White Paper

Building Effective Models to Identify Medicine Shortages in Low- and Middle-Income Countries

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Summary

Introduction

In recent months, disruptions to pharmaceutical supply chains have been reported as countries began imposing export bans, domestic and international travel restrictions, and restrictions on the domestic transportation of goods. This paper describes an attempt to use data collected by IQVIA to identify statistically significant declines in the supply of pharmaceuticals in the private sector in 22 low- and middle-income countries.[1] The work forms part of a wider collaborative effort between IQVIA and CGD aimed at understanding how COVID-19 has impacted supply chains for vital medicines. This project is supported by the Department for International Development (DFID) (also known as UK Aid) in the UK and the Bill and Melinda Gates Foundation (BMGF).

Methods

Models were built that could identify products notified by manufacturers as being in shortage in Germany and in Canada. The models were designed to detect actual values significantly below those forecasted for one and two months into the future. Models were refined to limit the identification of products to only those that had declined to a similar extent or duration as those that had been notified as being in shortage.

The best performing model, one that was built using Exponential Smoothing for Time Series (ETS) and using an 80% confidence interval, was then applied to monthly sales data collected by IQVIA from private sector wholesalers in 22 low- and middle-income countries. Supply disruption was only flagged if actual values were lower than the forecast for the next two consecutive months ("two-month period"). Therefore, if the forecast was based on data for March 2020, then disruption was only flagged if the actual values for April and May 2020 were found to be significantly below the forecasts for April and May 2020.

60 products (molecule-pharmaceutical form combinations) were included in the study. 38 of these were directly affected by the Indian export ban in March 2020, while the others constituted a subset of Essential Medicines. The period leading up to April 2020 is defined as the "pre-pandemic period" and the period that followed is defined as the "pandemic period".

In order to determine if the COVID-19 pandemic disrupted pharmaceutical supply, the number of disruptions in the pre-pandemic period was compared to the number of disruptions in the pandemic period. The Chi-squared test for dependent samples was used to test for significance between these two periods. Two different definitions of disruption in the pre-pandemic period were used, one being more stringent than the other. One defined disruption in the pre-pandemic period as disruption in any one of the 6 two-month periods from October 2019 to April 2020 (i.e. it did not matter if disruption was noted in the period October-November 2019 or March-April 2020). The second test defined disruption in the pre-pandemic period as disruption seen only in the period immediately prior to the pandemic period (i.e. March-April 2020). The first definition, the more stringent test, is termed the "6 prior period" test. The less stringent test is termed the "immediate prior period" test.

1. Figures for the split between public and private expenditures on pharmaceuticals are given for 12 of these countries on the WHO Observatory website (7 Francophone Africa + Jordan, Philippines, Peru, Pakistan and Kenya). In only one case (Burkina Faso) was public expenditure on pharmaceuticals above 50%, and the median percentage was 19%. Data relates to ~2008.

Results

Overall, supplies in the pandemic period were shown to be significantly different to the pre-pandemic period, regardless of the definition of disruption in the pre-pandemic period used (i.e. “6 period test” or “immediate prior period” test). This was also true of the group of products directly affected by the export ban. However, supplies of the subset of essential medicines were only seen to be significantly different from those in the pre-pandemic period, when the less stringent test was applied (i.e. the “immediate prior period” test).

Countries differed in terms of disruptions to the supply chain, even within the same geographic region. 4 countries showed a negative impact on supplies in the pandemic period, regardless of the applied definition of disruption in the pre-pandemic period– namely South Africa, Mexico, Algeria and Pakistan. Moreover, countries differed within the same region. 6 Francophone African countries showed significant disruptions using the immediate prior period test, but 6 did not. Similarly, while Mexico shows evidence of significant disruption, regardless of the test applied, no disruption was noted in Peru.

Of the 60 products evaluated in this study, 7 showed significant disruption in the pandemic period, regardless of the definition of disruption in the pre-pandemic period. Using the less stringent test, this number increased to 15. Of these 15, disruptions were noted for both products affected by the Indian export ban (9/15) and for those not directly affected (6/15).

Not all formulations of the same molecule showed significant disruptions in the pandemic period. Therefore, oral solid formulations of paracetamol and metronidazole are not found to have suffered disruptions as a whole, while other formulations (e.g. rectal or oral liquid) did. No pharmaceutical form was unaffected by disruption.

Discussion

Our model was built to identify products facing shortages, and it was constrained to identify the group of products that experienced similar declines to those notified as facing shortages. This model’s detection of significant disruptions at both country and molecule levels when comparing the pandemic period with the pre-pandemic period also indicates that the model can be used to produce meaningful signals of supply disruption. The model could be further extended to other countries or implemented on an ongoing basis where monthly (or more frequent) sales or dispensing data are available. Signals would, of course, need to be investigated for validity given that volume declines can be the result of falling demand as well as shortage. Further work would also be needed to devise a method to determine when a supply disruption had been resolved.

Introduction

Pharmaceutical supply chains can be long, with manufacturing of active pharmaceutical ingredients (API) and finished product being carried out in different countries. At the same time, certain countries, notably India and China, have come to dominate the production of APIs and finished products, particularly for generic medicines. In recent months, disruptions to pharmaceutical supply chains have been inevitable as countries began imposing export bans, domestic and international travel bans, and restrictions on the domestic transportation of goods.

