The world needs pharmaceuticals from China and India to beat coronavirus

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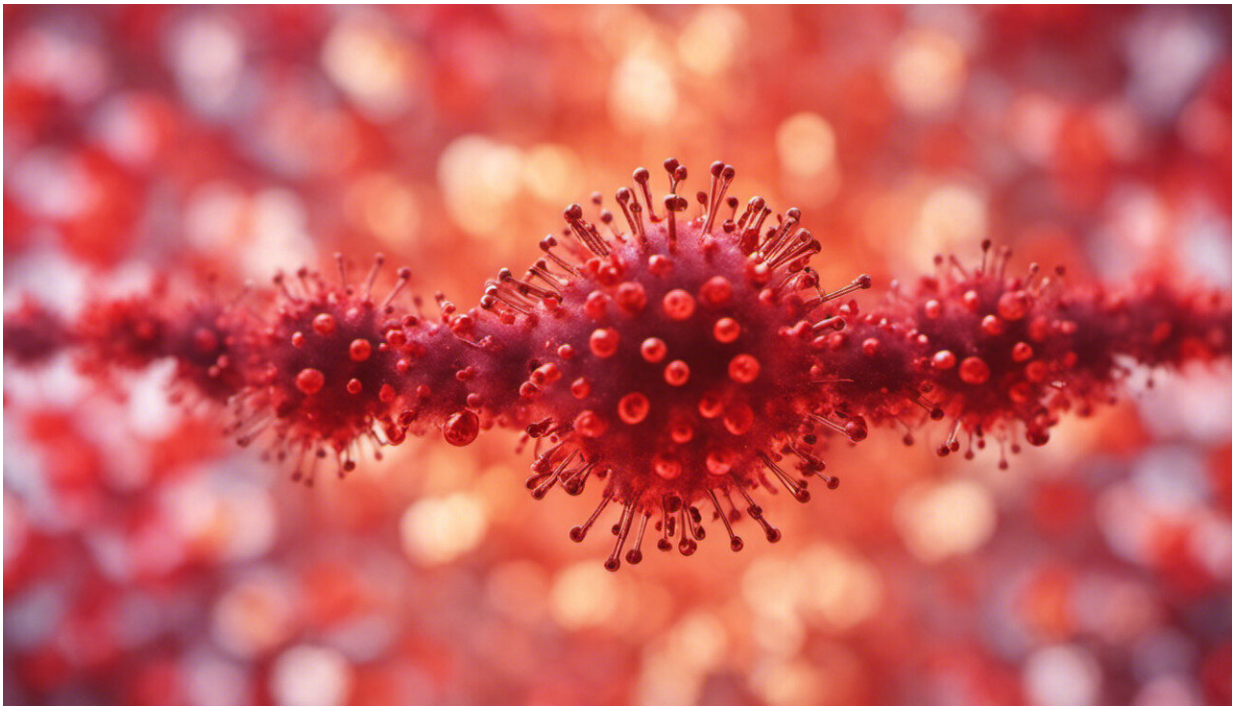

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The biggest pharmaceutical companies in the world, known as "big pharma", are American and European. The top five are Pfizer (US), Roche, Novartis (both Swiss), Merck (US) and GlaxoSmithKline (UK). Yet these companies—and the pharmaceutical industry as a whole—rely on global supply chains. And China and India play key roles in the

supply of both ingredients and finished drugs.

Hopes for a vaccine or a medicine that will treat COVID-19 rest on this crucial sector. Yet the globalisation of pharmaceuticals and what some see as an over-reliance on products from China and India has been criticised in the US, the UK and the European Union.

Whether it be hydroxychloroquine (the "miracle" drug Donald Trump has admitted to taking), remdesivir (an antiviral drug used as an emergency treatment for the most acute cases of COVID-19) or a future vaccine, the physical as well as social and economic health of the world depends on pharmaceuticals. Production from China and India will be crucial if the pandemic is to be brought under control.

The supply chain

The pharmaceutical manufacturing supply chain involves two main stages. The first is the production of active pharmaceutical ingredients (APIs). These are the key parts of a drug which produce an effect. Such production is chemical-intensive, involving reactors for drug substance manufacture. The second stage is a physical process known as formulations production. Substances known as excipients are combined with APIs to turn a drug into a consumable form, such as a tablet, liquid, capsule, cream, ointment or injectable product.

