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Cite this as: *BMJ* 2021;375:n2375<http://dx.doi.org/10.1136/bmj.n2375>

Published: 28 October 2021

Covid-19: global vaccine production is a mess and shortages are down to more than just hoarding

Vaccination efforts around the world are being restrained by a shortage of doses. **Jane Feinmann** looks at what is holding up the process

Jane Feinmann *freelance journalist*

In March 2021 drug manufacturers predicted that 12 billion doses of covid-19 vaccine, enough to fully immunise at least 70% of the world's population, could be manufactured by the end of the year.¹ That assessment was confirmed in September in a report by the International Federation of Pharmaceutical Manufacturers and Associations,² though it also warned that “most doses in the production queue are already allocated” to high income countries.

At the time of writing, only 1.3% of people in low income countries have received their jabs. Seventy countries have yet to vaccinate 10% of their populations, and 30 countries—including much of Africa—have vaccinated fewer than 2%.³ In Latin America, only one in four of the population has received a dose of covid vaccine.

The solution widely canvassed in high income countries is redistribution. The United States, United Kingdom, European Union, and Canada could have 1.2 billion doses available for redistribution by the end of the year. A spokesman for Pfizer has told *The BMJ* that the company will provide one billion doses to low and middle income countries in 2021 and a further billion in 2022—with “500 million doses at the not-for-profit price.”

But health experts from low and middle income countries remain unimpressed. They are demanding a more permanent and fundamental overhaul of vaccine production. Carissa F Etienne, director of the Pan American Health Organisation, has pointed to the urgent need “to build the infrastructure and technical capacity to break the cycle of dependency on a highly concentrated global vaccine market.”⁴

African leaders are also angry. “How can a continent of 1.2 billion—projected to be 2.4 billion in 30 years, where one in four people in the world will be African—continue to import 99% of its vaccines?” asked John Nkengasong, the virologist who heads the Africa Centres for Disease Control and Prevention in Addis Ababa, at a press conference in early 2021. Cyril Ramaphosa, president of South Africa, has said, “We just cannot continue to rely on vaccines that are made outside of Africa, because they never come.”

But why is the manufacturing of vaccines so uneven in the first place?

Basic ingredients

Essential kit for making vaccines has been in short supply—and this has exposed how the chain is reliant on a handful of countries. The kit includes filters, plastic pipes, and most importantly the giant sterile bags needed to grow the cells for all vaccines inside large vessels called bioreactors.

Bioreactor bags are mainly supplied by a German company, MilleporeSigma, a division of Merck, itself reliant on a web of small suppliers. Throughout 2021, extraordinary demand for these bags left vaccine manufacturers unsure whether supplies would continue “threatening global vaccines rollout.”⁵

Each vaccine consists of up to 200 components, including niche products suddenly in demand in unprecedented quantities affecting all markets. Lipid nanoparticles, the delivery technology crucial to introducing fragile mRNA molecules to human cells, were sold in gram quantities until Spring 2020. Then they were suddenly urgently in demand by the hundreds of kilos for mRNA based vaccines such as Pfizer-BioNtech's (fig 1).

