Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Contextualizing Wastewater-Based surveillance in the COVID-19 vaccination era

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ABSTRACT

SARS-CoV-2 wastewater-based surveillance (WBS) offers a tool for cost-effective oversight of a population's infections. In the past two years, WBS has proven to be crucial for managing the pandemic across different geographical regions. However, the changing context of the pandemic due to high levels of COVID-19 vaccination warrants a closer examination of its implication towards SARS-CoV-2 WBS. Two main questions were raised: 1) Does vaccination cause shedding of viral signatures without infection? 2) Does vaccination affect the relationship between wastewater and clinical data? To answer, we review historical reports of shedding from viral vaccines in use prior to the COVID-19 pandemic including for polio, rotavirus, influenza and measles infection and provide a perspective on the implications of different COVID-19 vaccination strategies with regard to the potential shedding of viral signatures into the sewershed. Additionally, we reviewed studies that looked into the relationship between wastewater and clinical data and how vaccination campaigns could have affected the relationship. Finally, analyzing wastewater and clinical data from the Netherlands, we observed changes in the relationship concomitant with increasing vaccination coverage and switches in dominant variants of concern. First, that no vaccine-derived shedding is expected from the current commercial pipeline of COVID-19 vaccines that may confound interpretation of WBS data. Secondly, that breakthrough infections from vaccinated individuals contribute significantly to wastewater signals and must be interpreted in light of the changing dynamics of shedding from new variants of concern.

1. Introduction

COVID-19, caused by the SARS-CoV-2 virus (Ghinai et al., 2020), is the first major global pandemic of the twenty-first century. Following the successful detection of SARS-CoV-2 in wastewater in The Netherlands, Italy, the United States, and Australia (Ahmed et al., 2020; La Rosa et al., 2020; Medema et al., 2020; Wu et al., 2020), more countries implemented wastewater-based surveillance (WBS) to better determine the presence and spread of the virus in communities. (Prado et al., 2020; Wurtzer et al., 2020; Kumar et al., 2020; Haramoto et al., 2020).

For decades, sewage analysis has been used to track various pharmaceutical compounds and pathogens circulating in the community. For example, WBS has been used to identify polio outbreaks, with one notable example the identification of silent transmission of wild poliovirus type 1 by Israel Public Health Services during routine surveillance in 2013. (Shulman et al., 2013) In Sweden, wastewater surveillance has been extended to include various viruses such as Norovirus and

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Hepatitis A virus. (Hellmér et al., 2014) During the early stages of the COVID-19 pandemic from 2020 onwards, WBS became an important complement to clinical surveillance in tracking community cases. (Ahmed et al., 2020; Peccia et al., 2020; Wu et al., 2022) Although wastewater data cannot substitute for clinical testing on the individual level, non-invasive WBS appears to be crucial when clinical testing capacity is scarce (Xiao et al., 2022) as it is faster to set up, requiring lower operational costs, and has been shown to foreshadow clinical infection trends. (Shah et al., 2022; Thompson et al., 2020) Moreover, WBS captures the signal from asymptomatic individuals that often go undetected by clinical surveillance. (Jones et al., 2020) The implication of this monitoring can lead to tangible public health interventions at different levels of resolution: from city-wide, neighborhood-wide, down to a single building. (Sharara et al., 2021) As such, several countries have adopted WBS to complement clinical data, most notably the establishment of the National Wastewater Surveillance System (NWSS) in the United States to response to the COVID-19 crisis. (Keshaviah et al., 2021; Kirby et al., 2021).

In response to the pandemic, the global healthcare community raced to develop vaccines that can mitigate the severity of the disease, with the development of different types of COVID-19 vaccines, ranging from mRNA-based vaccines to the more conventional inactivated viruses. At the time of writing, global vaccination efforts have resulted in the administration of more than 10.4 billion vaccine doses (including second and booster jabs) worldwide, which translates to an estimated 62 % of the world population as fully vaccinated (20 September 2022). (Ritchie, 2022) The increasing global vaccination rates introduce a new variable for WBS of SARS-CoV-2 and necessitates closer analysis to determine if there are any repercussions toward WBS efforts. In particular, this review will discuss: 1) if vaccination can lead to false positives or overestimation of prevalence due to the shedding of viral signatures i.e., so called "vaccine shedding"; and 2) if vaccination campaigns change the interpretation of wastewater data in light of reported clinical cases due to "breakthrough shedding". Investigating these factors will help inform the overall response of the WBS community toward this new phase of the COVID-19 pandemic.

