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The other side of Covid-19 vaccines: Is correct vaccine still under investigation?

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1. Introduction

After 2 years, the Covid-19 pandemic warns us that the current vaccination and therapeutic options are not effective enough in combating such infectious diseases. In this post-antibiotic era, we do believe that our current antibiotic and antiviral drugs were strong enough to control all kinds of diseases. In order to disrupt the chains of infection, and to stop/slow the spread of disease, "Herd immunity" should be achieved. "Herd immunity" refers to the way vaccines protect even those who are not vaccinated, by creating a shield of immune people around those who are susceptible [1,2]. Regarding the 'herd-immunity threshold', most estimates had placed the threshold at 60–70% of the population gaining immunity, either through vaccinations or past exposure to the virus [3].

Regarding the vaccination strategy, at present, the strange thing in most below countries as case studies for the current vaccines is that the number of infections increases daily after starting each mass vaccination, then the more injections the Covid-19 positive cases increase. It is difficult to explain when new SARS-CoV-2 variants have not appeared since the Delta variant last year. The decline in the protective effect of each vaccine over time (about 4 to 6 months after full dose) is unlikely to be a valid reason. It just only reflects the ineffectiveness of the current vaccines, although a typical flu vaccine has an efficacy of only 40- 60%. The most logical reason is "ineffective vaccination" or which might have weakened the immune system against the SARS-CoV-2.

Since the last year, the race to develop Covid-19 vaccines has been run at full pelt, the vaccine candidates urged on by fearful citizens and desperate governments worldwide. Finally, on 11 December 2020, Pfizer Inc. has been first across the finish line (approved by FDA, US Food and Drug Administration), followed by other big western rivals Oxford/AstraZeneca, Janssen, Moderna, Novavax. Now, Pfizer is on course to manufacture 3 billion doses this year and expects to produce 4 billion next year [4]. Besides, the world's biggest vaccine makers GlaxoSmithKline, Merck, and Sanofi have all failed to deliver Covid jabs at all. Meanwhile, both upstarts CureVac and Valneva, which had previously seemed set to make a potent contribution, are yet to deliver their vaccines to the market. In addition, recently CureVac abandoned its first attempt at a vaccine, but is pressing ahead with a "second generation" effort designed to provide "long-term protection against current and new variants in one vaccine". According to Geoffrey Porges, an analyst at SVB Leerink, the potential for rivals, especially

Sanofi, will come from behind soon. He thought that "I would never have predicted that they would have 60% market share but it's unlikely that will be sustainable" [4]. Currently, about 15 Covid vaccines are being used worldwide, but shortages in the supply of vaccines still have been a particular problem for low-income countries [5].

Back to the beginning of the Covid-19 pandemic, when the novel virus was first identified in the Chinese city of Wuhan in December 2019 [6]. On 24 December 2019, Wuhan Central Hospital sent a bronchoalveolar lavage fluid sample from an unresolved clinical case to sequencing company Vision Medicals. On 27 and 28 December 2019, Vision Medicals informed the Wuhan Central Hospital and the Chinese CDC of the results of the test, showing a new coronavirus. On 31 December 2019, the WHO office in China was informed of cases of pneumonia of unknown cause in Wuhan.

In early January 2019, Chinese scientists (a group led by Yong-Zhen Zhang, Fudan University) submitted the gene sequencing data for posting on Virological.org (a hub for prepublication data). The authors announced that they had isolated and fully sequenced the new virus. Since the release of the gene sequences, Dr. Vineet Menachery (University of Texas Medical Branch) said on Twitter that the new virus appears to be a group 2B coronavirus, which puts it in the same family as the SARS (severe acute respiratory syndrome) virus. Dr. Andrew Rambaut (the University of Edinburgh, administrator of Virological.org) said on Twitter that the new virus was 89% similar to SARS-related bat coronavirus in the Sarbecovirus group of beta coronaviruses. But that did not mean it came from bats. MERS-CoV was 88% identical to the nearest known bat virus, and MERS was endemic in camels [7]. Then, Health Organization (WHO) declared a Public Health Emergency of International Concern on 30 January 2020 (and a pandemic on 11 March 2020) [6]. Then, the race to develop Covid-19 vaccines starts.

In the case of Moderna, on 6 January 2019, Barney Graham (deputy director of the Vaccine Research Center, at the National Institutes of Health) got word through back channels that the new virus in China was probably a coronavirus, he reached out to Moderna's CEO, and urged Stephane Bancel, in favor of different proof of concept related to the Wuhan outbreak [8]. "If it's a SARS-like coronavirus, we know what to do," Graham wrote in his emails. "This would be a great time to run the drill for how quickly can you have a scalable vaccine." On Jan. 10, Graham finally got the news he'd been expecting: Chinese scientists had posted the genetic sequence for what they called the "Wuhan seafood market pneumonia virus." Then, on 19 February 2020, Moderna results from mouse studies hold promise. On 3 March 2020, the first volunteer (Jennifer Haller) agreed to the vaccine trial and received the first US vaccine on 16 March 2020 [8].

In the case of the Pfizer vaccine, the Clinical trials began in April 2020 [9]. For Oxford–AstraZeneca, in February 2020, the Jenner Institute agreed on a collaboration with the Italian company Advent Srl for the production of a batch of 1,000 doses of a vaccine candidate for clinical trials. But after the Gates Foundation urged Oxford to find a large company partner to get its COVID-19 vaccine to market, the university backed off of this offer in May 2020. The UK government then encouraged Oxford to work with AstraZeneca, a company based in Europe, instead of Merck & Co., a US-based company. Then, an initially not-for-profit licensing agreement was signed between the university and AstraZeneca PLC, in May 2020, with 1 billion doses of potential supply secured [10]. Regarding the Janssen (Johnson & Johnson) vaccine, the clinical trials were started in June 2020 [11]. Novavax started the clinical trial of its vaccine candidate on 5 May 2020 [12], the promising report of the Phase 1/2 clinical trial was released on 5 August 2020 [13].

The date of approval by the FDA for Pfizer, Moderna, and Janssen was 5 December 2020, 18 December 2020, and 27 February 2021. AstraZeneca vaccine was approved by the UK (on 30 December 2020) and EU (on 29 January 2021), but was not authorized for use in the US, because its one large-scale trial

of the vaccine conducted so far used outdated data. Novavax was approved by Indonesia on 1 November 2021 and will submit to FDA soon. WHO approved Sinopharm vaccine emergency use on 7 May 2021. Although the Janssen vaccine is a single-dose vaccine, other approved vaccines are double-dose vaccines, with an interval of 2-16 weeks days between doses. The second shot in multiple doses vaccine might refer to the ineffectiveness of the first dose, and act to the booster shot for achieving the minimal requirements of FDA/WHO approval. In this direction, Janssen is expected to be the best vaccine. Although the vaccine technologies for current vaccines have been developed tens of years ago, short-time development for Covid-19 vaccines in emergency use seems not enough for better design and clinical trials.