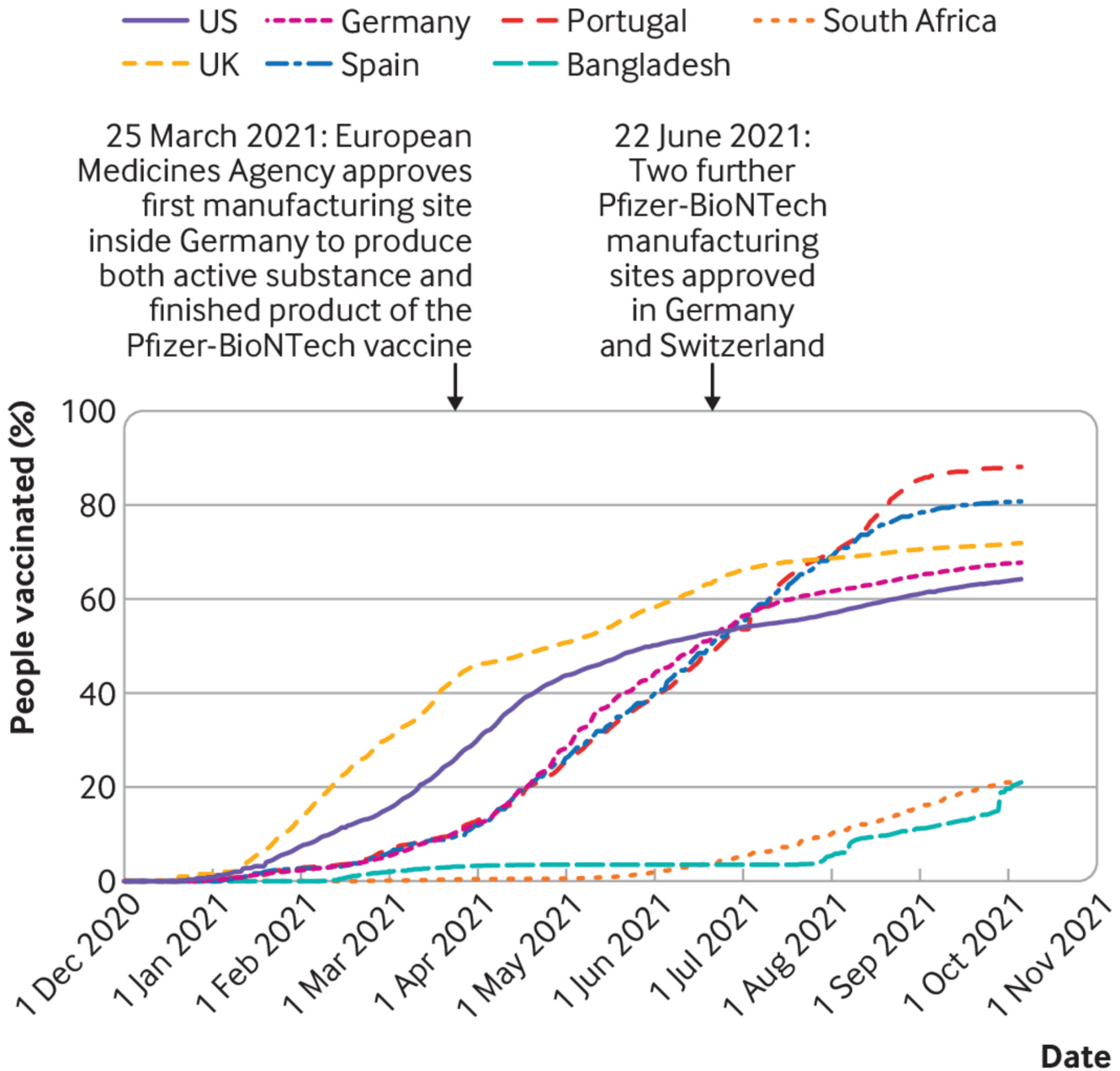


Fig 1 | The total percentage of people who have received at least one dose of (any) vaccine in each country from 1 December 2020 to 1 October 2021.

“It was a scale-up that hadn’t been done before,” says Pieter Cullis, chair of Acuitas, the British Columbian manufacturer. Lipid nanoparticles were identified as an urgent gap in the vaccine supply chain by US President Biden’s administration in January 2021, his second day in office. By June, Acuitas was contracting out manufacture. Pfizer now has a five year lipid supply agreement with the London listed company Croda, which has quadrupled production at its UK site to meet demand.⁶ Another company, CordenPharma in the US, supplied lipid nanoparticles to Moderna for its mRNA vaccine and has announced a major expansion of its facilities in Switzerland and France as well as Colorado.⁷ None of these manufacturers are outside Europe or the US.