Product shortages are not new. In some countries across Europe, the US and in Canada, for example, manufacturers are already obliged to notify governments if any of their products are likely to be in short supply. The completeness and timeliness of such notifications can be questioned, and even so, in many low- and middle-income countries, such mechanisms do not yet exist. Moreover, few low- and middle-income countries appear to have formal processes to measure disruptions to the pharmaceutical supply chain further downstream, and even where these may exist, they can be restricted to a specific, and sometimes limited, set of commodities.

This paper describes an attempt to use data collected by IQVIA to (i) identify statistically significant declines in the supply of pharmaceuticals; (ii) assess the impact of the COVID-19 pandemic on supplies of essential medicines and those directly affected by the Indian export ban of March 2020. In addition, we discuss the possibility of using similar methods to identify shortages on an ongoing basis and across a wider set of low- and middle-income countries. The work forms part of a wider collaborative effort between IQVIA and CGD aimed at understanding how COVID-19 has impacted supply chains for vital medicines. This project is supported by the Department for International Development (DFID) (also known as UK Aid) in the UK and the Bill and Melinda Gates Foundation (BMGF).

Methods and Data Sources

Building the Shortage Detection Model

The objective of a Shortage Detection Model is to detect significant declines in volumes as soon as possible. The method selected was to build a model that would detect significant deviations between actual values and those produced by a short-term forecast. In other words, to take an example, the model would aim to detect a statistically significant difference between actual values and a forecast for April 2020, with the forecast being built using actual values up until March 2020.

There are a number of different statistical methods that can be used to produce short-term forecasts. In this study, three methods were compared: AutoRegressive Integrated Moving Average (ARIMA), Exponential Smoothing for Time Series (ETS) and Neural Network (NN). All data processing was carried out using the software package "R" and 80%, 95% and 99% confidence intervals were given. A significant decline was defined as actual values below the 80%, 95% or 99% confidence interval as appropriate.

Models were evaluated in terms of their ability to detect significant declines in volumes of products in two countries where manufacturers notify governments of products in, or about to be in, shortage (Germany and Canada). The models were also evaluated in terms of their ability to distinguish between products notified as being in shortage and those not notified as being in shortage. Models were thus evaluated in two ways: first in terms of their "Precision", their ability to detect known products in shortage; and second in terms of their "Accuracy", their ability not to label products as being in shortage that are not in shortage.

The models were refined across a number of different stages. The model was first tested against German data and then refined with Canadian data. Information on the completeness of the data collected in these countries can be found at https://www.iqvia.com/landing/acts. The build process is described in the paragraphs below and portrayed schematically in Figure 1.

- **Stage 1:** Products notified as being in shortage by manufacturers in Germany between 2012-2019 were mapped to IQVIA's data. Of 233 products so notified in this period, 219 were were able to be mapped. A small subset of these products (4), together with a set of products selected at random (10) were then selected. Models were refined until all could differentiate between those products identified as being in shortage and those not in shortage.

- **Stage 2:** Review of the IQVIA data for Germany for the 219 products mentioned above indicated that about 40% would not be suitable for the model build. This was because of one of two reasons: (a) very small or zero volumes in multiple months, with very high variability between months, or (b) no change in trend +/- 4 months from the date of the manufacturer-notified shortage. Of the remaining 119 products, 92 were notified as being in shortage in just three months - July 2018, August 2018 and May 2019. 50 of these were selected at random, and the models tested against these 50 products and 500 controls (selected at random from all products not notified as being in shortage). Actual values were compared to a one-month forecast. Thus, for those products notified as being in shortage in July 2018, actual values were compared to a forecast for July 2018 based on 5 years' data up until June 2018.

- **Stage 3:** In the first analysis, models were run against all 550 products selected using 5 years of prior data. Results found that improvements could be made if products were first divided into two types based on the number of months with zero sales:

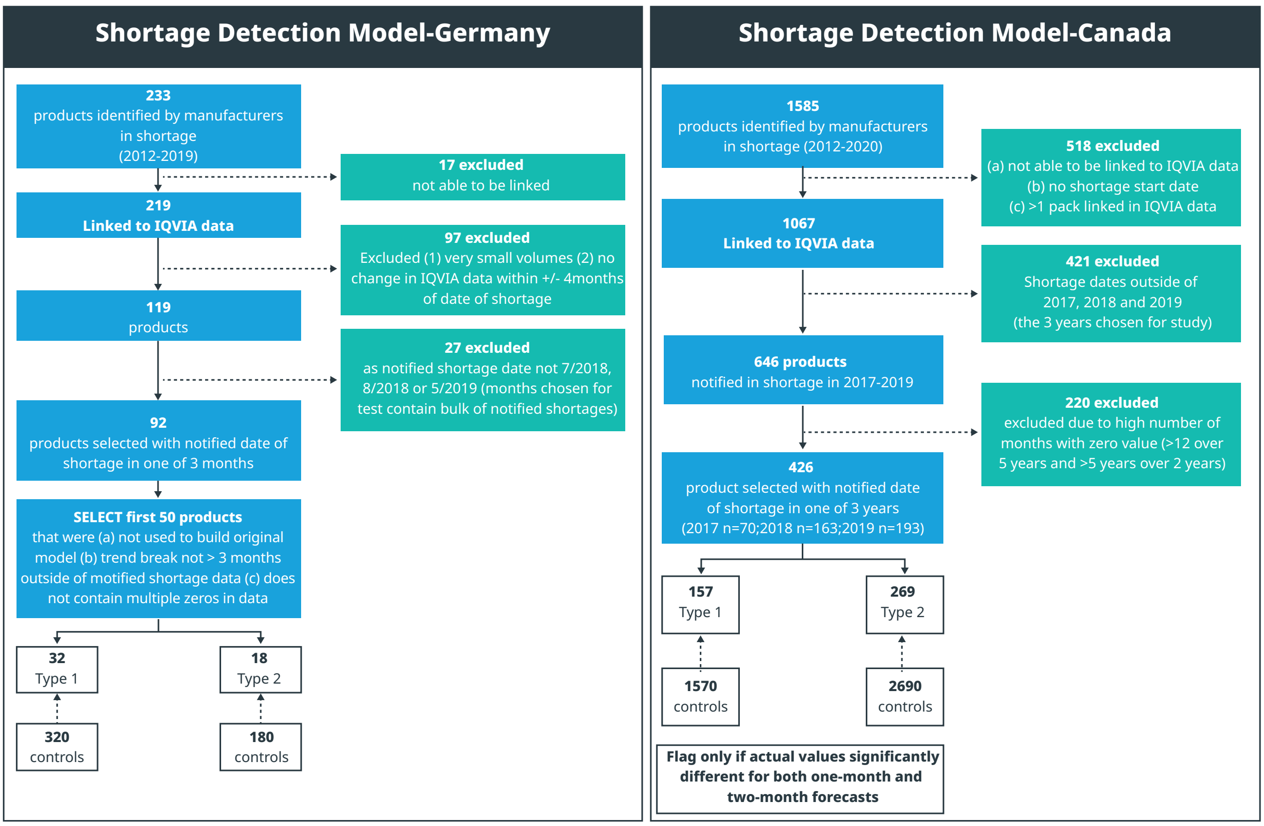
Type 1 products: Products with very few zero values across the 5 years of prior data. The input data used to build the forecasts for Type 1 products remained at 5 years.

Type 2 products: Products with multiple zero values in the first three years but few zeros in the last two years were placed in a separate category (Type 2). The input data used to build the forecasts for Type 2 products was restricted to 2 years.

- **Stage 4:** At this point it was decided to focus on the ETS model, as this had produced (marginally) better results than either the ARIMA or Neural Network models. The ETS model was then applied to the Canadian data in an attempt to identify products in shortage as notified by manufacturers there. The number of notified shortages is much larger in Canada than in Germany, with 1585 notified shortages between 2011-2020. Of these, 1067 could be linked to IQVIA data, and of the 1067, 646 fell between 2017-2019, the most recent period and the one chosen for study. Of these 646 products, 220 were excluded due to the number of months with zero sales (>12 months in 5 years and >5 months in 2 years). Of the remaining 426 products, 157 were categorized as Type 1 and 269 as Type 2. In Germany, the test required a ratio of 10:1 "Cases" to "Controls". As such, there were 426 products notified as being in shortage ("cases"), and 4260 products that had not been notified as being in shortage ("controls").

- **Stage 5:** Initial results had relatively high precision but low accuracy. In other words, the model correctly identified products that manufacturers had notified as being in shortage, but it also identified a high proportion of other products as suffering from a significant decline. It was found, however, that accuracy could be improved (and precision only somewhat negatively affected) if products were flagged as showing a significant decline only if actual values were significantly lower than both the one-month and two-month forecasts. Thus, products that were flagged by manufaccturers to be in shortage in say May 2018 were only flagged as being in shortage by the model if actual values were significantly lower than the forecast produced for both May and June 2018 using data up until April 2018.

Figure 1: Schematic of process of building and testing Shortage Detection Model against manufacturer-notified shortages in Germany and Canada



Applying the model to low- and middle-income country data

PRODUCT SELECTION

Products selected for this study fall into two types: (a) molecules and forms banned from export by India in March 2020, and (b) a set of 25 products that had been specifically selected as being of importance to low- and middle-income country healthcare systems. Twenty-one of these molecule-form combinations were selected on the basis of the following criteria: (i) sold through the private sector in most countries; (ii) apparently dependent on India in at least one other country of interest to development partners (Ghana) and (iii) categorized as both Vital Essential Medicines in two national Essential Medicine Lists and an Essential Medicine by the WHO. The remaining three products were added from the current WHO Essential Medicine List and chosen to ensure an adequate representation across product forms and therapy classes.

Table 1 lists the products and forms evaluated in the study. Products banned by India from export were included in the study to evaluate the relative effects of export bans versus other restrictions that may have affected the pharmaceutical supply chain as a result of the COVID-19 pandemic.