2. SARS-CoV-2 wastewater based surveillance

Wastewater-based surveillance works on the assumption that it is possible to detect pathogens excreted in bodily fluids that reach the sewer system. The ability to identify and quantify SARS-CoV-2 RNA in wastewater samples is linked to the virus's localization to the gastrointestinal (GI) tract, mediated by ACE-2 receptors. (Zhong et al., 2020) While respiratory symptoms are predominantly typical for COVID-19, 15.47 % of patients also developed GI problems such as nausea/vomiting (7.53 %) and diarrhea (11.52 %). (Ghimire et al., 2021).

Viral shedding in stool during infection of unvaccinated patients shows 10^2 to 10^8 genome copies (GC)/mL at peak shedding concentration with no difference between severe and mild cases. (Zheng et al., 2020) Additionally, shedding of SARS-CoV-2 in feces of asymptomatic cases has been reported. (Jones et al., 2020) Overall, $<$40 % of symptomatic patients have detectable SARS-CoV-2 RNA in their stool, with shedding that persists longer than in nasopharyngeal passageway by around 7 to 14 days and lower peak viral concentration. (Yan et al., 2021; Zhang et al., 2021; Mesoraca et al., 2020) These signals, however, do not necessarily translate to infectious viral particles, as numerous studies report failure to culture SARS-CoV-2 from PCR-positive feces and the prevalence of COVID-19 among wastewater treatment plant (WWTP) workers is not elevated, unlike for healthcare professionals. (Pedersen et al., 2022; Albert et al., 2021; Wölfel et al., 2020).

A typical WBS workflow consists of 1) wastewater sampling, either at building or local neighborhood sanitary lines or at the WWTP; 2) concentration and extraction of viral genetic information from the samples; 3) quantification of the RNA recovered, typically by reverse transcription, quantitative PCR (RT-qPCR), or digital droplet (RT-ddPCR). (Polo et al., 2020; Abdeldayem et al., 2022; Zhou et al., 2021) These molecular methods use primers that target short fragments of specific genetic regions such as nucleocapsid (N) gene, envelope (E) gene, RNA-dependent RNA polymerase (RdRp) gene, spike (S) gene, or ORF1. (Zhou et al., 2021; Kumar et al., 2021; CDC, 2022) Other variants of primers that can identify variants of concerns (VOCs) have been developed. (Lee et al., 2021; Lee et al., 2021; Lee et al., 2022) Therefore, it is important to highlight that detection of SARS-CoV-2 in wastewater only requires the presence of somewhat intact genetic fragments, not infectious viral particles.

3. Discussion

3.1. COVID-19 vaccination and false positive results in SARS-CoV-2 WBS

As of writing this paper, there is no evidence, either direct or indirect, that suggests COVID-19 vaccination - with vaccines that are currently approved by WHO (Fig. 1) - leads to shedding of viral particles by individuals not exposed to SARS-CoV-2. In fact, based on the vaccine mechanism, it is very unlikely that any kind of vaccine-derived viral signature can be found in excreted bodily fluid, much less in concentrations sufficiently high to be detectable in wastewater. Based on historical data, vaccine-derived viral shedding occurs when vaccines consist of replicative viruses, either live attenuated or live replicative viral vaccines such as the case with adenovirus vaccines. (Gray and Erdman, 2018; Scott et al., 1972; Stanley and Jackson, 1969) Here, an important distinction needs to be made between adenovirus vaccine and adenovirus-vector-based vaccines, where the latter lack the genes responsible for viral reproduction and hence do not result in virus shedding. (Hasanpourghadi et al., 2021).

3.1.1. Vaccine-derived viral shedding in bodily fluids relevant to WBS

We carried out an analysis of available literature that reports vaccine-derived viral shedding in bodily fluids for viruses that have been / can potentially be detected in wastewater (e.g., SARS-CoV-2, poliovirus, arboviruses). Two tables were compiled to summarize the findings according to their shedding route (Table 1 - feces and Table 2 - urine, and in the upper respiratory tract). We start with a description of previously established vaccine-shedding examples and then provide a focused analysis of the vaccine-shedding potential of current SARS-CoV-2 vaccine candidates.