On 29 October 2021, FDA approved the emergency use of Pfizer-BioNTech pediatric vaccine for children 5 through 11 years of age (the vote was 17 in favor with one abstention) [14]. On 2 November 2021, CDC Advisory Committee on Immunization Practices (ACIP) recommended that children 5 to 11 years old be vaccinated against COVID-19 with the Pfizer-BioNTech pediatric vaccine (there are about 28 million children in the United States in this age group) [15].

2. Vaccine in the research and development: technologies and funds

2.1 Pfizer-BioNTech vaccine

The Pfizer–BioNTech Covid-19 is an mRNA-based Covid-19 vaccine developed by the German biotechnology company BioNTech and for its development collaborated with American company Pfizer. Pfizer develops and produces medicines and vaccines for immunology, oncology, cardiology, endocrinology, and neurology. The vaccine is given by intramuscular injection. It is composed of nucleoside-modified mRNA (modRNA) encoding a mutated form of the full-length spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles.

Pfizer-BioNTech's vaccine requires long-term storage at minus 70 °C or lower. Before mixing, the Pfizer vaccine may be stored in the refrigerator between 2°C and 8 °C for up to 1 month [9]. The standard dose of Pfizer is 30 micrograms with the interval between Pfizer doses being 21 days. Pfizer-BioNTech Covid-19 Vaccine for children 5 through 11 years of age is administered as a two-dose primary series, 3 weeks apart, but is a lower dose (10 micrograms) than that used for individuals 12 years of age and older (30 micrograms) [14].

As reported in November 2020, Pfizer does not receive funding from the US government, but its partner BioNTech received $445 million from the Germany Government to help accelerate the vaccine by building out manufacturing and development capacity in its home market. The US Government, was committed to buying hundreds of millions of vaccines in advance to ensure Americans were among the first in line if it clinches an emergency-use authorization or approval from the FDA. The Trump administration agreed in July to pay almost $2 billion for 100 million doses, with an option to acquire as many as 500 million more, once that clearance comes. [16, 17].

2.2. Moderna vaccine

Moderna vaccine is an RNA vaccine composed of nucleoside-modified mRNA (modRNA) encoding a spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles. Moderna's vaccine requires long-term storage at minus 20 degrees Celsius and is stable for 30 days between 2° to 8°C [18]. Each dose of Moderna contains 100 micrograms of a vaccine. A two-dose vaccine with The interval between Moderna doses is 28 days [19]. In 2016, Moderna received $8 million with the potential for up to $125 million from the Biomedical Advanced Research and Development Authority, a component of the US Department of Health and Human Services, to accelerate the development of an mRNA vaccine for Zika [20].

As reported in August 2020, under a deal worth up to $1.525 billion, Moderna agreed to deliver 100 million doses of its mRNA vaccine candidate if it succeeds in late-stage testing. The pact also includes an option for another 400 million doses. Combined, Moderna has scored $2.48 billion in R&D and supply funding from the U.S. government for its program [21]. In April 2021, Moderna received as much as $236 million in additional reimbursement for costs associated with its late-stage vaccine trial on about 30,000 volunteers, including safety monitoring. The additional money is on top of the $5.75 billion that the government already poured into Moderna to help it develop, test, and manufacture [20].

2.3. Johnson & Johnson vaccine

The Janssen Covid-19 vaccine or Johnson & Johnson Covid-19 vaccine is a Covid-19 vaccine that was developed by Janssen Vaccines in Leiden, Netherlands, and its Belgian parent company Janssen Pharmaceuticals subsidiary of American company Johnson & Johnson. Janssen vaccine is a viral vector vaccine based on a human adenovirus that has been modified to contain the gene for making the spike protein of the SARS-CoV-2 virus that causes Covid-19. The vaccine requires only one dose and does not need to be stored frozen. Unpunctured vials may be stored between 9 to 25 °C for up to twelve hours and the vaccine can remain viable for months in a standard refrigerator [11].

On 30 March 2020, The U.S. Government signed a $450 million Coronavirus vaccine contract with Johnson & Johnson. That's according to a $456 million order with Johnson & Johnson's Pharmaceuticals arm Janssen, which specified a "new vaccine asset for 2019 Novel Coronavirus (COVID-19)" Forbes found. It's the largest reported amount spent on a vaccine project to date, even though the pharma giant hasn't yet started any clinical trials as other firms have [22]. As reported on 15 November 2020, Johnson & Johnson will spend about $604 million expanding its deal with the U.S. government to develop a Covid-19 vaccine, seeking to catch up with rivals who have forged ahead in the race. In addition, the Biomedical Advanced Research and Development Authority (BARDA) commits about $454 million in additional money to the Phase 3 Ensemble trial, which seeks to evaluate the efficacy of the company's vaccine candidate as a single-dose. Johnson & Johnson and BARDA, under the U.S. Department of Health and Human Services, already committed more than $1 billion in March 2020, to co-fund the research in an about 50-50 split [23, 24].

2.4. Oxford/AstraZeneca vaccine

The Oxford–AstraZeneca COVID-19 vaccine was developed in the United Kingdom by the Oxford University and British-Swedish company AstraZeneca. AstraZeneca vaccine is a viral vector vaccine (just like the Johnson & Johnson vaccine), using as a vector the modified chimpanzee adenovirus ChAdOx1. The vaccine is given by intramuscular injection The vaccine is stable at refrigerator temperatures [10]. The interval between two doses is 4-12 weeks [25]. As reported in April 2021, at least 97% of the funding for the development of the Oxford/AstraZeneca Covid-19 vaccine has been identified as coming from taxpayers or charitable trusts. Less than 2% of the identified funding came from private industry. (Total funding amount is about 171 million USD over many years) [26].

2.5. Novavax vaccine

Novavax, Inc., is an American biotechnology company based in Gaithersburg, Maryland that develops vaccines to counter serious infectious diseases. Before 2020, company scientists developed experimental vaccines for Ebola, influenza, respiratory syncytial virus (RSV), and other emerging infectious diseases. In 2020, the company redirected its efforts to focus on the development and approval of its vaccine for Covid-19. The Novavax Covid-19 vaccine is developed by Novavax and the Coalition for Epidemic Preparedness Innovations. In January 2020, Novavax announced the development of a vaccine candidate, named NVX-CoV2373. NVX-CoV2373 has been described as both a protein subunit vaccine and a virus-like

particle vaccine through the producers call it a "recombinant nanoparticle vaccine". The vaccine is produced by creating an engineered baculovirus containing a gene for a modified SARS-CoV-2 spike protein.