Table 1: Products and pharmaceutical forms evaluated as part of the study

INDIAN EXPORT BAN	ESSENTIAL MEDICINES
CHLORAMPHENICOL (any form)	ACICLOVIR | Oral solid
CLINDAMYCIN (any form)	AMIKACIN | Parenteral †
ERYTHROMYCIN (any form)†	AMIODARONE | Oral solid †
METRONIDAZOLE (any form)	AMLODIPINE#TELMISARTAN | Oral solid
NEOMYCIN (any form)	AZATHIOPRINE | Oral solid†
ORNIDAZOLE (any form)	BECLOMETASONE | Inhaled†
PARACETAMOL (any form)†	CARBAMAZEPINE | Oral Liquid
PYRIDOXINE#THIAMINE (any form)	CARBAMAZEPINE | Oral solid
PYRIDOXINE (any form)	CIPROFLOXACIN | Oral solid
THIAMINE (any form)	DEXAMETHASONE | Parenteral††
TINIDAZOLE (any form)	DIGOXIN | Oral solid†
	ENALAPRIL | Oral solid
	FLUOXETINE | Oral solid
	HYDROCHLOROTHIAZIDE | Oral solid
	MEROPENEM | Parenteral †
	METHYLPREDNISOLONE | Parenteral
	METOCLOPRAMIDE | oral solid †
	MUPIROCIN | Topical
	OMEPRAZOLE | Oral solid †
	OXYTOCIN | Parenteral
	PYRIDOSTIGMINE | Oral solid
	RANITIDINE | Oral solid ‡
	SPIRONOLACTONE | Oral solid
	SULFADIAZINE | Topical
	VALPROIC ACID | Oral Liquid

†Banned form export by UK in March-April 2020

††Banned from export by UK in June 2020

‡ Banned from export by UK in October 2019

UNITS OF MEASURE

In the model build, models had been tested in terms of their ability to identify shortages of a specific manufacturer's product pack. This was because manufacturer-notified shortages refer to specific packs or forms, as there are some pack sizes or strengths of product of the same manufacturer's brand that are not in shortage. In applying the ETS model to low- and middle-income country data, and, in the interest of determining whether there are shortages of the molecule in general as opposed to shortages of just a particular manufacturer's product, products containing the same molecule and of the same pharmaceutical form were aggregated, regardless of strength or manufacturer. In other words, the models looked for a shortage of, for example, aciclovir capsules or tablets, rather than a shortage of a specific manufacturer's tablet or a particular strength of tablet. Volumes were measured using the IQVIA "Standard Unit". In this study, the IQVIA Standard Unit equates to the number of tablets or capsules for oral solid forms, the number of vials, infusion bags or ampoules for parenteral forms, the number of doses of inhaled medicines for inhaled forms, the number of grams of ointment or cream for topical forms, the number drops of ophthalmic or otic forms, the number of suppositories or pessaries for rectal or vaginal forms respectively and the number of 5ml doses of oral liquid formulations.

STUDY PERIODS

A rolling 5 years of data were used as input data for the short-term forecasts. Short-term forecasts were produced from October 2019 onward up until May or June 2020, depending on the availability of data for each country. Data for May and June were only available for Francophone countries and Kenya. Data for June were not available for any of the other countries included in the study.

Forecasts were produced from October 2019, as this provided an opportunity to gauge the frequency of disruptions in supplies well prior to any disruptions caused by the COVID-19 pandemic.

STUDY COUNTRIES

The countries included in the study are a subset of those for which IQVIA collects monthly data from wholesalers supplying the private sector. The countries included in this study are dominated by those from Sub-Saharan Africa but include countries from the Middle East and North Africa, Latin America, South Asia and Europe.

Information regarding the completeness and coverage of the datasets outside of Africa, as well as the dataset from South Africa, can be found at https://www.iqvia.com/landing/acts.

Table 2: Countries included in the study

COUNTRY	REGION
BENIN	Francophone Africa
BURKINA FASO	Francophone Africa
CAMEROON	Francophone Africa
CHAD	Francophone Africa
CONGO	Francophone Africa
COTE D'IVORE	Francophone Africa
GABON	Francophone Africa
GUINEA	Francophone Africa
KENYA	Francophone Africa
MALI	East Africa
NIGER	Francophone Africa
SENEGAL	Francophone Africa
SOUTH AFRICA	South Africa
TOGO	Francophone Africa