Non-mRNA vaccines have also been affected by component issues. The Novovax vaccine uses a laboratory made version of the Sars-CoV-2 spike protein that requires a crucial ingredient, saponin,

an extract of the rare Chilean soapbark tree, previously used for root beer and Slurpees.⁸ Shareholders have worried throughout 2021 that problems in harvesting the tree might contribute to continuing repeated delays in rolling out the vaccine.

Global supplies of AstraZeneca’s covid-19 vaccine—the workhorse of the World Health Organization led global vaccine alliance supplying the bulk of doses to low and middle income countries around the world—have been hit by a shortage of serum for the vaccine. AstraZeneca has several of its own plants, as well as those of subcontractors, making serum and other components across Europe. But *Politico* reported that a plant in the Netherlands wasn’t producing enough to be included in the company’s application for approval to European regulators at the end of December 2020.⁹ An emergency import of serum from the US—more than half the amount

required, according to *Politico*—could not prevent a knock-on effect to 2021 vaccine stocks.

Local supply first

Vaccine manufacturers have attempted to reduce bottlenecks by exporting to low and middle income countries before the final manufacturing step: putting vaccine into vials, known as fill and finish. By March 2021, the global covid vaccine alliance Covax had drawn up a list of several hundred facilities worldwide that fill vials with injectable drugs including insulin, monoclonal antibodies, and antibiotics and could also fill and finish covid-19 vaccine vials.¹⁰

A more powerful practice—“local supply first”—has had a more substantial effect. The Biden administration maintained the previous policy of “America first” in regard to vaccine distribution.¹¹ This policy was cited by pharmaceutical experts as the reason why Germany required its own manufacturing facilities for the Pfizer-BioNTech vaccine, approved by the European Medicines Agency on 26 March 2021.¹² AstraZeneca, with Covax, set up licensing agreements to fill and finish its vaccine with several regional manufacturers, notably the Serum Institute in India, one of the largest drug companies in the world—with an agreement to be the major supplier of vaccines to Africa.¹³

But this agreement meant nothing when India was hit by its second wave of covid-19. The Indian government blocked the export arrangement so it could keep stocks made in its borders for domestic supply—a move only recently reversed.¹⁴

Meanwhile 40% of 10 million doses of Johnson & Johnson vaccines, filled and finished by Aspen Pharmaceuticals in South Africa, were being sent to Europe under a “gentleman’s agreement,” while South Africa was desperate for stocks. This agreement was rescinded only after a backlash.¹⁵

“Every country wants to vaccinate their own people first, indeed they have a duty to do so,” says Stephen Morris, research fellow in vaccine process analytics at University College London’s Department of Biochemical Engineering, “That inevitably means that countries with existing drug or vaccine manufacturing experience will have among the highest rates of vaccination.”

Manufacturing infrastructure

In April, the African Vaccine Manufacturing Summit pledged to ramp up capacity in manufacturing vaccines to be used on the continent from 1% to 60% by 2040.¹⁶ A *Nature* investigation found that manufacturing capacity already exists in Senegal, Tunisia, Cape Town, and Algiers, with Nigeria and Ethiopia planning to increase capacity. India and Indonesia are also making hepatitis B vaccine using recombinant protein, which is “a well established production methodology currently in late stage clinical trials for covid-19,” says Morris.

Much has been made of intellectual property and patent issues (box 1), but more local efforts are already moving vaccine manufacture outside the US and Europe in a way that hasn’t happened before. Perhaps surprisingly, the cutting edge mRNA vaccines are the likeliest candidates to establish new production lines in low and middle income countries. “Once the technology transfer has taken place, it’s possible to set up a plant for mRNA faster than for viral vector vaccines,” says Morris.

Box 1: mRNA vaccines waiver

Access to mRNA covid-19 vaccines in low and middle income countries—potentially saving millions of lives—could at least partly depend on a battle over patents.

It’s happened before: in the decade that the first HIV drugs turned AIDS into a manageable condition in the United States, other countries (South Africa and India) had to take to international courts for the right to make affordable generic versions of drugs still under patent.

