient
- Sourcing the drug from another geographical origin (e.g., from another supplier within the EU Single Market)
- Prioritisation of indications when delivering medication ("triage")

Evidence shows that the recent drug shortages differed from previous incidents. In 2014 and 2018, European hospital pharmacists reported that 85% and 83%, respectively, of their shortages could be resolved by substitution. In 2020, however, despite a smaller amount of experienced overall shortages, only 42% could be resolved by substitution. Consistent with these trends, the number of pharmacists reporting negative impact on patient care of the shortages increased substantially from 47% in 2018 to 59% in 2020.

This raises the question whether the currently perceived shortages differ from previous shortages. Albeit the mixed data availability about drug shortages across countries, the drug and antibiotics shortages experienced in 2022-2023 might well be within the range that one would have expected from before the pandemic. Hence, it seems that the recent shortages rather signify a "return to normal" than an extraordinary drug crisis. Yet, there is reason to believe that the gravity of these shortages has increased as it is becoming harder for pharmacists to find suitable substitutions when confronted with a shortage. This implies that drug shortages not only affect mostly specific package sizes and formulations of drugs but emerge due to the poor availability of the underlying active pharmaceutical ingredient (API).

2 Developments in the European consumption of antibiotics

The European Centre for Disease Prevention and Control (ECDC) provides annual reports about the antimicrobial consumption in the EU/EEA.[15] The latest report was released in November 2022, spanning the period 2012-2021.[16] This report's results for trends in community and hospital consumption of antibiotics (medications classified in the J01 group according to the ATC classification of drugs) are summarized in Figure 1. Community consumption is higher than hospital consumption by a factor of ten. The lowest levels

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[12] Malcolm W, Seaton RA, Haddock G, Baxter L, Thirlwell S, Russell P, Cooper L, Thomson A, Sneddon J. Impact of the COVID-19 pandemic on community antibiotic prescribing in Scotland. JAC-Antimicrobial Resistance 2020, 2(4): dlaa105.

[13] Rezel-Potts E, L'Esperance V, Gulliford M. Antimicrobial stewardship in the UK during the COVID-19 pandemic: a population-based cohort study and interrupted time-series analysis. British Journal of General Practice 2021, 71(706): e331-8.

[14] Lau B, Tadrous M, Chu C, Hardcastle L, Beall RF. COVID-19 and the prevalence of drug shortages in Canada: a cross-sectional time-series analysis from April 2017 to April 2022. Canadian Medical Association Journal 2022, 194(23):E801-6.

[15] See https://www.ecdc.europa.eu/en (accessed on 21 March 2023).

[16] See https://www.ecdc.europa.eu/sites/default/files/documents/ESAC-Net_AER_2021_final-rev.pdf (accessed on 21 March 2023).

of consumption can be found in the Netherlands, Estonia, Austria, and Latvia. Cyprus, Greece, and Romania show particularly high levels of consumption, up to twice as much as the countries with the lowest consumption levels.

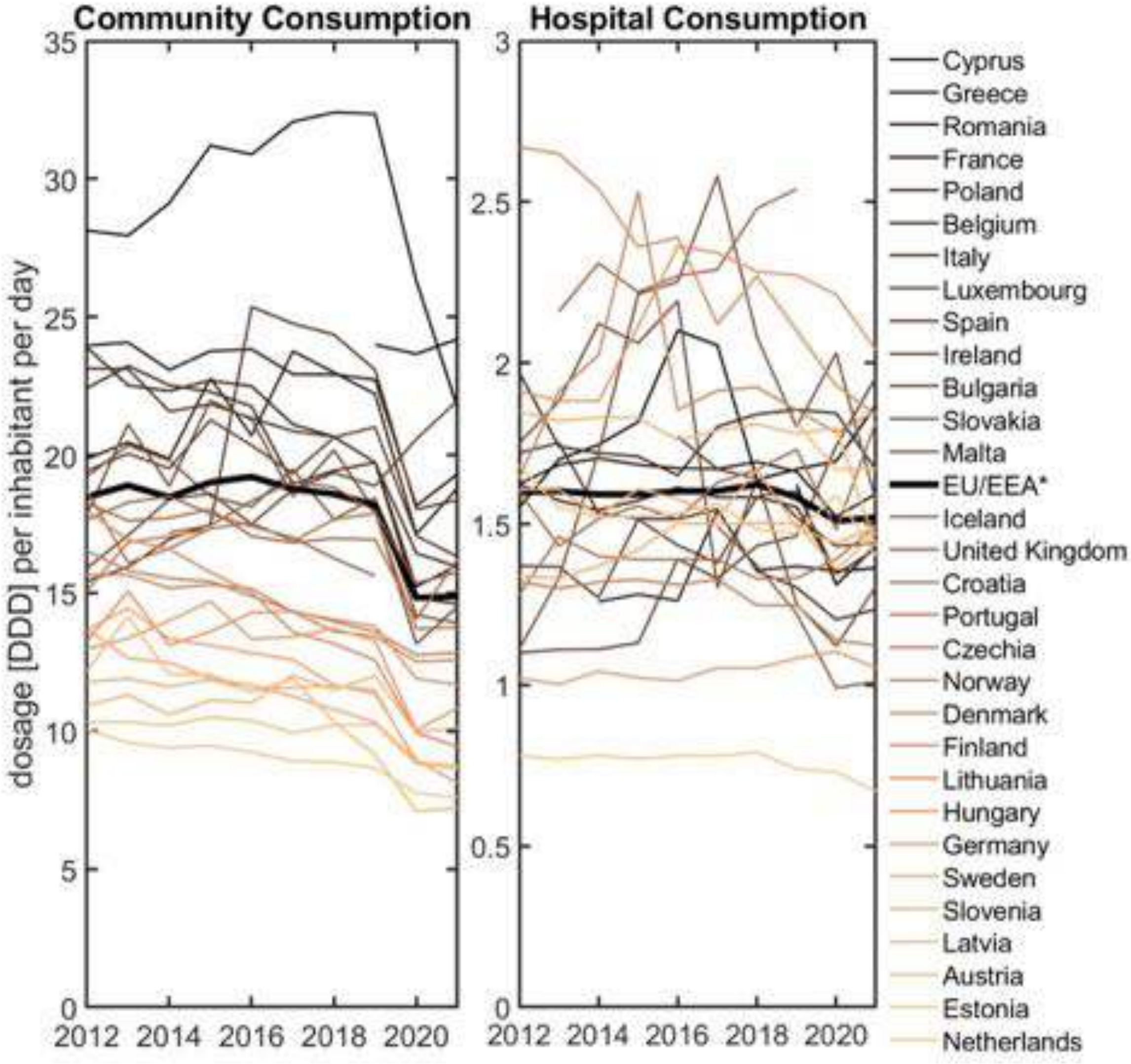

Figure 1: ***Trends in community and hospital consumption of antibiotics****. Results are reported in defined daily dosages (DDD) per inhabitant and per day. Source: ECDC.*

Many countries showed robust trends of declining consumption from 2012 to 2018; the ECDC reported statistically significant decreases in nine countries. This decrease is in line with efforts to decrease antimicrobial consumption in order minimize the build-up of antimicrobial resistance. Furthermore, the consumption data indicates that the pandemic acted as a strong negative demand shock. Most countries showed a sharp decline in consumption from 2018 to 2020.

Consumption data suggests that the antibiotics market experienced a pronounced negative demand shock during the pandemic, which was followed by a sudden spike in demand after the pandemic. This explains one part of the picture. Drugs are provided internationally. To understand the origins of the 2022-2023 antibiotics shortages, the evolution of the international trade and production system over the recent years needs to be quantified.