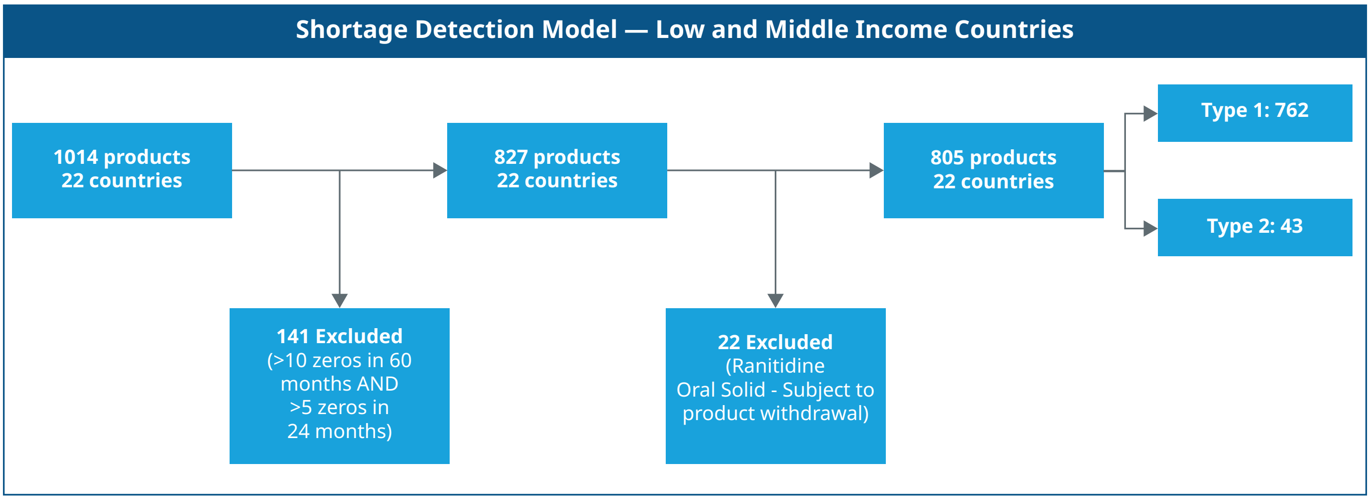
COUNTRY	REGION
PHILIPPINES	East Asia and Pacific
COUNTRY	**REGION**
TURKEY	Europe and Central Asia
COUNTRY	**REGION**
MEXICO	Latin America and Caribbean
PERU	Latin America and Caribbean
COUNTRY	**REGION**
ALGERIA	Middle East and North Africa
JORDAN	Middle East and North Africa
LEBANON	Middle East and North Africa
COUNTRY	**REGION**
PAKISTAN	South Asia

INCLUSIONS AND EXCLUSIONS

In total 1014 country, molecule and form combinations (which will be referred to as "products") were found across the 22 countries. Of these, 142 were excluded, due to both ≥ 10 zero values in the 5-year input data and ≥ 5 zero values in the 2-year input data (i.e. 5 or more zeros in 24 months). Of the remaining 872 country, molecule and form combinations, 826 were Type 1 (5-year input data) and 46 were Type 2 (2-year input data). The predominance of Type 1 country, molecule and form combinations indicates that aggregating the data to this level removes much of the "noise" seen when analysing trends in volume of specific manufacturer packs.

For certain analyses, notably those involving a change at country level or overall, data relating to ranitidine were excluded. Ranitidine was subject to a product withdrawal in late 2019, which was reflected in the export ban seen in the UK at this time. Ranitidine was thus flagged by the model as showing significant declines in late 2019 in many countries, such shortages appearing to ameliorate in early-mid 2020. When we looked at change over time, therefore, it was deemed more appropriate to exclude ranitidine. With the exclusion of ranitidine, there were 762 Type 1 products and 43 Type 2 products (see Figure 2).

Figure 2: Schematic of exclusions from shortage detection model as applied to 22 low and middle income countries



EVALUATION OF LOW- AND MIDDLE-INCOME COUNTRY RESULTS

In order to determine if the COVID-19 pandemic disrupted the pharmaceutical supply in the 22 low- and middle-income countries, the number of disruptions in the pre-pandemic period was compared to the number of disruptions in the pandemic period. The Chi-squared test for dependent samples was used to test for significance between these two periods. Two different definitions of disruption in the pre-pandemic period were used, one being more stringent than the other. One defined disruption in the pre-pandemic period as disruption in any one of the 6 two-month periods from October 2019 to April 2020 (i.e. it did not matter if disruption was noted in the period October-November 2019 or March-April 2020). The second test defined disruption in the pre-pandemic period as disruption seen only in the period immediately prior to the pandemic period (i.e. March-April 2020). The first definition is the more stringent test and is termed the "6 prior period" test, while the less stringent test is termed the "immediate prior period" test.

Results

Shortage Detection, Canada, 2018 data

As noted above, the model was built using data from Germany and Canada and refined according to the results found. The final model was applied to data from 2018 in Canada; the final modification being that products should only be flagged as showing a significant decline if both the one- and two-month forecast were significantly higher than the actual volume sold. In 2018, Type 2 products (those showing multiple zeros on a monthly basis) constituted 63% of all products notified as being in shortage, and, thus, also of controls.

Table 3: Comparison true and false positives, Canada, 2018 data, 99% Confidence Interval Type 2 products

SALES IN MONTH IDENTIFIED BY MODEL AS SHOWING SIGNIFICANT DECLINE:	
	vs 12 month average (IQR)
FALSE POSITIVE	-71% (-91% to -45%)
TRUE POSITIVE	-72% (-87% to -58%)
	vs 3 month (IQR)
FALSE POSITIVE	-64% (-91% to -31%)
TRUE POSITIVE	-71% (-86% to -39%)
	vs 1 month (IQR)
FALSE POSITIVE	-57% (-87% to -28%)
TRUE POSITIVE	-71% (-86% to -39%)

False positive: Products flagged by model but not notified as being in shortage by manufacturers
True positive: Products flagged by model and notified as being in shortage
IQR: Interquartile Range

Overall, "Precision" of the ETS model used was 61%, and "Accuracy" 47%, using an 80% confidence limit. The relatively high "Accuracy" figure (the number with a significant decline not notified by manufacturers) suggested that the model may still be flagging products incorrectly. Accuracy could be increased by using 95% and 99% confidence intervals, but this reduced Precision. However, further examination of the Type 2 products not notified as being in shortage yet flagged as showing a significant decline (so-called "false positives") demonstrated that these were largely indistinguishable from those that had been notified as being in shortage (so-called "True positives", see Table 3 below).