Polio vaccine is the most well-studied case of fecal vaccine shedding. Polioviruses spread mainly through the fecal-oral route. Viruses can migrate from the GI tract to the central nervous system causing flaccid paralysis. (Bandyopadhyay et al., 2015) To date, two principal poliovirus vaccines are used worldwide: 1) inactivated poliovirus vaccine, administered through intramuscular injection (IPV), and 2) live-attenuated poliovirus vaccine, orally administered (OPV). OPV elicits strong gut immunity that reduces viral transmission and confers herd immunity, whereas IPV confers humoral immunity that protects from severe polio symptoms such as paralysis. (Bandyopadhyay et al., 2015; Pearce, 2004; Sabin, 1985; Melnick, 1984) Cases of vaccine shedding occur exclusively in OPV. The vaccine shed in stool can be spread to household contacts through fecal-oral transmission. (Altamirano et al., 2018; Holubar et al., 2017; Duintjer Tebbens and Thompson, 2015) IPV-vaccinated people, on the other hand, have not been observed to shed polio virions. (USCDC, 2022) Clinical studies have reported that OPV shedding occurs in 10 % – 100 % of vaccines for durations from a few until up to 60 days. (Martinez et al., 2004) Virus shedding reached median peak $\log_{10}$ concentration of 5.0 cell culture infectious dose 50 % (CCID50) per gram of stool (Brickley et al., 2019), with a maximum of $1.3 \times 10^{10} \pm 5.6 \times 10^{1}$ GC/g of stool (Table 1). (Taniuchi et al., 2014) As such, OPV is known to be detected at high enough concentration in rivers and sewersheds and its surveillance has been conducted by countries transitioning from OPV to IPV to manage poliovirus infections. (Njile et al., 2019; Nakamura et al., 2015; Pavlov, 2006; Lago and Gary,

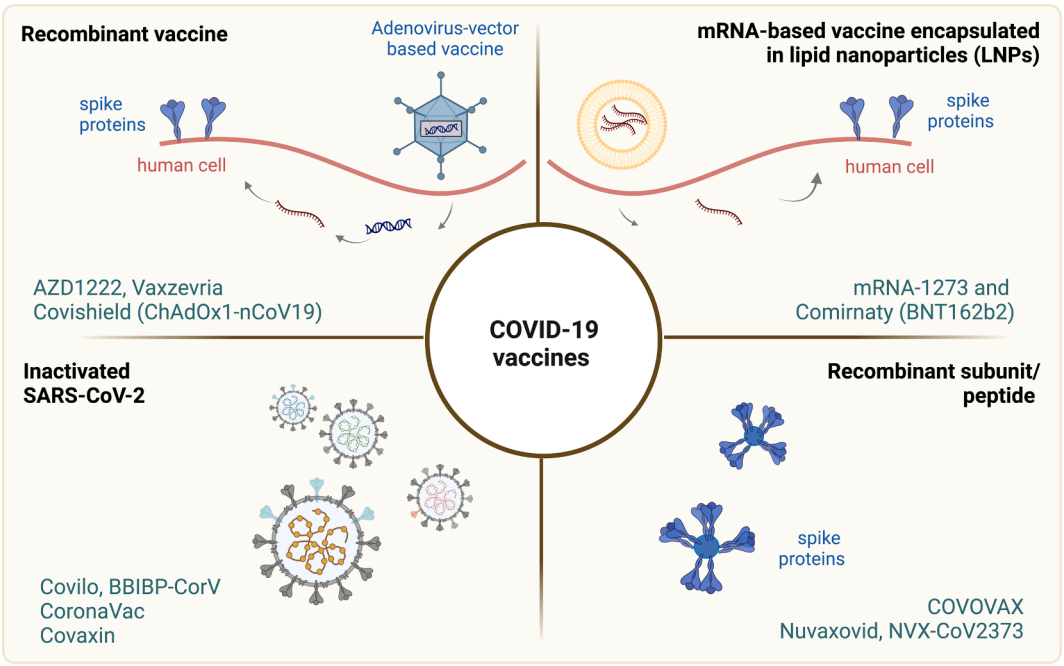

Fig. 1. Summary of the COVID-19 vaccines currently approved for use and their mechanism. In bold black is the reported platform/technology used for vaccine development: vectored vaccine, mRNA vaccine, inactivated whole virus, and recombinant subunit/peptide. In light green are the names of the approved vaccines. All vaccines function by challenging the human immune system with viral antigens: 1) vectored vaccines and mRNA vaccines carry and deliver nucleic acid information to produce spike protein antigens; 2) recombinant subunit/peptide vaccine delivers SARS-CoV-2 antigens that were produced *in-vitro;* 3) inactivated whole virus challenges the immune system with a replication-incompetent strain of virus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2003; Yoshida et al., 2002; Matsuura et al., 2000).