3 A deep dive into the dynamics of the global antibiotics trade network

We consider the antibiotics trade network segmented along the following steps of the value chain:

- Step 1: Intermediaries. Mostly metabolites made via fermentation from raw materials like yeast.
- Step 2: Active Pharmaceutical Ingredients (API). APIs are chemically modified intermediates with structural antimicrobial activity. They are the “acting substances” in the final drug product.
- Step 3: Unpackaged products. Medicaments containing the APIs for therapeutic or prophylactic uses, not yet measured in doses or in forms of packings for retail sale.
- Step 4: Packaged products. Medicaments packaged for retail sale.

3.1 Intermediaries

Key intermediaries for different types of antibiotics are listed in Table 1 together with the number of site locations in different world regions.[17] The table also gives the APIs in which the intermediaries are used along with the Harmonized System six-digit code (HS6 code) that can be used to quantify trade flows dominated by these APIs.

			Location of manufacturing sites				
Intermediary	**Used in production of API**	**HS6 code for API**	**Europe**	**US**	**China**	**India**	**Rest of world**
Tetracycline	Tigecycline	294130	2	-	4	-	-
6-Aminopenicillanic Acid	Amoxicillin, Flucloxacillin, Tazobactam	294110	1	-	5	-	1
7-aminocephalosporanic acid	Cephalosporins	294190	-	-	6	-	-
Erythromycin	Clarithromycin, Azithromycin	294150	1	1	1	3	-

Table 1: Overview of key antibiotic intermediaries, the APIs for which they are used along with the corresponding HS6 codes and location sites. Source: Wellcome Trust, Boston Consulting Group.

A strong concentration of production sites becomes evident. 16 out of 25 (64%) manufacturing sites are located in China. The necessary intermediaries to produce cephalosporins exclusively reside in China.

3.2 Active Pharmaceutical Ingredients

As of 2020, according to a report from Clarivate, 182 companies were rated as “established” suppliers of active pharmaceutical ingredients (APIs), meaning that they supplied to highly regulated markets like Europe or North America.[18] Of those producers, 66 (36%) were located in China, 41 (23%) in India, 25 (14%) in the US and 22 (12%) in Japan. The most prominent production location in Europe is Italy, with 19 companies (10%). Compared to intermediaries, there is still a large amount of concentration of manufacturing sites in China and India, but less so than for intermediaries.

[17] See https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf (accessed on 21 March 2023).

[18] See https://www.pharmaceuticalonline.com/doc/what-can-the-antibiotic-shortage-teach-us-about-weathering-api-supply-disruptions-0001 (accessed on 21 March 2023).

To understand the network structure of the international antibiotic production we go beyond the location of manufacturing sites and consider international trade flows of APIs over and above packaged and unpackaged products, see the appendix for methodological details. In particular, we perform a temporal global network analysis of trade relations in APIs, unpackaged and packaged products. For each year from 2010 to 2021 we extract all imports and exports reported in the UN COMTRADE database [19] in goods assigned to an HS4 or HS6 code in the categories 2941 (APIs), 3003 (unpackaged antibiotics) and 3004 (packaged antibiotics).

For each year, we extract a network in which nodes correspond to countries and directed links to the amount of trade flows reported from one country to the other (either as imports from one or exports to the other country). From these networks, one obtains direct dependencies of a country in the form of imports.

In addition, we modify existing systemic trade risk indicators to capture total network dependencies. [20] This systemic trade risk indicator gives a value for each country and year. It captures how susceptible global supply is to disruptions that originate from the considered country, which then propagates along the links in the trade network to other parts of the world (see the technical appendix for methodological details). Links are weighted by an indicator for political stability[21] of the exporting country to capture geopolitical dependences. The indicator is normalised between nil and one.

Figure 2: ***Systemic trade risk (importance) of countries in 2010.*** *Indicator values are visualized by means of pill symbols. The upper part of the pill represents the systemic trade risk indicator for APIs and the lower left (right) part for unpackaged (packaged) antibiotics. High trade importance can be observed for China, but also US and some European countries show higher values particularly for packaged products. Source: own calculations based on COMTRADE.*

Figure 2 gives a global overview of the trade risk values for 2010. Considering APIs, the highest indicator values are clearly observed for China. Little change in the indicator values can be observed for most countries compared to 2021 (see Figure 3). India shows an increasing tendency in its importance.

An interactive online dashboard that allows exploration of systemic dependencies in antibiotics trade can be accessed under https://vis.csh.ac.at/antibiotics-shortage/. There, also results for individual HS4 and HS6 codes can be explored.

[19] See https://comtradeplus.un.org/ (accessed on 21 March 2023).
[20] Klimek P, Obersteiner M, Thurner S. Systemic trade risk of critical resources. Science Advances 2015, 1(10):1500522.
[21] https://info.worldbank.org/governance/wgi/

Figure 3: ***Systemic trade risk indicators for countries in 2021.*** *The indicator values for European countries have clearly decreased compared to 2010 whereas India displayed increasing importance in the global trade network. Source: own calculations based on COMTRADE.*

3.3 Packaged and unpackaged products

As opposed to APIs, for packaged and unpackaged products many countries show a clear trend over time. France, the UK, and Germany showed comparably high indicator values for packaged products in 2010. Israel showed relatively high values for unpackaged products whereas the US had high importance values for both types of products. Yet, by 2021, systemic trade risk has become concentrated on China (unpackaged products) and India (packaged products). USA and Italy still have higher than average values, while all other countries play a fairly negligible role. The online dashboard allows further exploration of these results for specific categories of antibiotics and years.

Figure 4 summarises these results. Overall, there are tendencies of increasing trade risk. China shows the highest indicator values for APIs, India for unpackaged and packaged products.

3.4 Trade clusters

To better understand the "influence spheres" of individual countries, we perform a cluster analysis on the trade networks (see technical appendix). The idea is to identify the groups of countries that share more and stronger trade relations with other countries of the same group compared to countries outside of the group. How well the network can be separated into such group is quantified by the network modularity[22] which takes on a value between nil (i.e., no cluster structure in the network) and one (i.e., perfect separation of clusters).

[22] Blondel VD, Guillaume J-L, Lambiotte R, Lefebvre E. Fast unfolding of communities in large networks. Journal of Statistical Mechanics: Theory and Experiment 2008, P10008.