These results indicate that, in many cases, sales of products in Canada experience declines that are similar in extent and duration to those notified by manufacturers as being in shortage. The model can thus be seen to be working as it should, even if the number of products identified as being in significant decline at any point in 2018 was higher than those notified by manufacturers.

It was, therefore, decided to apply this latest model without change, to low- and middle-income data, with a preference for using an 80% confidence interval. However, in order to further minimise the potential for false positives, forecasts were produced beginning from a period well before that which might be expected to have been affected by the COVID-19 pandemic. In this way, the results from this prior period can be used to evaluate the "strength" of a flag indicating significant decline in the pandemic period.

Shortage detection, Low- and Middle-Income Countries, 2019-2020

Results for each product by country using 80%, 95% and 99% confidence intervals are found in Appendix 1. Aggregate results are discussed below.

Overall, supplies in the pandemic period were shown to be significantly different to the pre-pandemic period regardless of the definition of disruption in the pre-pandemic period used (i.e. "6 period test" or "immediate prior period" test). This was also true of the group of products directly affected by the export ban (see Table 4). However, supplies of the subset of essential medicines were only seen to be significantly different from those in the pre-pandemic period when the less stringent test was applied (i.e. the "immediate prior period" test).

Countries differed in terms of the impact of the disruptions to the supply chain, even within the same geographic region. 4 countries showed a negative impact on supplies regardless of the test applied – namely South Africa, Mexico, Algeria and Pakistan. When compared to the prior 6 periods, moreover, supplies of these products in Peru appeared to improve, and Peru showed no impact of the pandemic when results from the pandemic period were compared to those from the prior period only. It is also interesting to note the variation in results for the Francophone African countries. 6 countries showed significant disruptions when results from the pandemic period were compared to those from the prior period, but 6 did not. Similarly, the results for Mexico and Peru are very different.

Table 4: Change in supply of medicines pre and post pandemic period

	Significant increase in supply disruptions between pandemic and pre-pandemic periods	
	6 Prior Period Test†	Immediate Prior Period Test‡
OVERALL	Sig. ($p<0.05$)	Sig. ($p<0.05$)
EXPORT BAN	Sig. ($p<0.05$)	Sig. ($p<0.05$)
ESSENTIAL MEDICINES (NO EXPORT BAN)	NS	Sig. ($p<0.05$)

† Pre-pandemic disruption defined as disruption in any one of the 6 two-monthly periods from October 2019 to April 2020 (i.e. it did not matter if disruption was noted in the period October-November 2019 or March-April 2020).
‡ Pre-pandemic disruption defined as disruption seen only in the period immediately prior to the pandemic period (i.e. March-April 2020).

Table 5: Change in supply of medicines pre- and post-pandemic period by country

		Significant increase in supply disruptions between pandemic and pre-pandemic periods	
		6 Prior Period Test	Immediate Prior Period Test
EAST AFRICA	Kenya	NS	Sig.(p<0.05)
FRANCOPHONE AFRICA	Benin	NS	Sig.(p<0.05)
	Burkina Faso	NS	NS
	Cameroun	NS	NS
	Congo	NS	NS
	Cote d'Ivoire	NS	Sig.(p<0.05)
	Gabon	NS	Sig.(p<0.05)
	Guinee	NS	NS
	Niger	NS	Sig.(p<0.05)
	Senegal	NS	Sig.(p<0.05)
	Tchad	NS	NS
	Togo	NS	Sig.(p<0.05)
SOUTH AFRICA	S.Africa	Sig.(p<0.05)	Sig.(p<0.05)
EAST ASIA AND PACIFIC	Philippines	NS	NS
EUROPE	Turkey	NS	Sig.(p<0.05)
LATIN AMERICA	Mexico	Sig.(p<0.05)	Sig.(p<0.05)
	Peru	Sig.(p<0.05) [BUT POSITIVE]	NS
MIDDLE EAST & NORTH AFRICA	Algeria	Sig.(p<0.05)	Sig.(p<0.05)
	Jordan	NS	NS
	Lebanon	NS	NS
SOUTH ASIA	Pakistan	Sig.(p<0.05)	Sig.(p<0.05)

Note: Supplies of medicines in Peru improved versus the pandemic period when compared to the prior 6 periods.