The baculovirus then infects a culture of Sf9 moth cells, which create the spike protein and display it on their cell membranes. The spike proteins are then harvested and assembled onto a synthetic lipid nanoparticle about 50 nanometers across, each displaying up to 14 spike proteins. It requires two doses and is stable at 2 to 8 °C refrigerated temperatures. In phase 1 of the clinical trial, two dose levels of 5 micrograms and 25 micrograms have been evaluated [27, 28]. In July 2020, the company announced it might receive US$1.6 billion from Operation Warp Speed to expedite the development of its coronavirus vaccine candidate by 2021 – if clinical trials show the vaccine to be effective [29, 30].

2.6 Sinopharm vaccine

The Sinopharm BIBP Covid-19 vaccine is inactivated virus COVID-19 vaccine developed by Sinopharm's Beijing Institute of Biological Products. This vaccine could be transported and stored at normal refrigerated temperatures. In April 2020, China approved clinical trials of Sinopharm [31].

3. Low-dose vaccine strategy

Since 2016, a dose-reduction strategy has successfully vaccinated millions of people in Africa and South America against yellow fever. For example, a fifth of the regular dose of the yellow fever vaccine can still provide immunity for a year or more [32, 33]. Juan-Giner et al. [34] reported that one-fifth of fractional doses of the four WHO-prequalified yellow fever vaccines were non-inferior in seroconversion 28 days post-vaccination compared with the standard dose. The use of fractional dosing could expand the outbreak stockpile up to five times.

However, till now no similar approach has been applied to Covid-19, despite vaccine shortages worldwide. For the Covid-19 vaccine, dose-reduction would minimize the side effect, thus optimal dose (just-right dose) is important. The regular dose of Pfizer is 30 micrograms, which is much lower than that of Moderna (100 micrograms). As result, after injection, there are fewer reports on the side effects of the Pfizer vaccine.

Regarding Moderna, in the earliest trial (early 2020), three dose levels have been investigated, such as 25, 100, or 250 micrograms [35]. The highest dose proved too toxic. The lowest dose elicited the weakest immune response. Thus, the middle dose seemed to offer the best balance. That 100-microgram dose ultimately became the one authorized for mass use in dozens of countries since the end of 2020. However, in February 2021 Moderna scientists later showed that a half-dose (50 micrograms) seemed to be just as good as the standard dose [36]. Then in July 2021, a quarter dose (25 micrograms) has been reported with a strong immune response [37]. In another direction, providing half doses to a certain number of people could provide a greater level of population immunity than would providing standard doses to half as many people [38].

In the case of AstraZeneca in December 2020, a surprising result indicated that when a lower initial dose of the two-dose vaccine showed higher efficacy. As reported from two different regimens: a haft dose followed by a full dose giving 90% efficacy; and two full doses giving only 62% efficacy [39].

4. Adverse effects of Covid-19 vaccines

4.1. Pfizer–BioNTech vaccine

Most side effects of the Pfizer–BioNTech Covid-19 vaccine are mild to moderate in severity and are gone within a few days. They are similar to other adult vaccines and are normal signs that the body is building protection against the virus. During clinical trials, the common side effects affecting more than 1 in 10 people are (in order of frequency): pain and swelling at the

injection site, tiredness, headache, muscle aches, chills, joint pain, and fever. Fever is more common after the second dose [9].

4.2. Moderna vaccine

The most common adverse events were pain at the injection site, fatigue, headache, myalgia (muscle pain), and arthralgia (joint pain). The US CDC has reported anaphylaxis (a severe allergic reaction) in 2.5 cases per million doses administered and has recommended a 15-minute observation period after injection. Delayed cutaneous reactions at injection sites resulting in rash-like erythemas have also been observed in rare cases but are not considered serious or contraindications to subsequent vaccination. The incidence rate for local adverse erythema is about 10.8%, in 1.9% of cases redness may extend to a size of 100mm or greater [18]. On 23 June 2021, the US CDC confirmed that myocarditis or pericarditis occurs in about 13 of every 1 million young people, mostly male and over the age of 16, who received the Moderna or the Pfizer–BioNTech vaccine. In October 2021, Finland, Iceland, Norway, Sweden, and Denmark paused the use of the Moderna vaccine in young people, offering or recommending the similar Pfizer–BioNTech vaccine instead. This policy was a precautionary measure following the release of an unpublished study reporting an increased incidence of treatable mild myocarditis and pericarditis occurring more frequently in young men after the second dose of mRNA vaccines, with a higher incidence with Moderna. On November 10, Germany's vaccine advisory recommended the Pfizer–BioNTech Covid-19 vaccine instead of the Moderna vaccine for people under 30 years of age and pregnant women [18].

4.3. AstraZeneca vaccine

The most common side effects in the clinical trials were usually mild or moderate and got better within a few days after vaccination. Vomiting, diarrhea, fever, swelling, redness at the injection site, and low levels of blood platelets occurred in less than 1 in 10 people. Enlarged lymph nodes, decreased appetite, dizziness, sleepiness, sweating, abdominal pain, itching, and rash occurred in less than 1 in 100 people. An increased risk of the rare and potentially fatal thrombosis with thrombocytopenia syndrome has been associated with mainly younger female recipients of the vaccine. Anaphylaxis and other allergic reactions are under investigation [10]. In March 2021, Sweden joins Germany, France, and 15 other countries in suspending AstraZeneca's vaccine over possible side effects on blood clots [40]. In April 2021, Denmark announced that it permanently stopped using the AstraZeneca vaccine [41].

4.4. Johnson & Johnson vaccine

The most common side effects are pain at the injection site, headache, tiredness, muscle pain, and nausea, affecting more than 1 in 10 people. Coughing, joint pain, fever, chills, redness, and swelling at the injection site occurred in less than 1 in 10 people. Sneezing, tremor, throat pain, rash, sweating, muscle weakness, pain in the arms and legs, backache, weakness, and feeling generally unwell occurred in less than 1 in 100 people. Rare side effects (that occurred in less than 1 in 1,000 people) are hypersensitivity (allergy) and itchy rash. An increased risk of the rare and potentially fatal thrombosis with thrombocytopenia syndrome (TTS) has been associated with mainly younger female recipients of the vaccine. This syndrome, marked by the formation of blood clots in the blood vessels in combination with low levels of blood platelets 4–28 days after the administration of the vaccine, occurred at a rate of about 7 per 1 million vaccinated women ages 18–49 years old and occurs more rarely in other populations (i.e. women 50 years and older, and men of all ages) [11].