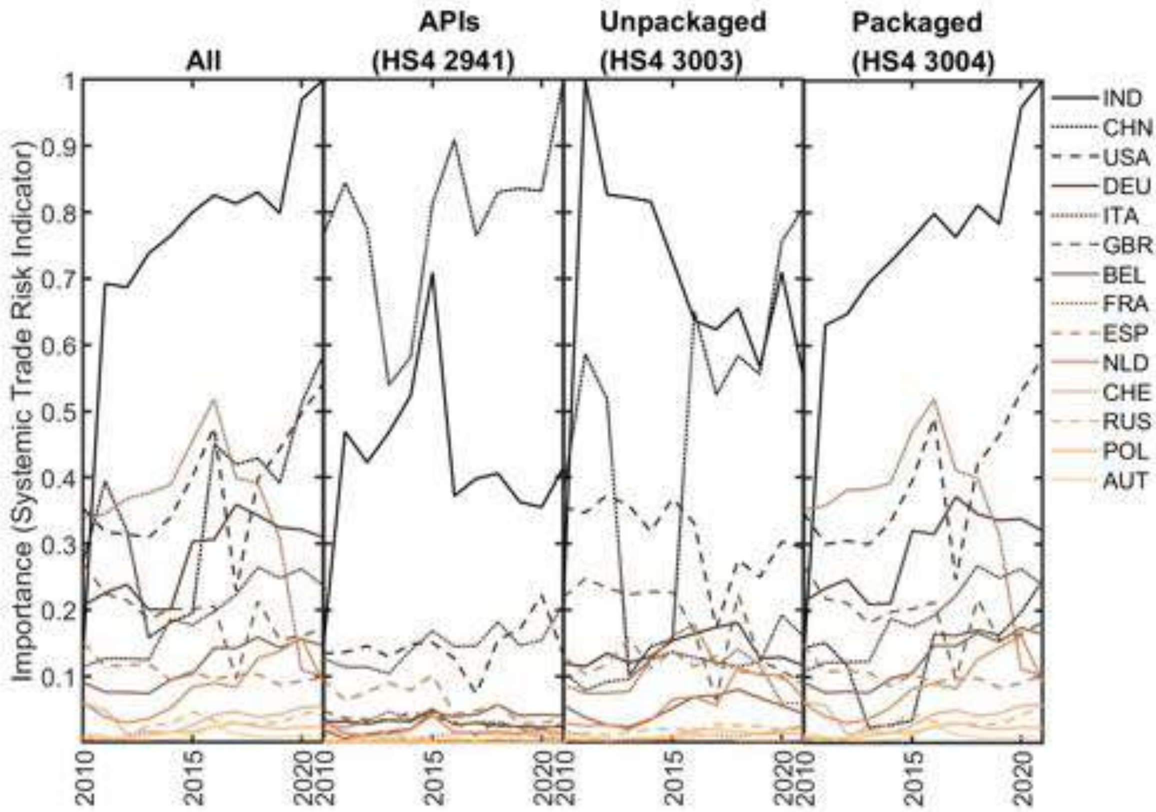

Figure 4: Importance of countries in spreading shocks along the trade networks ("Systemic Trade Risk Indicator") for selected countries from 2010 to 2021 for the trade of all antibiotics, APIs, as well as unpackaged and packaged antibiotics. Source: own calculations based on COMTRADE.

The results of the cluster analysis are shown in Figure 5 for all antibiotics trade, APIs, as well as unpackaged and packaged products, respectively. Overall, there is a decreasing modularity from 2010 to 2021. In other words, countries deepen their trade relations. That is, the number of countries that only trade with each other tends to decrease over time. The years influenced by the pandemic showed a particularly low network modularity.

There is no consistent trend, however, on the sublevels of APIs, unpackaged and packaged products. The results suggest that the overall modularity decrease is mostly driven by the trade of packaged products. For APIs there is even a trend of increasing modularity, suggesting a tendency for this trade network to become more segmented. This finding hints at an increasing brittleness of the antibiotic production ecosystem.

Trade in packaged antibiotic products became more and more internationalised since 2010. Trade flows in the ingredients necessary to manufacture the products became increasingly compartmentalised with China and India playing prominent, yet different roles in the trade networks.

Considering trade flows of all antibiotics in 2010, China and India formed a trade cluster with their local neighbours. The trading partners include Southeast Asia, Oceania, and parts of Africa. Large parts of Europe formed a trade cluster with North America. By 2021, China has formed a cluster with Europe and North America. India still formed a cluster with its local neighbours, Southeast Asia, Oceania, but also with many West African countries.

A similar pattern becomes evident in the trade of packaged products. By 2021, there is both an Indian and a Chinese "influence sphere". This indicates a growing tendency that China and India are not in direct competition with each other in terms of supplying Europe with (ingredients for) antibiotics, but rather form separate influence spheres in different parts of the global trading system.

3.5 Systemic risk and country profiles

This leads to another question: How did systemic trade risk change during the pandemic? From 2019 to 2021, China and India saw steep increases in their systemic trade risk indicator. In the trade of all antibiotics, the indicator value for the top 3 ranking countries all showed a strong increase, namely for India from 0.80 to 1.00, for China from 0.39 to 0.59 and for the US from 0.44 to 0.54. The picture is similar for APIs. China showed an increase from 0.84 to 1.00 whereas USA and India showed no strong upwards movement. Consistent upward trends during the pandemic can also be seen for packaged products with India increasing from 0.78 to 1.00, China from 0.16 to 0.25 and USA from 0.46 to 0.58.

Our analysis allows to quantify the susceptibility of single country to impacts originating from any other countries. We distinguish between two types of impacts:

- Direct impacts, i.e., direct effects between the exporting and the importing country
- Total impacts. These include direct impacts plus network effects which stem from indirect dependencies. This is, shocks that spread along multiple steps in the trade network.

For each country we compute its susceptibility to direct and total impacts from each other country and rank the countries accordingly. In the following, we report these results for Austria, Germany, and the US. The full results for all countries analysed can be explored online in the dashboard.