Fecal vaccine shedding has also been reported for the rotavirus vaccine. (Lee et al., 2021; Anderson, 2008) Rotavirus infection is prevalent in children under the age of 5, leads to severe diarrhea, and presents oral-fecal transmission. (Dennehy, 2000) To date, the only widely used rotavirus vaccines are developed using the live-attenuation strategy and are orally administered. These include the monovalent Rotarix (RV-1), the pentavalent RotaTeq (RV-5), Lanzhou lamb rotavirus vaccine (LLR), and Rotavin-M1 vaccine. All of these vaccines are shed in stool samples with prevalence ranging from 14 % to 90 % of the analyzed cohort and concentration ranging from $< 1.0 \times 10^3$ to 1.9×10^8 GC/g of stool to 1.7×10^9 GC/g stool. (Li et al., 2018; Hsieh et al., 2014) The reported shedding length is up to 45 days post-vaccination and could be much longer as that was the end duration of the trial for RIX4414 vaccine. (Phua et al., 2005) These shed vaccines are also detectable in wastewater. For example, RotaTeq, a live attenuated rotavirus A (RVA) vaccine, was identified in Japanese sewage. (Ito et al., 2021) Another study conducted by Bucardo, et al., had identified the partial VP7 gene of rotavirus in Nicaragua wastewater samples. This gene fragment had a high sequence similarity to the vaccine strain RotaTeq-WI79-4, but the authors noted that more data is needed to confirm the true origin of the gene. (Bucardo et al., 2011).

Adenovirus vaccines are also known to be shed in stool. The adenovirus vaccine is a live orally administered vaccine used to prevent febrile acute respiratory disease. Adenovirus type 4 and 7 are used by United States military personnel. (USCDC, 2022) The prevalence of adenovirus vaccine shedding in stools has been reported from 27 % to 64 % of the studied cohort depending on the serotype, with duration up until 21 days post-administration. (Lyons et al., 2008; Schwartz et al., 1974) However, none of the studies reported the shedding concentration. To the best of our knowledge, no one has reported adenovirus vaccine in wastewater, but wild-type adenoviruses are known to be detected in raw sewage and treated wastewater in different countries with concentrations as high as 4.6×10^6 GC/L of sample. (Elmahdy et al., 2019; Fong et al., 2010; Osuolale and Okoh, 2015).

Beside fecal matter, urine and upper respiratory tract fluids also contribute to wastewater, and thus any vaccines that are shed through those routes might contribute to wastewater data. Measles is a systemic disease caused by the measles virus (MeV). (Moss, 2018; Griffin, 2018; Bester, 2016; de Vries et al., 2012) MeVs are spread by aerosol or respiratory droplets and diffuse from the respiratory tract to lymphoid tissues reaching other organs. Fever and rash are manifestations of the cellular immune response and coincide with body virus clearance. Many live attenuated measles vaccines are available. (Griffin, 2018; Bester, 2016) Usually, two doses are administered subcutaneously and in combination with other vaccines such as rubella, mumps, or chickenpox (Table 2). Measles vaccine shedding has been documented before. (Kaic et al., 2010; Eckerle et al., 2013; Rota et al., 1995) The earliest study tested urine samples of a vaccinated cohort by RT-PCR and reported that MeV can be detected from day 1 post-vaccination until day 14 in 39 % of all urine samples, with the majority of positive samples coming from children. (Rota et al., 1995).