Their target was the Trade Related aspect of Intellectual Property Rights (TRIPS) agreement, a 1994 World Trade Organization (WTO) accord that prevents the copying of technologies developed in economically advanced countries and was widely recognised almost from the start to work against public health.

India and South Africa won the case. In 2001, the WTO announced the Doha Declaration¹⁷ calling for “flexibility” in intellectual property protection to ensure that TRIPS be “part of the wider national and international action to address public health problems afflicting developing countries and least developed countries.”

The declaration was back in the spotlight in October 2020 as India and South Africa again called on WTO to temporarily waive TRIPS, this time to “unleash a cascade of production [of covid-19 vaccines as] a vital and necessary step to bringing an end to this pandemic.”¹⁸ This time, patents protecting not just the vaccine blueprints but also vaccine components would need to be shared generously.

US President Biden has backed a call from over 60 former heads of state and over 100 Nobel prize winners for a TRIPS waiver.¹⁹ But with mRNA vaccines proving so successful and opening up possibilities for other non-covid applications, BioNTech (the company that developed the Pfizer-BioNTech vaccine) and its homeland Germany are unwilling to waive intellectual property rights that could open up competition, including to China and Russia. Reuters reported that the company’s value is such that it could lift the German economy by 0.5% on its own this year.

The German stance is entirely justified according to the UK government, which has stated: “a waiver of the TRIPS agreement would risk undermining [the drug industry’s] ability to respond to current—and potentially future—crises.”²⁰

Vickie Hawkins, UK executive director of Médecins Sans Frontières, disagrees. “Massive public investment—over £7bn on the development and manufacture of the six front runner vaccine candidates—and not the [intellectual property] system has been the incentive for innovation during the pandemic,” she wrote in a letter to the UK prime minister in May. A TRIPS waiver, she says, would be a first step in enabling vaccine manufacturers to “engage in technology transfer with other capable manufacturers in low and middle income countries . . . to allow for the scale-up and diversification of global manufacturing capacity to better meet the demands of this pandemic.”

With patents being agreed with individual countries, some experts point out that there are no patents on mRNA vaccines in any African country. This means that an mRNA hub would not need direct transfer of technology from Pfizer-BioNTech or Moderna, as “enough information on production process is available publicly,” Marie-Paule Kieny, chair of the board of the medicines patent pool in Geneva and president of the French scientific committee on covid-19 vaccines, said after a recent visit to South Africa.²¹

The main barrier to expanding capacity is “the know-how required for complex and sensitive vaccine manufacturing rather than the patents per se,” according to Germany’s health minister Jens Spahn.²² That’s a more complex issue. Zoltan Kis, research associate at the Future Vaccine Manufacturing Hub in the Department of Chemical Engineering at Imperial College, London, says there just aren’t enough production and quality control experts in the industry that are familiar with and qualified for producing these new vaccines. “With intellectual property coming in the form of trade secrets and know-how, the active involvement of the technology originators would be required for the successful rapid transfer of the technology to low and middle income countries,” he told *The BMJ*.

“With traditional vaccines, you need a big factory to make the protein or the virus, and it takes a long time to grow them,” explains Robert Langer, the David H Koch Institute professor at Massachusetts Institute of Technology and one of the founders of Moderna, in a December 2020 interview.²³

Growing cell lines can take months, says Morris, and tiny variations in the process can make all the difference to quality and yields. In February 2021, filtration problems at a plant in Seneffe, Belgium, with a contract to produce covid-19 vaccine for European countries reduced production by 75 million doses leading to a major row between AstraZeneca and the EU. The beauty of mRNA is that you don't need to worry about that, says Langer. "If you inject nano-encapsulated mRNA into a person, it goes into the cells, and then the body is your factory. The body takes care of everything else from there."