Countries also differed in terms of the products affected by supply disruption, as shown in Table 5. Some countries' supplies were disrupted for both those affected by the Indian export ban and those that were not, namely Senegal, South Africa, Turkey, Algeria and Pakistan. Other countries' disruptions seem to be driven by those products affected by export bans, namely Benin, Cameroun, Cote d'Ivoire, Gabon and Mexico. Kenya and Togo are somewhat different in the sense that only supplies of those products not affected by the Indian export ban appear in aggregate to be significantly disrupted. (see Table 6)

Table 6: Change in supply of medicines pre and post pandemic period by country (Immediate Prior Period Test)

		Significant increase in supply disruptions between pandemic and pre-pandemic periods	
		Export ban	Essential Medicines (no export ban)
EAST AFRICA	Kenya	NS	Sig.(p<0.05)
FRANCOPHONE AFRICA	Benin	Sig.(p<0.05)	NS
	Burkina Faso	NS	NS
	Cameroun	Sig.(p<0.05)	NS
	Congo	NS	NS
	Cote D'ivoire	Sig.(p<0.05)	NS
	Gabon	Sig.(p<0.05)	NS
	Guinee	NS	NS
	Niger	NS	NS
	Senegal	Sig.(p<0.05)	Sig.(p<0.05)
	Tchad	NS	NS
	Togo	NS	Sig.(p<0.05)
SOUTH AFRICA	S.Africa	Sig.(p<0.05)	Sig.(p<0.05)
EAST ASIA AND PACIFIC	Philippines	NS	NS
EUROPE	Turkey	Sig.(p<0.05)	Sig.(p<0.05)
LATIN AMERICA	Mexico	Sig.(p<0.05)	NS
	Peru	NS	NS
MIDDLE EAST & NORTH AFRICA	Algeria	Sig.(p<0.05)	Sig.(p<0.05)
	Jordan	NS	NS
	Lebanon	NS	NS
SOUTH ASIA	Pakistan	Sig.(p<0.05)	Sig.(p<0.05)

60 products were evaluated in this study. 7 showed significant declines across the total of all 22 countries when compared to the 6 prior periods, and 15 showed significant decline when compared to the prior period only (see Table 7). Disruptions are noted for both products affected by the Indian export ban and for those not directly affected.

It is also noticeable that not all formulations of the same molecule showed significant declines. Thus, oral solid formulations of paracetamol and metronidazole are not found to have suffered significant decline in the aggregate. At the same time, shortages are found for all pharmaceutical forms considered in this study.

Table 7: Significant changes in supply of medicines pre and post pandemic period by product

		Significant increase in supply disruptions between pandemic and pre-pandemic periods	
CATEGORY	Product	**6 Prior Period Test**	**Immediate Prior Period Test**
INDIA EXPORT BAN	Clindamycin | Oral Solid	NS	Sig.(p<0.05)
	Erythromycin | Oral Liquid	Sig.(p<0.05)	Sig.(p<0.05)
	Erythromycin | Oral Solid	NS	Sig.(p<0.05)
	Erythromycin | Topical	Sig.(p<0.05) *(but positive)*	NS
	Metronidazole | Oral Liquid	NS	Sig.(p<0.05)
	Metronidazole | Oral Solid	NS	Sig.(p<0.05)
	Metronidazole | Vaginal	Sig.(p<0.05)	Sig.(p<0.05)
	Paracetamol | Oral Liquid	Sig.(p<0.05)	Sig.(p<0.05)
	Paracetamol | Parenteral	NS	Sig.(p<0.05)
	Paracetamol | Rectal	Sig.(p<0.05)	Sig.(p<0.05)
	Pyridoxine#thiamine | Oral Solid	Sig.(p<0.05) *(but positive)*	NS
	Tinidazole | Oral Solid	NS	Sig.(p<0.05)
ESSENTIAL MEDICINES (NO EXPORT BAN)	Aciclovir | Oral Solid	Sig.(p<0.05)	Sig.(p<0.05)
	Ciprofloxacin | Oral Solid	NS	Sig.(p<0.05)
	Digoxin | Oral Solid	Sig.(p<0.05) *(but positive)*	NS
	Methylprednisolone | Parenteral	Sig.(p<0.05)	Sig.(p<0.05)
	Mupirocin | Topical	Sig.(p<0.05)	Sig.(p<0.05)
	Valproic acid | Oral Liquid	NS	Sig.(p<0.05)

Note: Supplies of pyridoxine+thiamine capsules/tablets and topical erythromycin improved versus the pandemic period when compared to the prior 6 periods.

Within the Francophone African region alone, results were somewhat different (see Table 8). Overall, fewer products appeared to have been significantly disrupted across the group of countries.

Both May and June data were available for the Francophone African countries and for Kenya. Of the 60 products evaluated in those countries, 13 were identified as in significant decline in two consecutive periods following the introduction of the export ban and movement restrictions. This would indicate that there was very severe disruption to supplies of these products. This is because the forecast for the second period will be based on months that already indicate the beginning phase of a significant decline. Such forecasts will thus be very much lower than those in previous periods. The list of products showing such trends is given in Table 9. Topical erythromycin had shown a similar pattern prior to the pandemic period, and so its inclusion in the list below may simply reflect the start of continuing supply disruptions unconnected with the pandemic, but none of the other products had shown significant declines in the months following October 2019.