As with measles, the rubella virus spreads through coughs or sneezes. Viruses can be detected in different bodily fluids and urine samples in the first week after the onset of the symptoms. (Lambert et al., 2015) Rubella vaccination is generally combined with other live attenuated virus vaccine strains. (Schenk et al., 2021; Reef and Plotkin, 2006) Rubella vaccine shedding is poorly reported, with only one report of a case study where a young woman showed disease symptoms after the vaccination with PCR positive urine for the rubella 27/3 vaccinal strain. (Gualberto et al., 2013) Another group from Japan has reported isolation of vaccine-derived measles and rubella viruses from nasopharyngeal swabs of four children up until the 26th day post-vaccination (Table 2). (Aoki et al., 2016).

Another vaccine that has known shedding in the upper respiratory tract is influenza vaccine. There are three types of influenza viruses (A, B, and C). Influenza A and B types are the most common cause of seasonal epidemics and they can lead to complications and mortality. (Paul

Table 1
Studies reporting vaccine shedding in feces.

Vaccine target and name	Administration route	Type of vaccine	Shedding route	Shedding characteristics (time and prevalence)	Source
*Poliovirus / Sabin oral polio vaccine (OPV)	Oral	Live attenuated virus	Fecal	30 % – 80 % study cohort prevalence (dependent on prior OPV vaccinations) 7 to 60 days post-vaccination	(Martinez et al., 2004; Abraham et al., 1993)
Poliovirus / Sabin trivalent oral polio vaccine (tOPV)	Oral	Live attenuated virus	Fecal	10.7 % culture-positive and 17.6 % qPCR positive $1.3 \times 10^{10} \pm 5.6 \times 10$ GC/g of stool	(Taniuchi et al., 2014)
Poliovirus / monovalent polio vaccine type 1 (mOPV1)	Oral	Live attenuated virus	Fecal	100 % (12/12) viral shedding for 11–17 days and reached a median peak log10 viral shedding titer of 5.0 CCID50 per gram of stool (IQR: 4.7–5.9)	(Brickley et al., 2019)
Poliovirus / trivalent polio vaccine (Orimune/tOPV)	Oral	Live attenuated virus	Fecal	92 % study cohort prevalence (1 week post vaccination) and 81 % study cohort prevalence (3 weeks post vaccination)	(Laassri et al., 2005)
Poliovirus / trivalentpolio vaccine (tOPV)	Oral	Live attenuated virus	Fecal	55.4, 64.1, and 27.7 % of the samples were tested positive for types 1, 2, and 3 polio viruses, respectively. Poliovirus type 2 shedding recorded up to 4 to 8 weeks post-vaccination Poliovirus type 1 and 3 shedding recorded up to 1 to 8 weeks post-vaccination, with 70 % shedding of poliovirus type 3 ceasing after 1 week	(Buonagurio et al., 1999)
Rotavirus / Pentavalent rotavirus vaccine (RotaTeq/RV5)	Oral	Live attenuated virus	Fecal	21.4 % study cohort prevalence 3 to 9 days post-vaccination Titers ranging from 10 to 10^6 PFU/ml (10 % feces - PBS slurry)	(Yen et al., 2011)
Rotavirus / Lanzhou lamb monovalent rotavirus vaccine (LLR)	Oral	Live attenuated virus	Fecal	14.0 % study cohort prevalence 2 to 13 days post-vaccination $< 1.0 \times 10^3$ to 1.9×10^8 gene copies/g of feces	(Li et al., 2018)
Rotavirus / Neonatal G3P rotavirus vaccine (RV3-BB)	Oral	Live attenuated virus	Fecal	70 % – 78 % study cohort prevalence Up to 7 days post-vaccination $10^{5.9}$ to $10^{6.9}$ gene copies/g of feces	(Cowley et al., 2017)
Rotavirus /Pentavalent rotavirus vaccine (RotaTeq/RV5) and Monovalent rotavirus vaccine (Rotarix/RV2)	Oral	Live attenuated virus	Fecal	86–90 % study cohort prevalence Peak vaccine shedding between 4th and 7th-day post first dose vaccination During the peak shedding period, shedding loads reach as high as 1.7×10^9 GC/g stool (RV2) and 2.6×10^7 GC/g stool (RV5)	(Hsieh et al., 2014)
Rotavirus/ two oral doses of RIX4414	Oral	Live attenuated virus	Fecal	76 %–80 % of infants on the seventh day after administration of the first dose Virus decreased steadily to 18 %–24 % of infants at day 30, to 11 %–16 % of infants at day 45	(Phua et al., 2005)
Adenovirus / Adenovirus serotype 4 and 7 vaccine (ADV-4 & ADV-7)	Oral	Live virus	Fecal	27 % (ADV-4) at least one time during the study and 60 % (ADV-7) study cohort prevalence (from day 7 to day 21)	(Lyons et al., 2008)
Adenovirus / Adenovirus type 4 and type 7	Oral	Live virus	Fecal	27 % (ADV-4), 60 % (ADV-7) a cohort of 30 people 7, 14, 21 days post-vaccination, no positive at day 28	(FDA, 2019)
Adenovirus / Adenovirus serotype 1, 2, and 5 vaccine (ADV-1, ADV-2, & ADV-5)	Oral	Live virus	Fecal	33 % (ADV-1), 38 % (ADV-2), and 64 % (ADV-5) study cohort prevalence 3 to 21 days post-vaccination.	(Schwartz et al., 1974)