On 13 April 2021, the FDA and CDC asked states to temporarily halt using J&J's vaccine "out of an abundance of caution" following reports that six women, ages 18 to 48, developed cerebral venous sinus thrombosis in combination with low blood platelets. But then shortly, FDA and CDC have lifted this recommended pause on Johnson & Johnson (Janssen) COVID-19 [42]. However, soon after U.S. regulators paused the use of

the J&J single-dose vaccine, health authorities in many European countries and South Africa announced that they were also putting it on hold.

5. Nanotoxicology of lipid nanoparticles and mRNA-loaded nano-lipids

For the biomedical application of nanoparticles, their nanotoxicology and nanotoxicity are very important [43, 44]. Currently, no study on the effect of mRNA-loaded nano-lipids, when they get into the vascular system, by accident in vaccine design. As nanocarriers, lipid nanoparticles are the important component of the Pfizer/BioNTech and Moderna mRNA Covid-19 vaccines, playing a key role in protecting and transporting the mRNA effectively to the right place in cells. Using nanotechnology, lipid nanoparticles are well suited to the stable and efficient delivery of various therapeutics [45].

Biological lipids have been considered as the drug nanocarriers having minimum carrier cytotoxicity. Thus, nano-lipids would permit better-controlled drug release due to increased mass transfer resistance For drug/vaccine delivery application, the administration route is often determined by the properties of the nanocarriers and therapeutic indications. For example, after intravenous administration, many lipid nanoparticles can accumulate in the liver. However, intravenous administration may also lead to the accumulation of lipid nanoparticles in multiple lymph nodes throughout the body, which could increase immune responses to mRNA vaccines [46]. Please also note that current Covid-19 vaccines are given by intramuscular injection. Recently, in October 2021, the oral and intranasal Covid-19 vaccines showed promising results in the hamster model [47]. Some works reported the biological response and cytotoxicity induced by lipid nanocapsules [48]. In the case of Pfizer, there are suspicions on the nanoparticles in the Pfizer vaccine trigger rare allergic reactions. As reported, life-threatening responses seen in at least eight people could be linked to polyethylene glycol, known to trigger reactions to some drugs [49].

6. Vaccination campaigns and Covid rates in the global use

6.1. Cases in India with AstraZeneca vaccine

In April 2020, Pune-based SII, the world's largest vaccine manufacturer in terms of numbers, partnered with Oxford University to manufacture their Covid-19 vaccine in India. The SII produced 5,000 doses of the vaccine per minute in their assembly lines.

In October 2020, the Delta variant was firstly detected in India. On 16 January 2021, India started a mass vaccination campaign with two kinds of vaccines: Covishield (the local name for the Oxford-AstraZeneca) and Covaxin (manufactured by Bharat Biotech pharmaceutical India company. This vaccination campaign is considered as world's largest mass vaccination.

In January 2021, India Government approved an emergency use approval (EUA) for the Covishield vaccine in India. Doses of the vaccines were transported from Pune to multiple hubs in the country. On 16th January 2021, the first dose of the vaccine was administered to recipients based on a priority list prepared by the government. Figure 1 presents the new cases and vaccination statistics in India. As seen in Figure 1, surprisingly after 2 months of widespread injection (March 2021), the number of infections began to increase, then peaked after 4 months (May 2021). By June 3, 2021, India's deaths exceeded 300,000. Thus, published data indicated that that the number of infections increased daily after starting each mass vaccination, then the more injections, the Covid positive cases increased. Thus Covishield/ AstraZeneca vaccine seems to be particularly ineffective against the SARS-CoV2 in India.

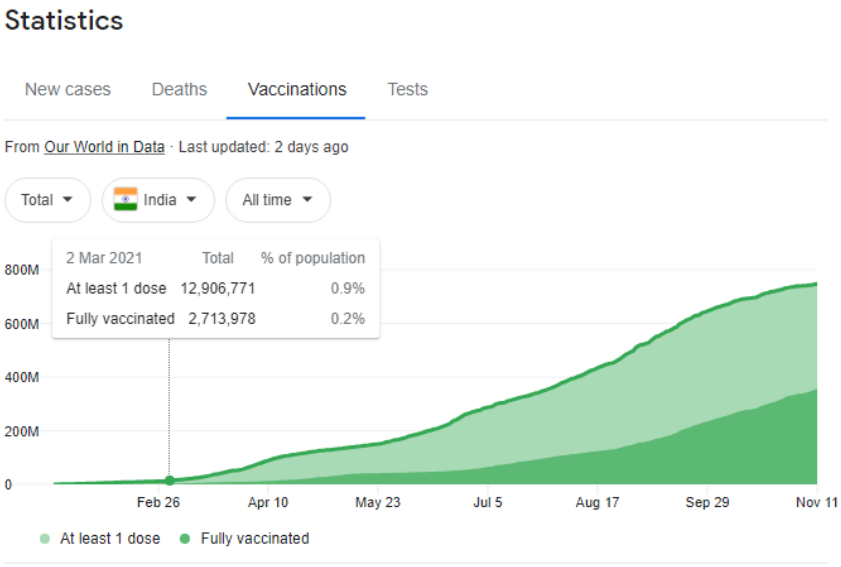

Figure 1: New cases (a) and vaccination (b) statistics in India. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

6.2. Cases in Israel with the Pfizer–BioNTech vaccine

Israel is a small country with about 9 million people that has deployed vaccination nationwide quite early (the world's fastest) on December 20, 2020. Israel prioritizes using only Pfizer for vaccination, due to signing an agreement with the company on sharing the medical data (on January 2021) [50]. In other words, Israel had promised Pfizer that it would use the company's vaccine exclusively [51]. Although the rate of vaccine coverage increased very quickly in the early stages (50% of the population received the first dose in February 2021), it slowed down soon after (68% of the population received the first dose in September 2021).

After the first injections from December 29, 2020, when 50% of the population was covered by February, the lockdown was carried out until 31 January 2021. The boost shot (3rd dose) is applied from 31 July (for people over 60) and from 13 August (for people over 50). However, on 13 September 2021, the 4th dose was recommended when the 3rd dose has been given to over 2.8 million people. At that time, to prepare the supply for the 4th dose, Moderna and AstraZeneca were additionally ordered. (on 21 October 2021), possibly because they found on 23 July that the Pfizer vaccine is just 39% effective against the Delta variant in Israel [52]

Figure 2 presents the new cases and vaccination statistics in Israel. As seen in Figure 2a, there are 3 wide peaks of new cases around September 2020 (first wave, before vaccination), January 2021 (second wave, just after 1st dose), and September 2021 (3rd wave, just after 3rd dose), with the number of new cases in these 3 peaks increase with increasing the number of doses (wave 1 < wave 2 < wave 3). These data indicate that the number of infections increases daily after starting each mass vaccination, then the more injections the Covid positive cases increase. It should be not only attributed to the decrease in the effectiveness of the Pfizer vaccine over time but also due to the vaccination, especially since no new variant was detected after October 2020 (Delta variant found in Israel on 19 December 2020).