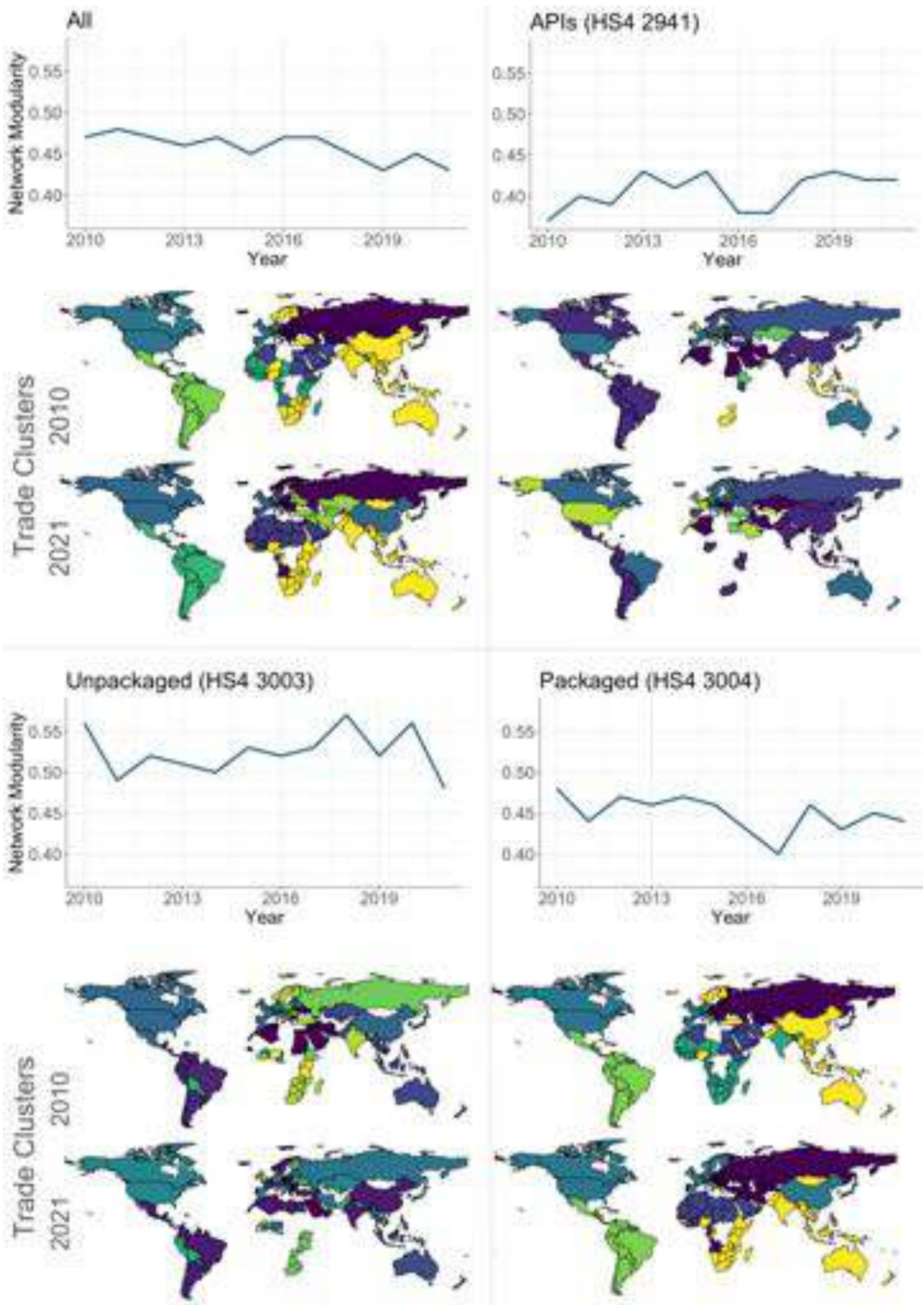

*Figure 5: **Analysis of trade clusters**. Network modularity by year is shown for all antibiotics trade, for APIs as well as for packaged and unpackaged products. Also shown are world maps for 2010 and 2021 for each product category were countries belonging to the same trade cluster are indicated by colour. Source: own calculations based on COMTRADE.*

4 Conclusions

Following the struggle to ensure timely availability of COVID-19 vaccines, the pharmaceutical industry now faces another shortage crisis in the provision of antibiotics, affecting many parts of the world. This has occurred after a consolidation phase of production structures, which has led to concentration processes in the geographic production of intermediaries and APIs since 2010, resulting in an increasingly interconnected global antibiotics value chain. This increased interconnectedness indicates a higher degree of specialization and division of labor, but it also renders the system more vulnerable to disruptions.

The COVID-19 pandemic upset the trade system's balance, reflecting the distribution of international production structures. The implementation of non-pharmacological interventions to combat COVID-19 reduced the spread of pathogens and, as a result, the demand for antibiotics decreased. In 2022, most countries phased out these interventions, leading to a quick "return to normal" in the incidence of infectious diseases and the demand for drugs. However, international supply did not react accordingly, resulting in shortages that could not be resolved through substitution, which had decreased substantially during the pandemic.

Policy levers

To strengthen the resilience of the global antibiotics provision, a multi-pronged approach is required, and policy makers can explore the following options based on our analyses:

- **Understanding the scope of the problem is crucial.** Data availability remains a major issue, however. Efforts need to be undertaken not only to track drug shortages but, more importantly, to identify non-substitutable drug shortages. Substitutes can be easily identified if disruptions occur in the upper tiers of the supply chain. In such cases, when unpackaged products or active pharmaceutical ingredients (APIs) are available, but other components such as blisters are missing, pharmacies can solve the problem by magisterial preparation.

- **Demand forecasting.** Health authorities need to have a better understanding of the demand trends for antibiotics in the population. It is necessary to monitor long-term trends in the incidence of infectious diseases and link them to the necessary prescriptions. This goes beyond simply tracking antibiotics trade and consumption. It will require investments in improving the data, planning, and forecasting infrastructure.

Supply chain disruptions are a result of market structure problems across the value chain. The current supply networks are shaped by market processes that aim to achieve the most competitive combination of quality and price. However, deviating from these market results may come at a cost, which can be seen as an insurance premium that health agencies need to pay to prevent negative impacts on patients. This cost can take various forms depending on the chosen market design.[23]

- **Capacity markets and excess inventory.** In case of emergencies, adding production capacities that can provide the necessary drugs in a timely manner may address any resulting shortages from the outset. Such a scheme has recently been implemented in Germany for vaccines.[24] Instead of promoting production capacities, policymakers may also opt for inventories that hold excess stock beyond normal use. However, this poses challenges for policymakers, as they are required to provide a list of intermediates and APIs to be stored.

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[23] See for instance Ockenfels, A. (2021), Pandemiebereitschaft, internationale Kooperation und Marktdesign, Wirtschaftsdienst 8/2021, pp 595-596.

[24] See https://www.bundesgesundheitsministerium.de/presse/pressemitteilungen/vertraege-fuer-impfstoffversorgung.html (accessed on 22 March 2023).

- **Multiyear contracts.** Evidence-driven demand planning could form the basis for building stable supply relationships, such as through multiyear contracts with producers that contain robust provisions in case of non-delivery. This implies that risks are shifted from the public to suppliers, which is likely to increase the ask prices and thereby the costs that health procurement agencies incur.

- **Single market.** The European Union provides a powerful tool to mitigate supply risks across multiple players, namely the Single Market. In the recent antibiotics shortages, procurement from the Single Market cushioned the impact of the shortages. In addition, coordinated and more centralized EU inventories can help to reduce overall safety stock and thereby avoid inefficiencies. More generally, the EU provides a coordination platform that seeks to avoid "economic nationalism".[25]

- **Bargaining power**. Countries, regions, or health agencies might consider deeper cooperation and pursue joint forecasting and procurement strategies. For instance, procurement pools led by bigger countries acting as regional anchors have been suggested for high-, middle-, and low-income countries. [26] In addition, such procurement pools could ensure market access for low- and middle-income countries.

- **Diversification of supply.** Diversifying supply requires the presence of internationally competitive producers. Therefore, the dialogue concerning the expansion of the supplier base is inherently linked to a more extensive discussion on competitiveness, including elements such as trade and competition, innovation and technology policy, or market design and regulations. This is an intricate topic that must be attended to with tailored approaches. It has become clear that producer subsidies alone cannot avert shortages. The current scarcities occurred despite existing domestic production systems.

The availability of antibiotics is a critical factor in the discussion on antimicrobial resistance (AMR). The issues are connected, as shortages of antibiotics could have dire consequences for AMR, particularly due to the inappropriate use of substitutes. When first-choice antibiotics are not available, physicians might prescribe suboptimal replacements that could be less effective or more prone to resistance. They might also resort to specialised antibiotics that would otherwise be reserved for patients with more severe infections; if these antibiotics are out of stock, these patients are at an increased risk of poorer outcomes. Additionally, the fragility of the antibiotics production industry has an effect on AMR, as it discourages research and development activities due to small profit margins and high development costs. This creates a negative feedback loop: countries and health authorities attempt to reduce AMR by limiting the use of antibiotics, but this also reduces the diversity of antibiotics and, consequently, increases AMR. To address this problem, the development of reimbursement schemes has become a policy priority worldwide.