* There are three distinct poliovirus serotypes: types 1, 2, and 3 that are distinguished by a neutralization test (WHO).
GE: Genome Equivalents.
GC: Genome Copies.
PFU: Plaque-Forming Unit.
CCID50: cell culture infectious dose 50%.

Glezen et al., 2013; MacKellar, 2007) Two studies have reported vaccine shedding in the upper respiratory tract post vaccination using live attenuated influenza virus. The shedding characteristics are variable with influenza strain, with prevalence from 14 % to 81 % of the individuals analyzed and estimated viral load of less than 10^3 Tissue Culture Infective Dose (TCID)/mL of samples. (Lindsey et al., 2019; Mallory et al., 2011) However, the volume of respiratory tract fluid going into wastewater is likely small enough that it wouldn't significantly affect wastewater surveillance.

Yellow fever (YF) and dengue are two mosquito-borne diseases that have functioning vaccines that are shown to be shed in urine. The YF vaccine is a live attenuated virus (YF-17D strain) that is administered subcutaneously or intramuscularly and reproduces to confer long term immunity by upregulating monocyte and macrophage activity. (Staples et al., 2020; Collins and Barrett, 2017; Monath and Vasconcelos, 2015) However, the exact mechanism by which the vaccine induces systemic immune response is still unknown. (Bovay et al., 2021) After YF-17D vaccination, people usually develop viremia from day 2 to 16, with peak viral load on day 7. (Hou et al., 2017; Liang et al., 2016) Some studies exploring non-invasive tests for the YF diagnosis showed YF-17D detection in urine (Martínez et al., 2011; Domingo et al., 2011), leading to its potential to be detected in wastewater. Dengue vaccine shedding, on the other hand, is more rare and has thus far only been observed at lower viral loads. One study reported that CYD-TDV vaccination causes urinary shedding, with a prevalence of only 2 % (2/96) and a viral shedding load of 5.47 and 5.77 GC/mL of urine. (Torresi et al., 2017).

In conclusion, historical data have shown a precedent where vaccines were shed and detected in wastewater samples, as exemplified by poliovirus and rotavirus vaccines. However, vaccine shedding does not necessarily entail detection in wastewater as other important factors play a part, such as vaccine coverage in the population, the replication competency of the vaccines, and shedding concentration per capita.

Table 2
Studies reporting vaccine shedding in urine, and in the upper respiratory tract.