The most logical explanation is that probably mass vaccination might weaken the immune system. This hypothesis has been confirmed experimentally 5 months ago by researchers from

Britain's Francis Crick Institute (London, UK) [53]. The authors found that the Pfizer COVID-19 vaccine destroyed T cells, and weakened the immune system. This finding would explain why side effects are worse after a second dose of Covid-19 vaccine. For the cases of reinfection with Covid-19, their recovery could be slower than the patients without vaccination [54-56]. On the other hand, this finding also helps to understand the reason why the new cases increase after vaccination in many countries/regions. Inappropriate vaccine/vaccination would damage the (invisible) shield immunity (shield of immune people around those who are susceptible).

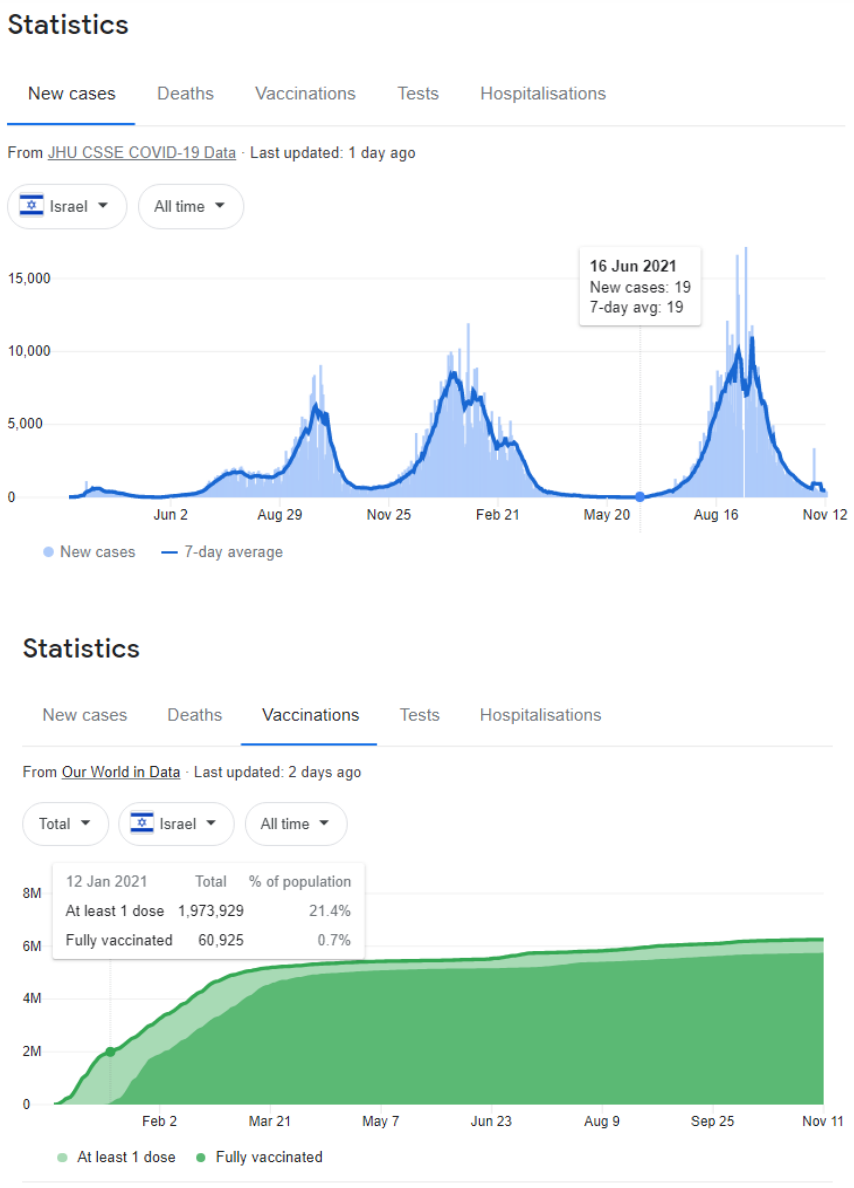

Figure 2: New cases (a) and vaccination (b) statistics in Israel. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

6.3. Cases in Germany with the Pfizer–BioNTech vaccine

Similar situation was also observed in Germany with Pfizer-BioNTec vaccine. As reported in November 2020 [16, 17], Pfizer-BioNTec does not receive funding from the US government, but its partner BioNTech (in Mainz) received $445 million from its Germany Government.

The Covid-19 vaccination campaign in Germany began on 26 December 2020 [57], mainly with Pfizer-BioNTech (86 million doses) [58]. The used doses of AstraZeneca, Moderna and Janssen vaccines totally are 13, 10 and 3.3 million, respectively [58], as showed in Figure 3. 55,869,314 people have received at least one dose (67.2 % of total population) as of 19 September 2021, while 52,503,166 people have been fully vaccinated (63.1 % of total population) [57].