- **Subsidised procurement prices.** The development of COVID-19 vaccines was accelerated by above-market prices, which helped to lower the overall costs of the pandemic. [27] To address drug shortages and antimicrobial resistance (AMR), reimbursement models have been proposed that decouple development costs from unit sales. These models could potentially mitigate shortages by establishing stable supply relationships. For example, in 2022, Sweden conducted a pilot study in which a minimum annual revenue was guaranteed for selected antibiotics in return for a guaranteed supply volume. The UK experimented with a 'Netflix-like' subscription model, in which an annual fee was paid, unrelated to the actual volume supplied. France implemented a pricing model where the guaranteed price must not be lower than the lowest price across four reference countries. Germany devised a 'degressive' pricing model in which unit prices decrease once a specific volume is exceeded. These models are costly for taxpayers, since they weaken the price efficiency that a

[25] See Usher, A. D. (2021), A beautiful idea: how COVAX has fallen short, The Lancet, 397(10292), 2322-2325.
[26] Berman D, Chandy SJ, Cansdell O, Moodley K, Veeraraghavan B, Essack SY. Global access to existing and future antimicrobials and diagnostics: antimicrobial subscription and pooled procurement. Lancet Glob Health 2022; 10: e293-97.
[27] See for instance Castillo, J. C., A. Ahuja, S. Athey et al. (2021), Market design to accelerate COVID-19 vaccine supply, Science, 371(6534), 1107-1109.

market-based procurement system looks to provide. Such measures could subsidise firms and bolster their competitive position. It is important to evaluate if such measures effectively incentivise research and development, which is likely to depend heavily on the contract design.

Appendix A: Country profiles

Germany

Germany is one of the systemically most important countries in the global antibiotic production ecosystem, ranked #4 in the trade of all antibiotics following India, China, and the USA. Our analysis reveals a highly heterogeneous profile of dependencies across different stages of the value chain. In the supply of APIs for penicillin Germany is highly dependent on China and India, see Figure 6. Chinese imports are much higher than imports from India, suggesting higher network-mediated dependencies on India coupled with strong direct dependencies on China. For other types of APIs, Germany imports large quantities from Netherlands and Switzerland.

Figure 6: German imports and exports for APIs used in the production of penicillin. *Note: This graph shows the countries from which Germany sources APIs for penicillin (HS6 294110). Shown are imports (blue) and exports (red) values for all trade activities between 2010-2015 (top line) and for 2016-2021 (bottom line), respectively. Countries are ranked from top to bottom by their system trade risk indicators in 2016-2021. Source: own calculations based on COMTRADE.*

In unpackaged antibiotics, Germany receives substantial imports from the US, Italy, and Spain whereas it reports particularly high exports to Ireland (which in turn reports high exports to the US in this category), see Figure 7. China and India play only a minor role in this trade network for Germany compared to APIs. However, China is also becoming an increasingly important indirect trade partner, moving from rank #7 in 2010-2015 to rank #4 in 2016-2021.

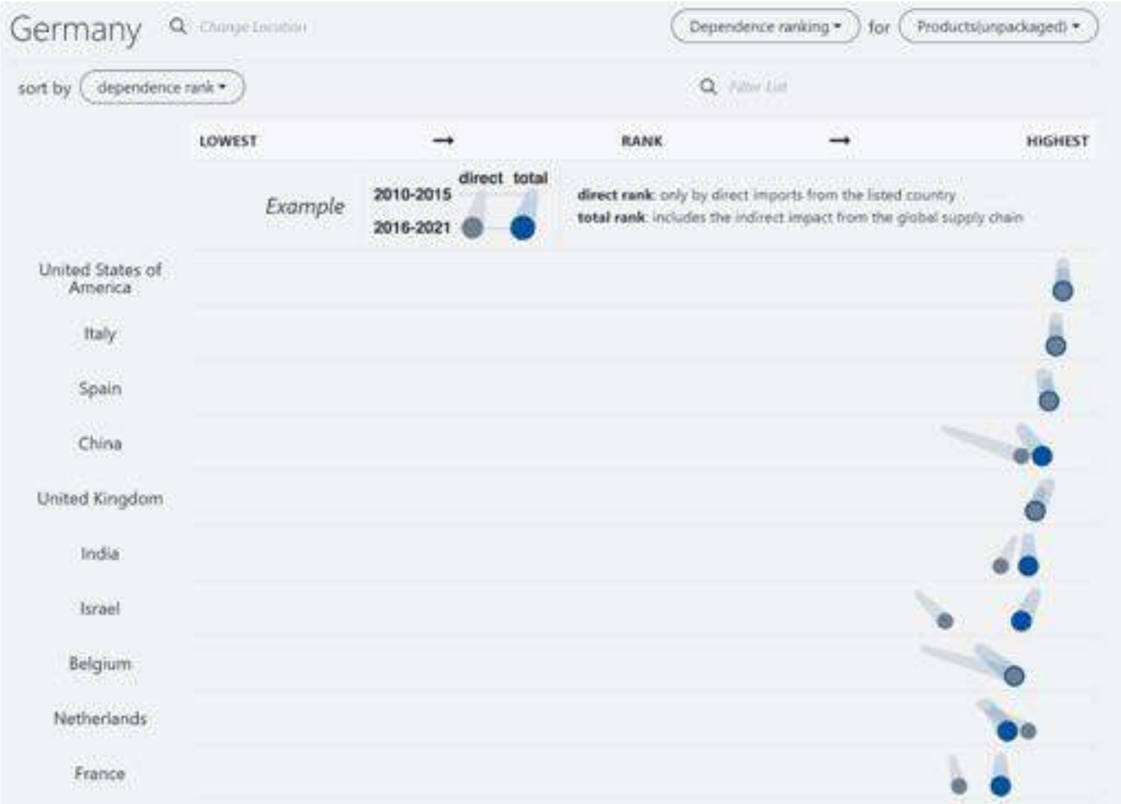

Figure 7: ***Ranking of countries on whose supplies of unpackaged products Germany depends****. Note: This graph illustrates the countries from which Germany sources unpackaged supplies (HS4 3003). Shown are direct (grey) and total (blue) ranks for all trade activities between 2010-2015 (upper line) and for 2016-2021 (lower circles), respectively. Source: own calculations based on COMTRADE.*

Overall, the data suggests a substantial trade deficit for Germany in APIs but a substantial trade surplus in packaged products. Considering all packaged antibiotics, Germany has strongest dependencies on the US, Italy, UK, France, and Belgium. Considering only penicillin, however, our analysis suggests an increasing network-mediated dependence on India (from rank #7 in 2010-2015 to rank #2 in 2016-2021), while most of the direct imports are sourced from Austria and Italy in this category.

USA

Following India and China, the USA are the third systemically most important country in the global antibiotics trade networks. Its most important trading partners for APIs include China, Italy, India, and Belgium, see Figure 8. Substantial trade deficits with China and Italy but trade surpluses with India and Belgium are reported. This is reflected in the dependence ranking, where the highest dependencies are observed for China and Italy. The US report much higher imports than exports in APIs for penicillin, tetracyclines and chloramphenicol (mostly from China), whereas it is a strong exporter of erythromycin, for which it hosts a manufacturing site (compare Table 1).