In July, Pfizer-BioNTech announced that it was collaborating with the South African biopharmaceutical company Biovac, with plans to produce 100 million doses of their mRNA vaccine annually from 2022 and for "all doses [to be] exclusively distributed within the 55 member states that make up the African Union."²⁴ In August, Brazilian company Eurofarma signed an agreement with Pfizer-BioNTech to part manufacture its mRNA vaccine, the companies' first expansion into Latin America.²⁵

A spokesperson for Pfizer told *The BMJ* that the company is "actively working with governments all around the world towards fair and equitable access to covid-19 vaccines, while also providing our expertise and resources for novel approaches that can help to strengthen healthcare systems where greater support may be needed."

A Bangladeshi company, Incepta, which already produces several non-coronavirus vaccines for export, is one of several candidates to have sought licences to manufacture mRNA vaccines currently produced by Pfizer-BioNTech.²⁶ "If the antigen was provided, production could start immediately, filling vials for about 500 million doses a year," Abdul Muktadir, chair of the Incepta, told Geneva Health Files in March.²⁷ So far, Pfizer has refused Incepta's approaches. A spokesperson declined to say why when asked.

Zahid Maleque, health minister for Bangladesh, has also asked AstraZeneca to provide their technology "so that we can produce

the vaccine locally,"²⁸ acknowledging the need to "establish required facilities and employ skilled technical [people]." To make use of such facilities would still require countries to spend hundreds of millions of dollars expanding research capacity and setting up regulatory bodies that meet international standards, as well as commitments from governments to purchase the vaccines and set up the supply chains necessary to feed manufacturing.

Back in July, the Coalition for Epidemic Preparedness Innovations (CEPI), which funds vaccine development and helped set up Covax, announced the Covax marketplace, an online innovation matching global suppliers to global vaccine manufacturers for the most critical categories, notably bioreactor bags, cell culture media, filters, lipids, vials, and stoppers. CEPI emphasises that this is a short term objective, part of its longer term \$3.5bn (£2.5bn; €3bn) investment plan to enable low and middle income countries to "take full ownership of their national health security." What is needed long term, they say, is local manufacturing of components and stages in the manufacturing process to expedite access to urgently needed vaccines for populations living in locations remote from the main manufacturing plants.

Jeremy Farrar, director of the Wellcome Trust, one of CEPI's funders, told *The BMJ* in February that "local access may depend on having more local manufacturing hubs, not only for vaccines but also essentials like dexamethasone and [personal protective equipment], down to the vials that you put vaccines into." He added, "This may create opportunities, as well. Countries with small populations but good manufacturing capacity will have opportunities in global as well as domestic supply: Singapore, Denmark, Senegal, or Ecuador, for example."²⁹