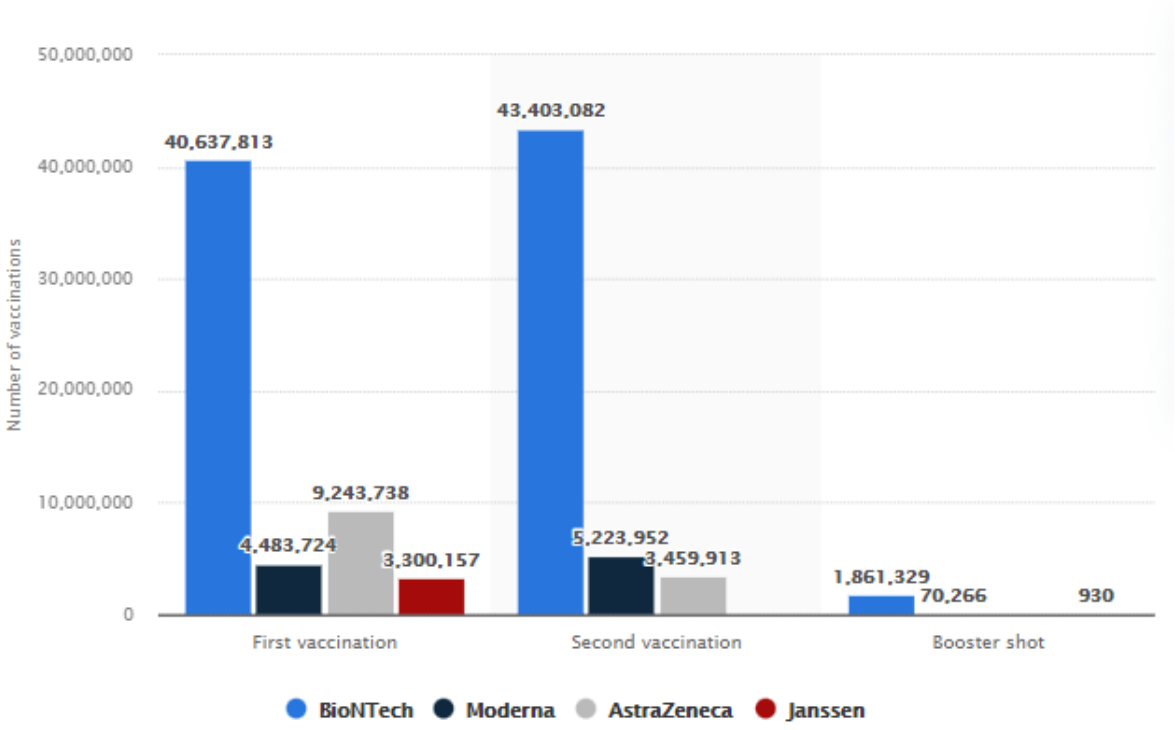

Figure 3: Covid-19 vaccinations in Germany in 2021 by manufacturer [58]

Figure 4 presents the new cases and vaccination in Germany. As seen in Figure 4a, there are several peaks after the vaccinated date. The peaks from December 2020 to June 2021 might be attributed to the vaccination of various vaccine types. Whereas, the higher peak after June 2021 could be attributed to two reasons: i) fast increase of vaccination rate (> 50 %), and (ii) third dose strategy. These data also indicate that the number of infections increases daily after starting each mass vaccination, then the more injections the Covid-19 positive cases increase. It should be not only attributed to the decrease in the effectiveness of the Pfizer vaccine over time, but also due to the vaccination, especially since no new variant was detected after June 2021 (Delta variant found in Germany in mid-May 2021).

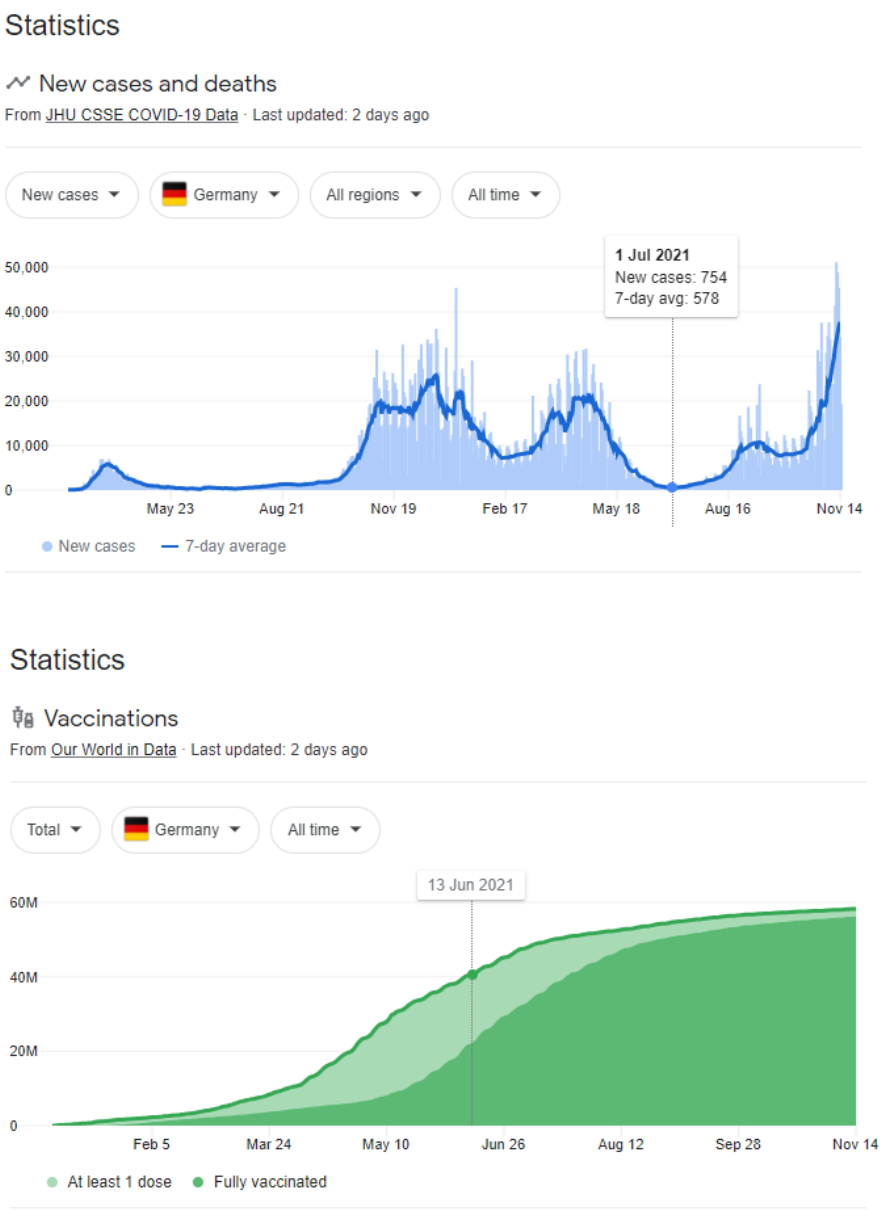

Figure 4: New cases (a) and vaccination (b) statistics in Germany. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

On 4 October 2021, The European Union's drugs regulator said that people with weakened immune systems should get a third dose of a Covid-19 vaccine from Pfizer-BioNTech or Moderna, but left it to member states to decide if the wider population should have a booster. As advised, people with severely weakened immune systems may be given a booster dose of either the Pfizer-BioNTech or Moderna jabs just 28 days after their second dose [59]. Whereas, healthy adults can receive a third, booster dose of the Pfizer-BioNTech Covid-19 vaccine six months after the second dose [60]. Thus, on 7 October 2021, the German authority on vaccines has suggested extra vaccine doses for people older than 70, as well as care home workers. It also recommended mRNA booster shots for people who received the Johnson & Johnson vaccine [61]. As of 4 November 2021, 1,932,525 boosters overall have been administered in Germany

(1,861,329 doses of Pfizer). However, after vaccination with the booster shots, the new cases increase dramatically (Figure 4).