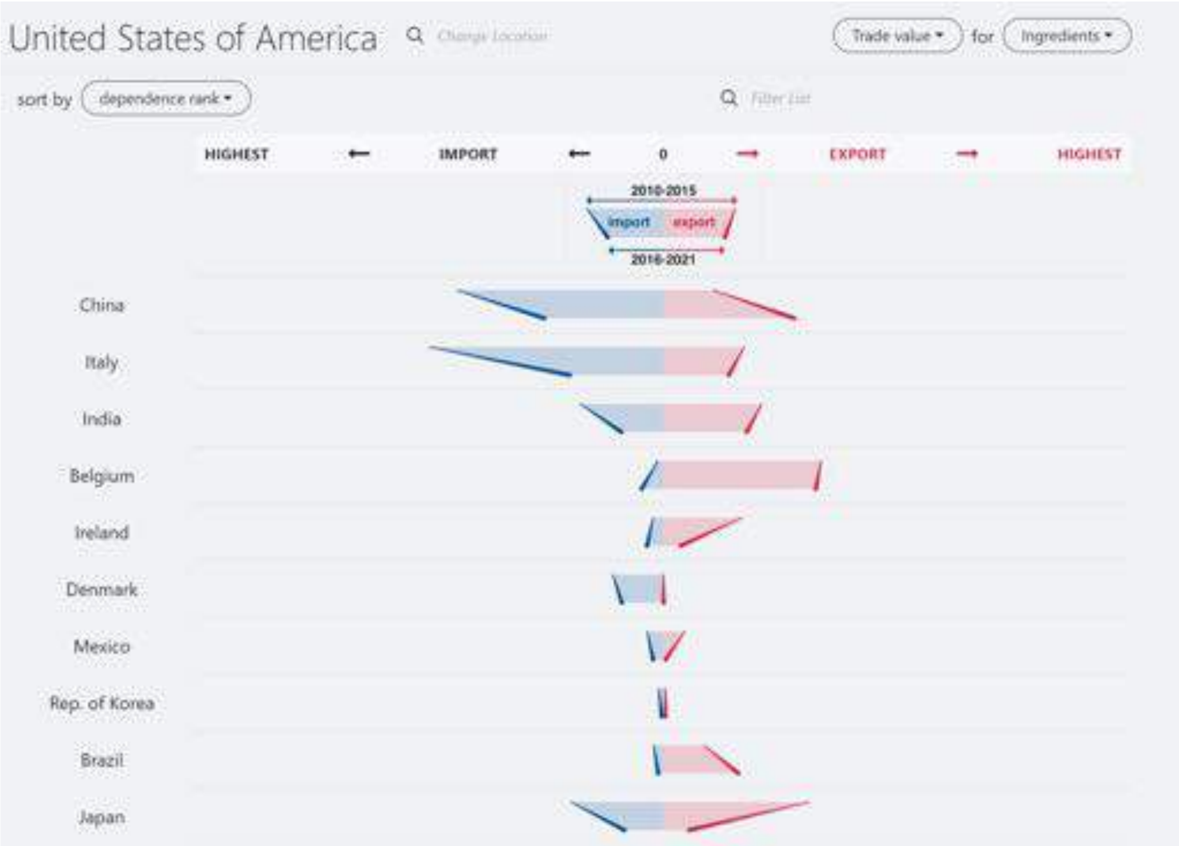

Figure 8: ***US imports and exports for APIs.*** *This graph shows the countries from which the US sources APIs (HS4 2941). Shown are imports (blue) and exports (red) values for all trade activities between 2010-2015 (top line) and for 2016-2021 (bottom line), respectively. Countries are ranked from top to bottom by their system trade risk indicators in 2016-2021. Source: own calculations based on COMTRADE.*

The strongest direct US trade partners in unpackaged antibiotics include Germany, Italy, the UK, and Canada. For penicillin, there are also particularly high imports from China and India, followed by Austria and India. The US further show a trade surplus with Germany, Canada, the UK, and Ireland. Most of its packaged products are imported from Germany, Ireland, Italy, Canada, Switzerland. In this category, our analysis reveals the highest systemic trade risk from India (rank #1), see Figure 9.

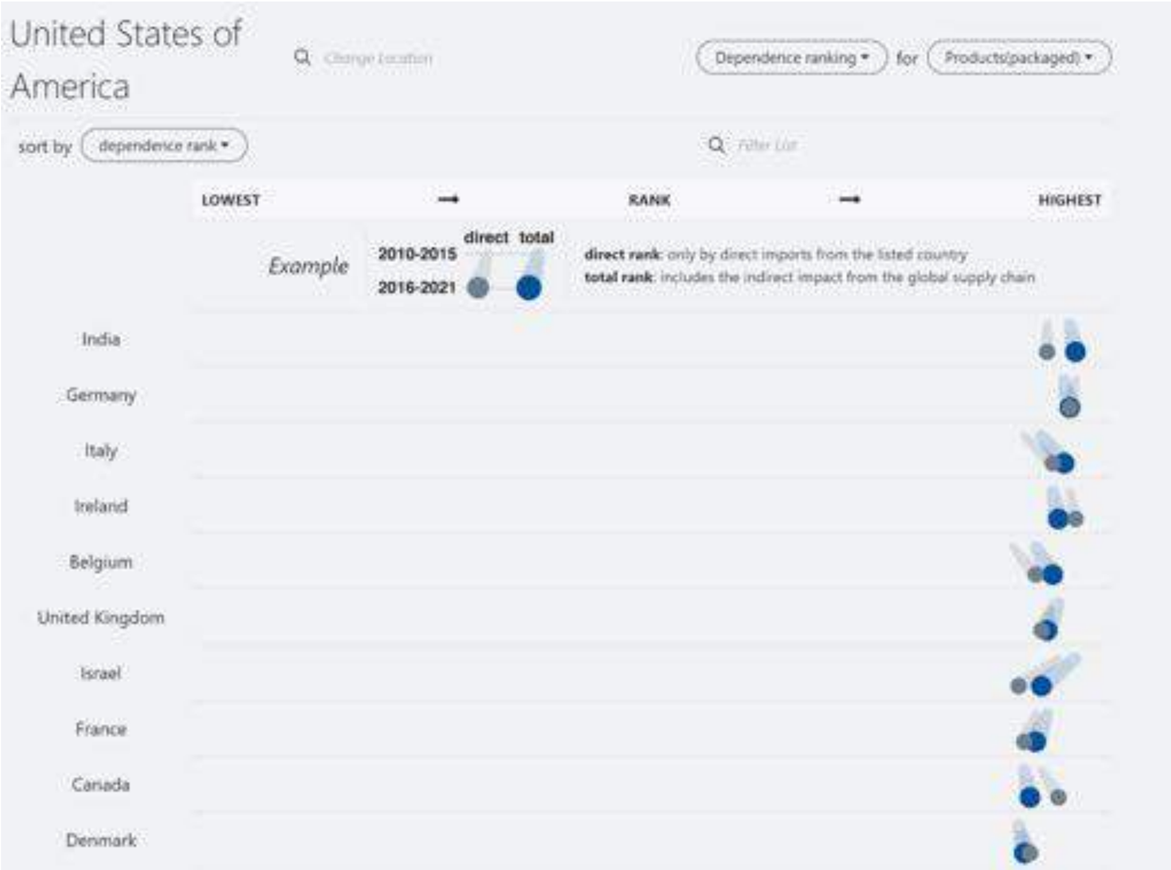

Figure 9: ***Ranking of countries on whose supplies of packaged products the US depends.*** *Note: This graph illustrates the countries from which the US sources packaged supplies (HS4 3004). Shown are direct (grey) and total (blue) ranks for all trade activities between 2010-2015 (upper line) and for 2016-2021 (lower circles), respectively. Source: own calculations based on COMTRADE.*

Overall, the US are tightly integrated with several European countries in the antibiotics trade networks and thereby, by extension, also with China. The indirect, network-mediated dependence on China is particularly strong for APIs (where China has rank #1 for the US) and unpackaged products (rank #2). For packaged products, however, India plays a much bigger role for the US (rank #1) than China (rank #13).

Austria

Austria plays a special role in the antibiotic production ecosystem. One of the few European antibiotics manufacturing sites is located in the town of Kundl.[28] During most of the period analysed, Sandoz, a key manufacturer of API amoxicillin, produced in Spain (Palafolls, Les Franqueses) and strengthened its amoxicillin production in Kundl, where Sandoz produces penicillin.