For more than a decade now, China has been the largest producer of APIs in the world. The US, Europe and Japan produced 90% of the world's APIs until the mid-1990s. But now it is estimated that Chinese manufacturers make around 40% of all APIs used worldwide and that China and India are the source of 75% to 80% of the APIs imported to the US. Janet Woodcock, the director of the Centre for Drug Evaluation and Research at the US Food and Drug Administration (FDA), told Congress in 2019: "The number of Chinese facilities producing APIs for

the US market has increased over the past decade, as part of a massive movement of pharmaceutical production offshore. This movement is being driven by the pharmaceutical industry's desire for cost savings and less stringent environmental regulations."

Pharmacy to the developing world

India plays a prominent role in the formulations segment of the industry. India is the third largest producer of pharmaceuticals in the world by volume. The country's Department of Pharmaceuticals reported that it supplies 20% of global exports of "generic" drugs. These are drugs that are no longer under patent and are open to any company to produce and sell, and are thus usually priced at a relatively low level. India has the largest number of FDA approved plants outside the US and it is estimated to supply 40% of the generic formulations in America.

It was the absence of product patents in pharmaceuticals from 1972 to 2005, combined with foreign investment restrictions in the 1970s and 1980s that led to the development of a rare and successful manufacturing industry in India—a country more known for its services role in the global economy.

India is also the major supplier of medicines to countries in the global south. This led the humanitarian organisation Médecins Sans Frontières to dub the country the "pharmacy to the developing world". Yusuf Hamied, then managing director of Indian pharmaceutical company Cipla, announced in 2001 that his firm would provide a year's supply of anti-retroviral medicines for US$350 a year (and is now less than US$100 a year) – a fraction of the US$10,000 they had been provided for until that point in time by American and European companies.

Indian companies, led by the likes of Cipla, Aurobindo, Emcure, Hetero, Macleods, Matrix, Ranbaxy and Strides have played an enormous role in

supplying anti-retroviral and anti-malarial medicines to the Global Fund to Fight AIDS, TB and malaria.

India is also a major vaccine producer. While the largest vaccine manufacturers in the world (in revenue terms) are GSK, Sanofi, Merck and Pfizer, India's Serum Institute is the world's largest vaccine producer by volume.

The Pune-based company makes 1.5 billion doses a year, 80% of which are exported and is UNICEF's largest vaccine supplier (US$307.8 million worth in 2018). India also produces 65% of the World Health Organization's requirement of DPT (diphtheria, pertussis and tetanus) and tuberculosis, as well as 90% of its measles vaccines.

Fear of dependence on China

This globalisation of the pharmaceutical industry has led to fears of over-reliance on particular sources of supply, especially China, for APIs. Such concern has been particularly prominent in the US. Last year a representative of the Defence Health Agency argued that "the national security risks of increased Chinese dominance of the global API market cannot be overstated".

The state of America's reliance on China for pharmaceuticals was documented in a book by health researchers Rosemary Gibson and Janardan Prasad Singh which highlighted that the last manufacturing plant for aspirin in the US closed in 2002, while the last acetaminophen (paracetamol) manufacturing plant in Europe closed in 2008.

India also gets most of its APIs from China—an issue of concern for its government, which has had a task force investigating this issue. The country once had considerable self-reliance in production of APIs, dating back to the establishment of two state-owned pharmaceutical

companies in the 1950s and 1960s. But in recent decades there are stricter environmental controls, which many believe has limited this aspect of the industry in India. China also has cheaper land, electricity and higher volumes of production.

So now India relies on China for about 70% of its supply of APIs. And for some well known drugs, such as paracetamol, amoxicillin and ibuprofen, India is almost 100% dependent on China.

While the US, Europe and India have worried about over-reliance on China, Africa is most dependent of all on the global pharmaceutical supply chain. Effectively all APIs and 80-90% of the finished medicines consumed on the continent are imported – mostly from India.

There has been significant concern for some time regarding the globalised nature of the pharmaceutical industry and its vulnerability, even before the pandemic. Gibson and Singh explicitly articulated fears over the potential implications of this in their 2018 book China Rx:

"The centralisation of the global supply for essential ingredients for drugs in China makes it vulnerable to interruption, whether by mistake or design. If disruptions occur for an essential ingredient made in China, the United States will wait in line along with Europe, India, and other countries to obtain it. If a global public health crisis occurs, China will likely keep its domestically produced medicines at home and stockpile them to secure access for its citizens before seeing to the needs of other nations."

Those were the fears before COVID-19, yet China has not acted in this way so far. And most of India's export bans have been rescinded. However, the tensions between nationalism and globalisation have plagued the initial search for treatments.

Miracle drugs and geopolitics

Although China did not initiate an export ban on pharmaceuticals, tensions escalated in early March when India's Ministry of Commerce and Industry announced restrictions on the export of 13 APIs including paracetamol, tinidazole, vitamin B1, B6 and B12, as well as any formulations made from those APIs. Reports emerged about concerns over drug shortages elsewhere in the world as a result, with European industry said to be "panicking".