6.4. Cases in South Africa with the Johnson & Johnson and Pfizer–BioNTech vaccines

South Africa started the vaccine campaign on 17 February 2021 after receiving the Johnson & Johnson batch with the first 1130 doses. In addition, in early February 2021, South Africa received 1 million doses of AstraZeneca, but then stopped using AstraZeneca because of no protective effect (efficacy of ~ 10 percent) [62]. Johnson & Johnson has been bought 11 million doses by South Africa, but by mid-April 2021, the Johnson & Johnson injection was stopped because the US recommended blood clotting due to Johnson & Johnson injection. Until mid-April, only 1% population is vaccinated. In mid-May 2021, South Africa restarted vaccination. South Africa has ordered 20 million doses of Pfizer (used ~17 million doses till now). Contrary to expectations of Pfizer vaccination, from the time of injection, the number of cases started to increase and peaked in mid-July. Figure 5 presents the new cases and vaccination statistics in South Africa. As seen in Figure 5a, as compared to the previous waves, after injection with Pfizer the latter wave lasts longer and decreases more slowly. Please note that Johnson & Johnson (single-dose vaccine) exhibited good protection before its suspension, without an increase of new cases.

Figure 5: New cases (a) and vaccination (b) statistics in South Africa. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

6.5. Cases in Canada with the Moderna vaccine

Both Pfizer–BioNTech and Moderna vaccines are used in the vaccination campaign of Canada, but Pfizer–BioNTech has higher contents of doses. In mid-March 2021, Canada received nearly 500,000 doses of Moderna and 8 million doses of Pfizer–BioNTech. In addition, ~28 million doses of Pfizer and ~7-12 million doses of Moderna (in June 2021) have been shipped to Canada from April to August 2021. Figure 6 shows the new cases and vaccination statistics in Canada. As seen in Figure 6a, as compared to the previous waves (lower vaccination rate), after 70% vaccine coverage the latter wave is significantly smaller. Thus the combination of Pfizer–BioNTech and Moderna vaccine provides better protection than the use of only Pfizer–BioNTech in South Africa.

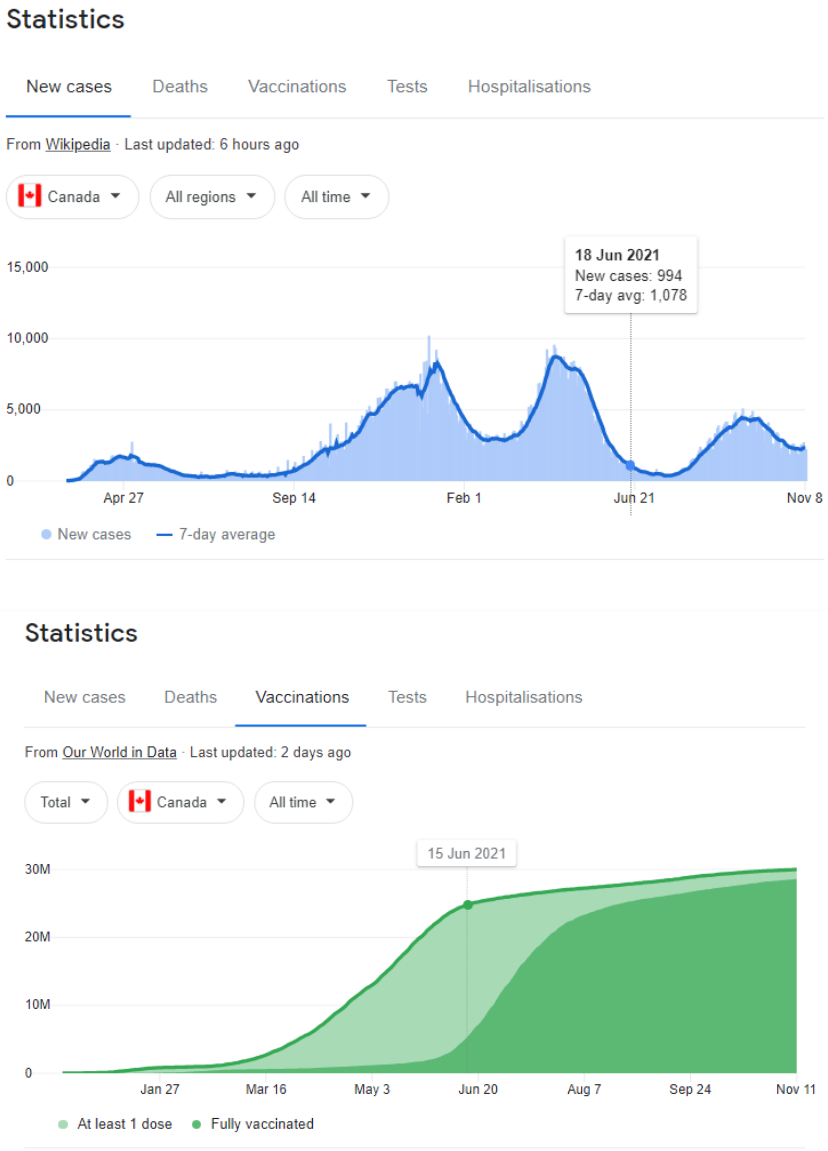

Figure 6: New cases (a) and vaccination (b) statistics in Canada. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

6.6. Cases in UAE with the Sinopharm vaccine

Since 9 December 2020, the UAE has started large-scale vaccination, mainly with the Sinopharm Covid-19 vaccine. Pfizer–BioNTech was used mainly in Dubai - the first Arab country to use the Pfizer vaccine. Then, the UAE is considered as the country having the fastest vaccination rates in the world, just behind Israel. On 24 December 2020. UAE lifted anti-epidemic national restrictions. However, just after starting mass vaccination, the number of new cases increased strongly (nearly 2 times high than before vaccination (Figure 7a). On 29 January 2021, European countries banned flights from the UAE (red zone). Therefore, in March 2021, UAE began to use the 3rd boost shot of Sinopharm for some volunteer groups. But, the situation became worse, as, in early May 2021, the Health Ministry announced that one-third of positive cases had already received 2 doses of Sinopharm previously.

In June 2021, to strengthen the immunity UAE decided to use the third/boost shot of Pfizer for those who had already received 2 doses of Sinopharm. The interval between this additional dose and the second dose of Sinopharm was 6-9 months, depending on the locality. As result, since July 2021, the number of new infections per day gradually decreased till now from ~1600 to ~70 cases per day (Figure 7a). This fact indicated that Sinopharm is less effective than Pfizer–BioNTech when used for the 3rd shot.