Table 2 shows the list of antibiotics not available in Austria as reported by the Austrian Federal Office for Safety in Health Care[29] as of March 9, 2023. The table includes the name of the product, the corresponding HS6 code in which most of the trade flows of the corresponding APIs are typically reported, as well the first and latest date, on which it was reported that a given drug is not available.

Despite Austria's domestic penicillin production, the shortage list contains products that are produced in Austria. Furthermore, for several products multiple package sizes are unavailable. For instance, for Clarithromycin Sandoz no less than six different package sizes and formulations are unavailable. Hence, domestic production does not automatically guarantee the domestic provision of goods. This is due to contractual obligations that manufacturers must fulfil. Hence, production capacities and the distribution of production may diverge, which is the case in Austria.

Figure 10-Figure 12 illustrate the close supply chain connection between Austria and Spain. The data reveals a high rank of Spain in APIs and unpackaged products compared to a much lower rank for Spain in packaged products. China is ranked second in APIs. Its direct rank decreased over the last ten years, i.e., China became less relevant as a direct trade partner for Austria. However, this did not change Austria's susceptibility to impacts originating from China, especially since China's total rank did not change for Austria. In other words, the dependence on China was "hidden in the network". There also are growing dependencies on the USA, Turkey, Belgium, and Switzerland.

For unpackaged antibiotics, Austria shows an increasing dependence on China and Bulgaria, while the importance on Germany and Italy remained stable and high. The picture changes with packaged antibiotics, where China does not appear among the ten highest ranking countries. Overall, the rankings remain stable in this category with substantial indirect dependencies on the USA.

[28] https://www.sandoz.com/news/media-releases/sandoz-announces-plans-further-strengthen-its-antibiotics-manufacturing-setup-europe
[29] https://medicineshortage.basg.gv.at/vertriebseinschraenkungen/faces/main-btf/main

Figure 10: ***Ranking of countries on whose APIs supplies Austria depends.*** *Note: This graph illustrates the countries from which Austria sources APIs (HS4 2941). Shown are direct (grey) and total (blue) ranks for all trade activities between 2010-2015 (upper line) and for 2016-2021 (lower circles), respectively. Source: own calculations based on COMTRADE.*

*Figure 11: **Ranking of countries on whose supplies of unpackaged products Austria depends**. Note: This graph illustrates the countries from which Austria sources unpackaged supplies (HS4 3003). Shown are direct (grey) and total (blue) ranks for all trade activities between 2010-2015 (upper line) and for 2016-2021 (lower circles), respectively. Source: own calculations based on COMTRADE.*

Figure 12: ***Ranking of countries on which Austria depends on its supplies of packaged products (HS4 3004).*** *Note: This graph illustrates the countries from which Austria sources packaged supplies (HS4 3003). Shown are direct (grey) and total (blue) ranks for all trade activities between 2010-2015 (upper line) and for 2016-2021 (lower circles), respectively. Source: own calculations based on COMTRADE.*

Name	HS6 code	First reported date	Latest reported date
Amoxicillin "ratiopharm" 1000 mg - Filmtabletten	294110	2022-10-04	2023-01-26
Amoxicillin "ratiopharm" 500 mg - Filmtabletten	294110	2022-12-15	2022-12-15
Amoxicillin/Clavulansäure Actavis 875 mg/125 mg Filmtabletten	294110	2022-02-08	2022-09-12
Amoxicillin/Clavulansäure Krka 875 mg/125 mg Filmtabletten	294110	2022-02-24	2022-12-19
Amoxicomp Genericon 1 g Filmtabletten	294110	2022-12-15	2022-12-15
Amoxilan 500 mg/5 ml - Trockensaft	294110	2023-02-06	2023-02-06
AmoxiPlus "ratiopharm" 625 mg - Filmtabletten	294110	2023-01-04	2023-01-04
Amoxistad 1000 mg Filmtabletten	294110	2022-11-14	2022-12-16
Amoxistad 500 mg Filmtabletten	294110	2022-12-19	2022-12-19
Amoxistad plus 875 mg/125 mg Filmtabletten	294110	2022-09-26	2023-02-23
Azithromycin +pharma 500 mg Filmtabletten	294150	2023-03-06	2023-03-06
Azithromycin 1A Pharma 500 mg - Filmtabletten	294150	2023-01-09	2023-01-09
Azithromycin Sandoz 200 mg/5 ml - Pulver zur Herstellung einer Suspension zum Einnehmen	294150	2023-02-01	2023-02-08
Azithromycin Sandoz 500 mg - Filmtabletten	294150	2023-01-20	2023-01-20
Azithromycin Stada 500 mg - Filmtabletten	294150	2023-01-16	2023-01-16
Azithromycin-ratiopharm 500 mg Filmtabletten	294150	2023-01-04	2023-01-04
Biocef 200 mg - Filmtabletten	294190	2022-08-29	2023-01-16
Biocef 40 mg/5 ml - Pulver zur Herstellung einer Suspension zum Einnehmen	294190	2023-02-02	2023-02-22
Ceclor 250 mg/ 5 ml - Granulat für orale Suspension	294190	2022-12-21	2023-02-20
Cefastad 250 mg/5 ml Trockensaft	294190	2023-01-16	2023-02-23
Cefastad 500 mg Kapseln	294190	2023-01-16	2023-01-16
Cephalobene 500 mg - Filmtabletten	294190	2022-08-16	2022-09-02
Ciprofloxacin "ratiopharm" 500 mg - Filmtabletten	294190	2022-11-10	2023-01-04
Clarithromycin 1A Pharma 250 mg - Filmtabletten	294150	2023-01-09	2023-01-09
Clarithromycin 1A Pharma 500 mg - Filmtabletten	294150	2023-01-09	2023-01-09
Clarithromycin Accord 250 mg Filmtabletten	294150	2023-01-13	2023-01-13
Clarithromycin ratiopharm GmbH 250 mg Filmtabletten	294150	2022-12-15	2022-12-15
Clarithromycin ratiopharm GmbH 500 mg Filmtabletten	294150	2023-01-16	2023-01-16
Clarithromycin Sandoz 125 mg/5 ml - Granulat für orale Suspension	294150	2023-01-16	2023-01-16
Clarithromycin Sandoz 250 mg - Filmtabletten	294150	2023-01-09	2023-01-09
Clarithromycin Sandoz 250 mg/5 ml - Granulat für orale Suspension	294150	2023-01-20	2023-01-20
Clarithromycin Sandoz 500 mg - Filmtabletten	294150	2023-01-09	2023-01-09
Clarithromycin STADA 250 mg - Filmtabletten	294150	2023-01-16	2023-01-16
Clarithromycin STADA 500 mg - Filmtabletten	294150	2023-01-16	2023-02-23
Clindac Sandoz 300 mg - Kapseln	294190	2023-02-22	2023-02-22
Clindac Sandoz 450 mg - Filmtabletten	294190	2023-01-10	2023-01-10
Clindac Sandoz 600 mg - Filmtabletten	294190	2023-01-10	2023-01-10
Clindamycin 1A Pharma 300 mg - Kapseln	294190	2023-02-08	2023-02-08
Clindamycin 1A Pharma 450 mg - Filmtabletten	294190	2023-01-09	2023-01-09
Clindamycin 1A Pharma 600 mg - Filmtabletten	294190	2023-01-09	2023-01-09
Curam intravenös 2000 mg/200 mg - Pulver zur Herstellung einer Infusionslösung	294110	2022-12-19	2022-12-19
Dalacin C 75 mg/5 ml - Granulat für orale Lösung	294190	2020-12-15	2020-12-15
Doxybene 200 mg - lösbare Tabletten	294130	2023-01-26	2023-01-26
Eucillin "B" - Salbe	294190	2021-07-20	2022-12-21