The Indian government also moved to address its own reliance on supply of APIs from China. On March 21, they announced a US$140m scheme, involving support for three bulk drugs parks as well as the manufacturing of 53 priority APIs, to "reduce … dependency on other countries for bulk drugs".

Tensions escalated as hydroxychloroquine (and a similar drug chloroquine) emerged as a potential treatment for COVID-19. Long established as an anti-malarial, but also used for treating rheumatoid arthritis and lupus, research from the Méditerranée Infection University Hospital Institute in Marseille found a significant reduction of the viral carriage in 20 COVID-19 cases treated with the drug.

On March 14, the UK announced an export ban on hydroxychloroquine. Then, Donald Trump began touting it as a "game-changer". The space and electric car entrepreneur Elon Musk also joined the hype.

Although US-based Mylan announced it would restart production of hydroxychloroquine in West Virginia, it was clear America and much of the world would require supply from India if this drug was to be effective in treating the disease.

India is estimated to produce 70% of the world's hydroxychloroquine,

with Ipca Labs and Zydus Cadila the two largest producers of the drug in the country. Ipca Labs accounts for more than 80% of India's hydroxychloroquine supply, yet there was a problem for the US here.

The FDA had restricted Ipca's exports from some of its facilities to the US, arising from problems found in quality control checks from 2014 onwards. But with hydroxychloroquine attracting such attention, the US lifted its ban on supply on March 23.

The Indian government, however, wanted to ensure it had sufficient supply for its own domestic needs. On the same day India's National Task Force for COVID-19 recommended hydroxychloroquine for treating high-risk cases. Two days later, India's Ministry of Commerce and Industry prohibited the export of the drug and formulations made from it, with exceptions (such as where pre-existing commitments had been made, as well as on humanitarian grounds).

But then doubts about hydroxychloroquine's effectiveness at treating COVID-19 began to emerge as the International Society of Antimicrobial Chemotherapy—which houses the journal where the Marseille-based research was published – criticised the study. Yet, on April 4, India banned the export of hydroxychloroquine without any exception.

President Trump didn't take long to respond. At his White House press conference on April 6, he warned "there may be retaliation" if India didn't supply hydroxychloroquine to the US. Just a day later, India's complete export prohibition was lifted. Supply would be allowed to more than 20 countries on a commercial and humanitarian basis. World leaders including Trump, Benjamin Netanyahu and Jair Bolsonaro all thanked Narendra Modi, the Indian prime minister.

Searching for medicines and vaccines

While the effectiveness of hydroxychloroquine is still hotly contested, the tribulations over the drug are an insight into some of the challenges to be overcome in fighting the virus.

Efforts to develop a vaccine are well under way yet projected to take considerable time, so the search continues for repurposed drugs to treat and reduce deaths from the disease. Having China and India involved as manufacturing partners for any treatment or vaccine will be vital given their unparalleled ability to produce in high volumes and cost effective economies of scale.

Manufacturing capabilities are also present in China and India for two other potential treatments. Favipiravir, normally used to treat influenza, was approved in China and Italy for experimental use against COVID-19 in March 2020. By late April, it was reported that Mumbai-based Glenmark had developed the API in-house and was applying for regulatory approval for its use against COVID-19. And another Indian firm, Strides, also announced it had commercialised and begun exporting favipiravir to a number of countries in the Middle East.

Meanwhile remdesivir (owned by US firm Gilead Sciences) has been authorised by the FDA to treat COVID-19 in emergency cases.

As early as mid-February, Gilead partnered with the China-Japan Friendship Hospital and the Chinese Academy of Sciences for human trials of remdesivir in Wuhan. A Chinese company quickly manufactured the API for remdesivir and by the end of March a total of five Chinese companies and the Taiwanese National Health Institute announced they had the capacity to produce the drug.

Patent barriers?

Remdesivir is distinct from the other drugs which have attracted attention as COVID-19 treatments so far in that Gilead has a patent for it, raising serious concerns of intellectual property issues restricting access to medicines or vaccines. Since mid-April, various Indian pharmaceutical companies had already begun developing remdesevir, as has Bangladeshi company, Beximco.

Facing a public health emergency, global trade rules permit governments to issue a compulsory license. Such a provision allows a manufacturer to produce a medicine without the permission of the patent holder, who is paid a royalty fee instead. A variety of countries including Chile, Ecuador, Israel, Canada and Germany have all moved to make it easier to issue a compulsory license, if needed, for COVID-19.