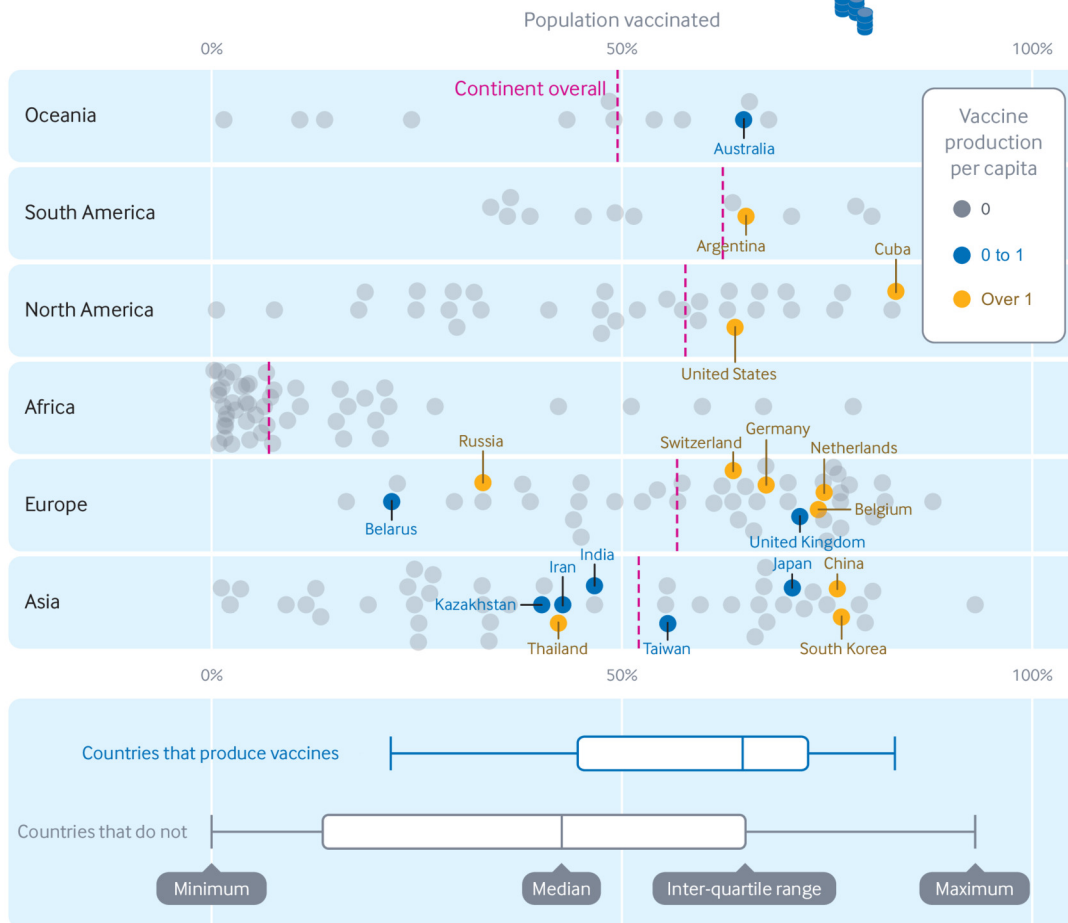
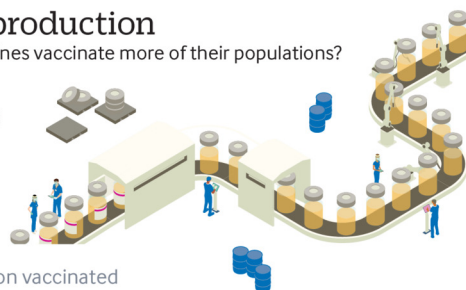
The International Federation of Pharmaceutical Manufacturers and Associations says that the drug industry's current production rate of 1.5 billion doses per month means that over 24 billion doses of covid vaccines could be produced by June 2022.³⁰ Ensuring they are made where they are needed is the next challenge.

thebmj Visual summary

Covid-19 vaccine production

Do countries that produce vaccines vaccinate more of their populations?

A country's covid-19 vaccine manufacturing base is now seen as a key factor in its ability to vaccinate its population. The US policy of applying "America first" to covid-19 vaccines has spread across the world, putting countries that lack a manufacturing base at a serious disadvantage. In the visualisation below, each country is represented as a circle. Its horizontal position represents the percentage of that country's population that has been vaccinated as of 30 Sep 2021. Countries that produce covid-19 vaccines are highlighted in blue (for those with lower production) or yellow (for those with higher production).



On average, countries that manufacture vaccines have been able to vaccinate more of their population. It's true that wealthy countries are likely to have greater manufacturing capacity as well as greater buying power and more robust healthcare systems. But this is not the full story. Poor and middle income countries such as Cuba and Argentina produce

a large amount of vaccine and have vaccination rates comparable to high income countries. On the other hand, the continent of Africa and much of South Asia have no vaccine production and low rates of vaccination. This dataset supports demands for investment in vaccine manufacturing in low and middle income countries as opposed to the donation of doses.

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Data sources: Vaccine production data - science analytics company Airfinity. Vaccination rates - Our World in Data © 2021 BMJ Publishing Group Ltd.

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Provenance and peer review: Commissioned; not externally peer reviewed.

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

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