Name	HS6 code	First reported date	Latest reported date
Eusaprim - Tabletten	294190	2022-06-23	2023-02-03
Halomycetin - Augensalbe	294140	2019-12-23	2022-06-27
Keflex 1000 mg Filmtabletten	294190	2022-12-21	2022-12-21
Levofloxacin 1A Pharma 250 mg - Filmtabletten	294190	2022-12-22	2022-12-22
Levofloxacin 1A Pharma 500 mg - Filmtabletten	294190	2022-10-12	2022-10-12
Levofloxacin Krka 500 mg Filmtabletten	294190	2023-01-24	2023-01-31
Levofloxacin Sandoz 500 mg - Filmtabletten	294190	2022-12-07	2022-12-07
Ofloxa-Vision sine 3 mg/ml Augentropfen im Einzeldosisbehältnis	294190	2023-01-25	2023-01-25
Ospamox 250 mg/5 ml - Pulver für orale Suspension	294110	2023-03-07	2023-03-07
Ospamox 500 mg - Filmtabletten	294110	2023-01-10	2023-01-10
Ospamox 750 mg - Filmtabletten	294110	2022-12-19	2022-12-21
Ospen 1,0 – Filmtabletten	294110	2022-10-07	2023-02-07
Ospen 400 - Saft	294110	2022-12-19	2022-12-19
Ospen 750 - Saft	294110	2022-12-14	2022-12-19
Ospexin 250 mg/5 ml - Granulat für orale Suspension	294190	2022-12-28	2022-12-28
Ospexin 500 mg - Filmtabletten	294190	2022-08-16	2022-09-09
Penbene 1 Mio. I.E. - Filmtabletten	294110	2022-12-19	2023-02-20
Penbene 1,5 Mio. I.E. - Filmtabletten	294110	2022-11-24	2022-11-24
Penicillin G-Natrium Sandoz 10 Mega IE - Trockensubstanz zur Infusionsbereitung	294110	2022-12-19	2022-12-19
Penicillin G-Natrium Sandoz 5 Mega IE - Trockenstechampulle	294110	2023-02-08	2023-02-08
Roxithromycin Sandoz 150 mg - Filmtabletten	294190	2022-10-31	2022-10-31
Rozex - Gel	294190	2022-12-22	2022-12-22
Standacillin 1 g – Pulver zur Herstellung einer Injektions-/Infusionslösung	294110	2023-02-08	2023-02-08
Standacillin 2 g – Pulver zur Herstellung einer Injektions-/Infusionslösung	294110	2023-01-30	2023-01-30
Tavanic 500 mg Filmtabletten	294190	2023-01-11	2023-01-11
Tobramycin B. Braun 1 mg/ml Infusionslösung	294190	2023-01-05	2023-01-30
Tobramycin B. Braun 3 mg/ml Infusionslösung	294190	2022-11-18	2023-01-30
Tricef 100 mg/5 ml - Trockensaft	294190	2023-01-31	2023-01-31
Tyrothricin "Provita" comp. - Lutschtabletten	294190	2022-07-28	2022-12-21
Unasyn - Filmtabletten	294110	2022-02-28	2022-02-28
Xiclav 1 g - Filmtabletten	294110	2022-11-04	2023-03-03
Xiclav 156,25 mg/5 ml - Trockensaft	294110	2022-03-10	2023-02-07
Xiclav 312,5 mg/5 ml - Trockensaft	294110	2022-01-13	2023-02-07
Xiclav 625 mg - Filmtabletten	294110	2023-02-06	2023-02-06
Xiclav duo 457 mg/5 ml - Trockensaft	294110	2023-02-06	2023-02-06
Xiclav Quicktab 1 g - Tabletten	294110	2022-09-01	2023-02-07
Zinnat 250 mg - Filmtabletten	294190	2023-01-11	2023-03-02

Table 2: List of antibiotics not available in Austria as of 9 March 2023. Source: BASG.

Appendix B: Data and Methods

Trade Data

The United Nations Comtrade database provides access to trade data and analytics. It contains detailed import and export statistics for over 200 countries and territories. The database has information on product type, exporter country, importer country, time, trade value, amount, etc. There is a WEB application that allows users to access and visualize trade data. Additionally, users can access and download the data via API (Application Programming Interface). We retrieved the trading data on a country level from 2010 to 2021 for harmonized codes[30]: 294110, 294120, 294130, 294140, 294190, 300310, 300320, 300410. Based on these product codes, we group the data in eight data subsets, one for each HS code, one for all four digits HS codes combined, and one for all six digits HS codes combined.

Network modularity

We constructed trade networks $M^h(t)$ based on downloaded data for year *t* for each subset *h*. Nodes in these networks are countries. If two countries traded in year *t*, there is a weighted link between these two countries with the weight being given by trade value of traded goods during this year. Note that a trade flow from country *i* to country *j* can in the be reported from i as an import and/or from j as an export. Trade flows $M_{ij}^h(t)$ *are defined* as the maximum of these two reported values.

In the next step, we filtered out all counties with less than ten inbound and outbound links. Thus, the resulting trading networks, on average, had 87 countries. Links weights are normalized as $\overline{M}_{ij}^h(t) = \frac{M_{ij}^h(t)}{\max\left(\Sigma_i M_{ij}^h(t), \Sigma_j M_{ij}^h(t)\right)}$. Trade clusters and modularity were obtained using the Louvain clustering algorithm on the normalized trade network. [31]

Systemic trade risk indicators

In this part of the analysis, we constructed two directed trade networks for the periods from 2010 to 2015 and 2016 to 2021, respectively, for each data subset. Nodes in these networks, T^{2015} and T^{2021}, respectively, are countries, as described above. All countries with at least one inbound and outbound link are included in the network, resulting in the inclusion of 155 countries on average. Links weights are further scaled by political stability estimates, *PS*(*i*) for country *i*, provided by World Bank via the World Governance Indicators[32] as previously suggested. [33] The so-called vulnerability matrices V can therefore be obtained from the trade flows T as $V_{ij}^k = \left(1 - \frac{PS(i)}{100}\right)\frac{T_{ij}^k}{\Sigma_i T_{ij}^k}$. The systemic trade risk matrix *STR*, which collects contributions from all network paths along which a node *i* in the network might influence another node *j* in the network, can then be defined as $STR^k = (\mathbb{I} - V^k)^{-1}$ where $\mathbb{I}$ is an identity matrix and the exponent –1 indicates the matrix inverse. The Systemic Trade Risk indicator for a single country is identified as the column sum of STR^k. In network-theoretic terms, Systemic Trade Risk can be interpreted as Katz or Bonacich Centrality with a damping factor for higher order network dependencies that is proportional to the political stability indicator of the exporting country. [34]

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[30] See https://www.wcoomd.org/en/topics/nomenclature/overview/what-is-the-harmonized-system.aspx, (accessed March 23, 2023)
[31] Blondel VD, Guillaume J-L, Lambiotte R, Lefebvre E. Fast unfolding of communities in large networks. J. Stat. Mech. (2008) P10008
[32] See https://info.worldbank.org/governance/wgi/ (accessed March 23, 2023).
[33] Klimek P, Obersteiner M, Thurner S. Systemic trade risk of critical resources. Science Advances 2015, 1(10):1500522.
[34] Bonacich P, Lloyd P, Eigenvector-like measures of centrality for asymmetric relations. Social Networks 2003. 23 (3): 191–201