Perhaps anticipating such a move, Gilead announced on May 12 that it had issued voluntary licensing agreements for remdesevir to one company in Pakistan (Ferozsons Laboratories) and four in India (Cipla, Hetero Labs, Jubilant Life Sciences and Mylan). The deal would involve transfer of technology and allow the five companies to make remdesevir for subsequent distribution in 127 countries, primarily in the global south .

Gilead has agreed a deal with these five generic companies to manufacture and supply this drug on which so much hope has been placed. Gilead has also entered discussions with the Medicines Patent Pool—a UN backed agency which tries to increase access to treatments for HIV/AIDS, hepatitis C, and tuberculosis. It has now expanded its remit to include "any health technology that could contribute to the global response to COVID-19".

Global public good

Any prospective vaccine faces a challenge of not just being effective,

but also requiring enormous manufacturing capacities to reach the majority of the world's population.

As of late May, more than 224 COVID-19 vaccine candidates are in development around the world, according to the Coalition for Epidemic Preparedness Innovations. While 42% are in North America, six of the ten which have already progressed to human trials are being developed in China. Many hopes are riding on a vaccine candidate at the University of Oxford, which began human trials on April 24. AstraZeneca has been given the worldwide development, marketing and distribution licensing rights for the vaccine. The UK company has also received more than US$1 billion in support for the vaccine from the US Biomedical and Advanced Research Authority. And AstraZeneca is in discussions over increasing production and distribution with India's Serum Institute, which has already been involved in collaborations with Oxford on the vaccine.

In addition to its involvement with the Oxford vaccine, Serum Institute is also working with the US-based Codagenix to develop a vaccine. Other manufacturers in India trying to develop vaccines include Bharat Biotech (with University of Wisconsin-Madison and FlyGen), Zydus Cadila, Biological E, Indian Immunologicals and Mynvax.

Given the chance of re-infection (unless billions of people are inoculated) any effective vaccine must be manufactured at considerable scale, a task which would benefit considerably from Chinese and Indian involvement. Ngozi Okonji-Iweala (Board Chair of Gavi, the Vaccine Alliance, and WHO Special Envoy on Global Collaboration to fight COVID-19) has warned: "It is the duty of every government to put its citizens first, but during a pandemic this duty also requires thinking and acting globally. If manufacturing agreements or export restrictions impede the deployment of vaccines and allow the virus to survive anywhere, nowhere can be safe from reinfection."

On May 4, a number of countries and global health organisations committed €7.4bn for a coordinated approach to COVID-19 through the development of vaccines, treatments and diagnostics. Notably, while China, the UK and several major European countries participated, the US, Russia and India were absent.

A lot depends, of course, on whether China and India share the products of their manufacturing with the rest of the world. India's restrictions on exporting key drugs in March (albeit later rescinded) are a worrying sign of things that may be to come. Recent history from mitigating the impact of HIV-AIDS demonstrates the huge benefits for global access to medicines when India is involved. The all-time high for AIDS deaths in the U.S. was in 1995. But for the world as a whole, mortality from HIV only fell from the mid-2000s, when anti-retrovirals became more widely available in the global south.

In contrast to some of the doomsday fears of what might happen amid a global public health crisis, China has not yet issued any restriction or ban on export of medical goods. Although often framed in the US as an unhealthy dependency on China, what is often overlooked is that China also relies on the US and major European countries for some of its medicines. In 2019, Germany was the largest source of China's medicine imports, followed by France, the US, Italy and Sweden. Much of China's anti-cancer drugs are imported. This inter-dependence in pharmaceuticals, rather than dependence, means China may not be as quick to putting up a seal around its border as some thought.

Confounding fears of "vaccine nationalism", China's President Xi Jinping announced at the World Health Assembly on May 18 that "COVID-19 vaccine development and deployment in China, when available, will be made a global public good, which will be China's contribution to ensuring vaccine accessibility and affordability in developing countries".

The dependencies and inter-dependencies of globalisation have been exposed by the COVID-19 pandemic—and nowhere more so than in the pharmaceutical industry. We don't yet know how the medicine and vaccine challenge will end. Whether it be hydroxychloroquine, favipiravir, remdesivir or something else, it is unclear which drug, if any, will work. It may be a vaccine. While it may be an American company or an Oxford lab that is hailed as a hero for a treatment or prevention, the task is not just about discovering a treatment or vaccine that works, but making it available to as many people as possible in as short a time as possible. Successful accomplishment of that task—especially in the global south—is difficult to envisage without Chinese and Indian involvement. COVID-19 ignores borders and the solutions to address it will need to overcome them too.

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