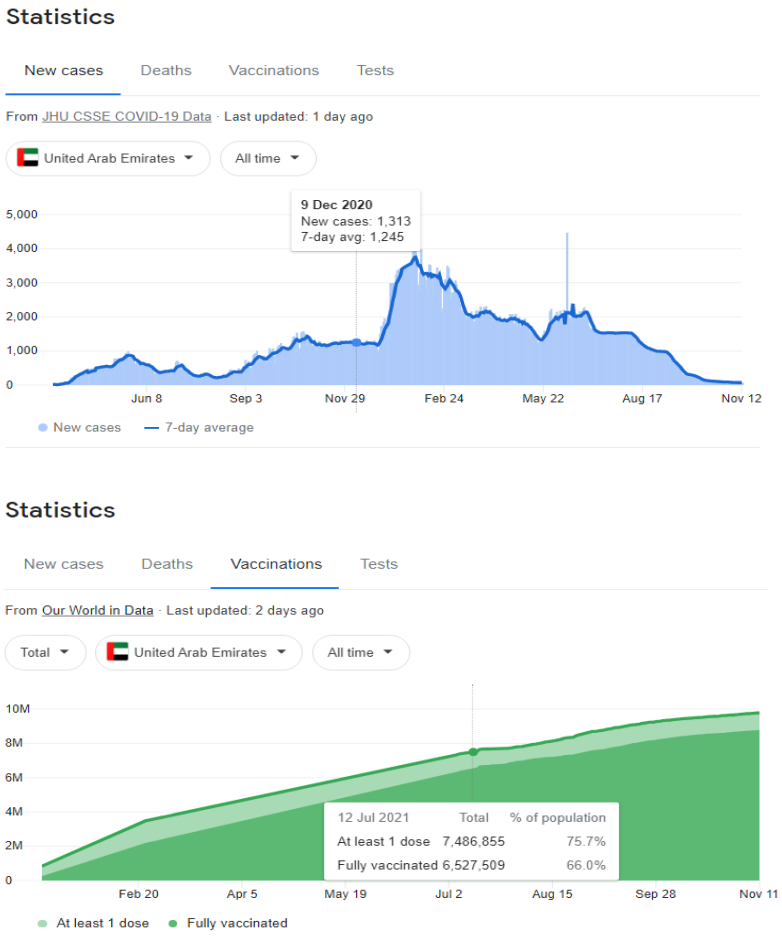

Figure 7: New cases (a) and vaccination (b) statistics in UAE. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

6.7. Cases in Saudi Arabia with the diverse vaccination

Saudi Arabia started a large-scale vaccination campaign on 17 December 2020, mainly with the Pfizer–BioNTech vaccine for its 30 million citizens. AstraZeneca vaccine was approved on 18 February 2021. As reported on 18 March, with these two vaccines, 2.3 million doses had been administered without blood clotting observation (as noticed for AstraZeneca vaccine [63]). On 19 May 2021, 11.5 million doses had been administered.

Figure 8 shows the new cases and vaccination statistics in Saudi Arabia. As seen in figure 6a, after using the AstraZeneca vaccine (since 18 February), the number of new cases increased indicating the higher effectiveness of Pfizer–BioNTech.

On 19 May 2021, Saudi Arabia required people to show green cards after the 1st day of August for participating in public activities as well as going to work. Thus it made the rate of vaccination increase dramatically. In addition, the Moderna vaccine was approved on 10 July 2021. as the 3rd shot, through its joint venture company with local Tabuk company). As a result, the rate of vaccination has rapidly increased from 13% to 42% only in 6 weeks. As shown in Figure 8a, the number of new infections per day decreased sharply from ~1000 cases (on 1 August) down to ~ 40 cases (in October/November). As reported on 4 November 2021, the vaccine coverage reached 70%. All data indicated that the high vaccine coverage and the use of various vaccines (Moderna/Pfizer/AstraZeneca) provided the best effects in controlling the pandemic with current vaccines.

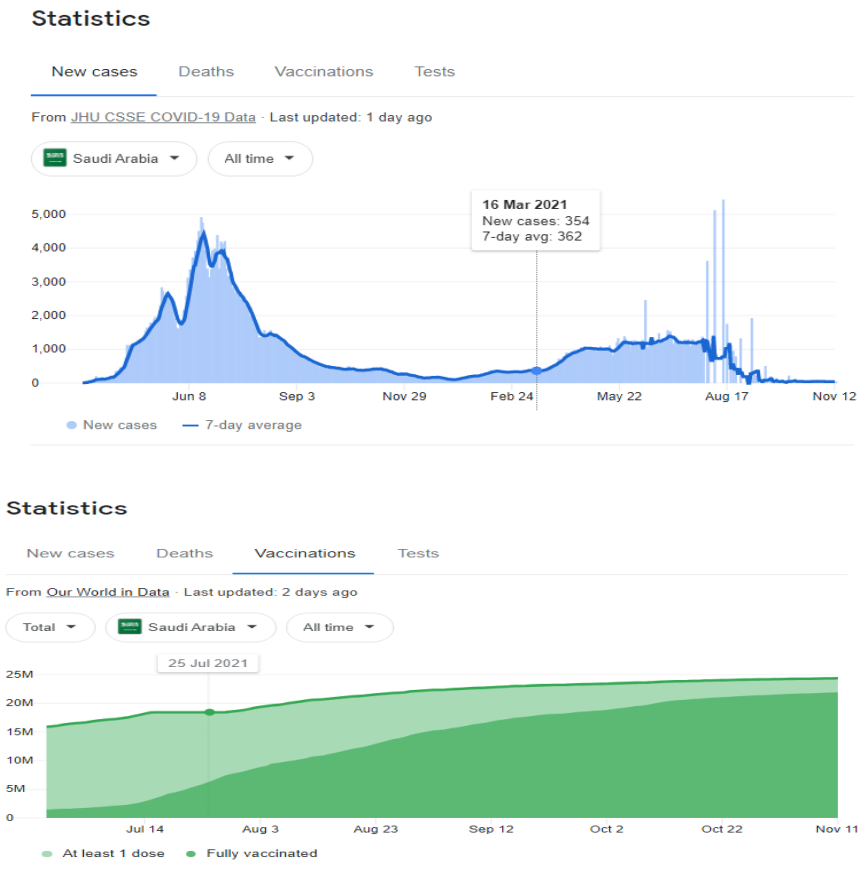

Figure 8: New cases (a) and vaccination (b) statistics in Saudi Arabia. Data source: https://github.com/CSSEGISandData/COVID-19, https://ourworldindata.org/covid-vaccinations?country=OWID_WRL

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