Table 8: Significant changes in supply of medicines pre and post pandemic period by product in Francophone African countries alone

		Significant increase in supply disruptions between pandemic and pre-pandemic periods	
		6 Prior Period Test	**Immediate Prior Period Test**
	All Product	NS	Sig.(p<0.05)
INDIA EXPORT BAN	Erythromycin | Oral Liquid	NS	Sig.(p<0.05)
	Metronidazole | Oral Liquid	NS	Sig.(p<0.05)
	Paracetamol | Oral Liquid	Sig.(p<0.05)	Sig.(p<0.05)
	Paracetamol | Rectal	Sig.(p<0.05)	Sig.(p<0.05)
	Tinidazole | Oral Solid	NS	Sig.(p<0.05)
	Erythromycin | Topical	Sig.(p<0.05) *(but improved)*	Sig.(p<0.05)
ESSENTIAL MEDICINES (NO EXPORT BAN)	Aciclovir | Oral Solid	Sig.(p<0.05)	Sig.(p<0.05)
	Methylprednisolone | Parenteral	Sig.(p<0.05)	Sig.(p<0.05)
	Valproic acid | Oral Liquid	Sig.(p<0.05)	Sig.(p<0.05)
	Digioxin | Oral Solid	Sig.(p<0.05) *(but improved)*	NS
	Oxytocin | Parenteral	Sig.(p<0.05) *(but improved)*	NS
	Pyridoxine#thiamine | Oral Solid	Sig.(p<0.05) *(but improved)*	NS

Table 9: Products in Francophone Africa and Kenya showing significant declines in two consecutive periods

CATEGORY	COUNTRY	MOL+FORM
India export ban	Benin	Erthyromycin | Topical Metronidazole | Oral Liquid Paracetamol | Rectal
India export ban	Cote d'Ivoire	Metronidazole | Oral Liquid Orinidazole | Oral Solid Paracetamol | Rectal
India export ban	Kenya	Paracetamol | Oral Liquid
India export ban	Togo	Paracetamol | Rectal
Essential medicines (no export ban)	Congo	Fluoxetine | Oral Solid Oxytocin | Parenteral
Essential medicines (no export ban)	Guinee	Methylprednisolone | Parenteral
Essential medicines (no export ban)	Kenya	Methylprednisolone | Parenteral
Essential medicines (no export ban)	Niger	Valproic acid | Oral Liquid

Discussion

Models were built that could identify products notified by manufacturers as being in shortage in Germany and in Canada. The models were designed to detect actual values significantly below those forecasted for one and two months into the future. Models were refined to limit the identification of products to only those that had declined to a similar extent or duration as those that had been notified as being in shortage.

The best performing model, the ETS model, was then applied to routine sales data on 60 products collected from private sector panels by IQVIA in 22 low income countries. These 60 products fell into two categories – those directly affected by the Indian export ban and those not affected directly by the export ban but forming a subset of Vital Essential Medicines. The model was used to test the hypotheses that supply disruptions in the private sector would be more common in the period immediately following the introduction of export bans, and that products directly affected by the export ban would be more severely affected than others.

It is clear from the results that the model detects a significant increase in supply disruption following the introduction of export bans and movement restrictions. Products directly affected by the Indian export ban appear to be more consistently disrupted than others, although both sets of products (i.e. those directly affected by the Indian export ban and the subset of Essential Medicines) showed significant disruptions in the aggregate and in particular countries.

The model was built to identify products in shortage and constrained to limit the identification of products to those that had declined to a similar extent or duration as those that had been notified as in shortage. That the model has now also been shown to detect significant effects at both country and molecule level in the pandemic period is indicative that the model can be used to provide signals suggestive of supply disruption. Of course, significant declines may not be caused by shortages alone. Reduced access to certain health facilities may also cause significant declines in volume, although it may be that the effects of declining demand would take somewhat longer to filter through the supply chain.

From our analyses, it is clear that analyses carried out at regional or molecule level will mask evidence of supply disruptions. Countries appear to vary in terms of the extent of supply disruption, even within the same region. Thus 6 countries in Francophone Africa showed disruptions, while 6 did not. Similarly, Mexico showed disruptions while Peru did not. Similarly, not all product formulations were equally affected.

Further work is needed, however, if the model is to be used to determine at what point it can be said that shortages have been resolved. The model will tend to advance the resolution in time. This is because the forecast for next period following a significant decline will incorporate that decline into future forecasts. Future forecasts will thus tend to be much lower than for prior periods. As such, actual values may remain at the same low levels but appear to be “above” the next forecast. Similarly, extension of the model (or ones like it) to other countries and to a wider set of countries would be dependent on the availability of monthly data that is relatively stable. Monthly (or more frequent) data are required if disruptions are to be detected quickly, and to provide a sufficient number of data points that adequately reflect seasonality or other routine trading patterns. Relatively stable data are required because, otherwise, confidence intervals will be very wide (so masking shortages) and/or because, with very variable data, “normal variability” may look very similar to a shortage. As a rule, a requirement for relatively stable data will tend to mean that the further down the supply chain data are collected the better. This is because upstream records (e.g. import data, export data or supplies into, as opposed to issues from, central medical stores) tend to involve large quantities, infrequent deliveries or issues.

Nonetheless, from all of the above, it appears that the model can be used to detect significant disruptions in pharmaceutical supplies. In the current environment, and given the above analysis, it is tempting to attribute all disruptions to shortages brought on by the COVID-19 pandemic. Disruptions may, however, result from other causes, and some of these causes may relate to falls in demand rather than in production. Our model can be extended to other countries or products where monthly sales data are available from either the public or private sector, but it should be remembered that such signals of disruption will need further investigation so that the cause, and, thus, the solution, can be determined.

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