Vaccine target and name	Administration route	Type of vaccine	Shedding route	Shedding characteristic (time and prevalence)	Source
Influenza / Ann Arbor strain live attenuated vaccine	Nasal	Live attenuated virus	Upper respiratory tract	79 % study cohort prevalence Peak shedding up to 11 days post-vaccination $< 10^3$ TCID/mL sample	(Mallory et al., 2011)
Influenza / Cal09 strain, NY15, H3N2, and B/Vic strain live attenuated vaccine	Nasal	Live attenuated virus	Upper respiratory tract	14 % (Cal09), 46 % (H3N2), 81 % (B/Vic), 63 % (NY15) on 2nd day post-vaccination Shedding was only assessed on the 2nd and 7th days post-vaccination	(Lindsey et al., 2019)
Measles/Priorix MMR vaccine	Not reported (it can be injected subcutaneously or intramuscularly)	Live-attenuated combined measles, mumps, and rubella vaccine	Urine	1/1 positive sample -urine - PCR, and BLAST identification - Schwarz vaccine strain (genotype A)	(Kaic et al., 2010)
Measles/MMRV vaccine Priorix-Tetra; GlaxoSmithKline	Not reported (it can be injected subcutaneously or intramuscularly)	Live-attenuated combined measles, mumps, rubella, and varicella vaccine	Urine	1/1 positive sample -urine (low viral concentration) - real-time RT-PCR - Schwarz vaccine strain	(Eckerle et al., 2013)
Measles/MMR vaccine	Not reported (it can be injected subcutaneously or intramuscularly)	Live- attenuated combined measles, mumps, and rubella vaccine	Urine	10/12 (83 %) positive childrens,56/144 (39 %) samples -measles vaccine strain, Moraten (Attenuvax; Merck, Sharp, and Dohme, West Point, Pa.) 4/4 positive adults	(Rota et al., 1995)
Rubella / Measles-rubella vaccine (MR), Serum Institute of India	Not reported	Live-attenuated combined measles and rubella vaccine	Urine	1 adult showed rubella clinical symptoms. Urine tested PCR positives for the RA 27/3 vaccinal strain (day 30 and 90 after vaccination).	(Gualberto et al., 2013)
Rubella / Measles-rubella vaccine (MR)	Not reported	Live-attenuated combined measles and rubella vaccine	Upper respiratory tract	4 children showed positive for vaccine-derived rubella virus from nasopharyngeal swab samples up until 26th day post-vaccine administration	(Aoki et al., 2016)
Yellow fever / Yellow Fever 17D	Not reported (it can be injected subcutaneously or intramuscularly)	Live-attenuated viral vaccine	Urine	18/129 samples positive amplification of the YF-17D genome	(Domingo et al., 2011)
Yellow fever / Yellow Fever 17D	Not reported (it can be injected subcutaneously or intramuscularly)	Live-attenuated viral vaccine	Urine	2/44 samples positive amplification of the YF-17D genome (urine collection performed at different times after vaccination)	(Martinez et al., 2011)
CYD-TDV (Dengvaxia, Sanofi Pasteur)	3 subcutaneous doses	live attenuated tetravalent dengue vaccine	Urine and saliva	4.2 % PCR positive urine(5.47 and 5.77 GE/mL) 2/96 involved people 3.2 % PCR positive saliva	(Torresi et al., 2017)

GE: Genome Equivalents.
GC: Genome Copies.
TCID: Tissue Culture Infective Dose.

Both poliovirus and rotavirus vaccines are replication-competent and they are shed in high concentration through stools. Moreover, they are widely administered in the populations where the vaccine strains were detected in wastewater. Hence it can be inferred that a vaccine needs to be widely distributed, replicating, and shed in high enough concentration in order to be detected in wastewater.

3.1.2. COVID-19 vaccination strategies

There are many types of COVID-19 vaccines at different stages of development, from those in clinical trials to those that are already authorized for use by WHO (Table 3). The different platforms (types of vaccines) currently authorized for use include: mRNA-based (e.g., mRNA-1273, Comirnarty), inactivated virus (e.g., BBIBP-CorV, CoronaVac, Covaxin), viral peptides (e.g., Nuvaxovid, Covovax), and adenovirus-vector based vaccines (e.g., Ad26.COV2.S, ChAdOx1 nCoV-19). (xxxx) All of these vaccines are administered via intramuscular injection. The adenovirus-vector vaccines lack the genes responsible for virus reproduction but carry the SARS-CoV-2 spike-protein gene used to produce the protein by the cells. (Hasanpourghadi et al., 2021) Consequently, the proteins will trigger the body's immune response and lead to immune memory that will help the organism recognize and respond to natural infection. The same principle is applied in mRNA-based vaccines that work by delivering a Spike-protein mRNA into the cells, mediated by lipidic nanoparticles, to produce the spike protein and elicit an immune response. (Heinz and Stiasny, 2021) Other approaches rely on introducing fragments or whole proteins from the virus in combination with adjuvants to boost the immune response such as the Nuvaxovid vaccine recently authorized in Europe. On the other hand, the inactivated viral vaccines (e.g., CoronaVac, BBIBP-CorV, and Covaxin) operate by exposing the human immune system to killed viruses. (Hotez and Bottazzi, 2022; Iversen and Bavari, 2021).

Analyzing the strategies used in approved and authorized COVID-19 vaccines (Fig. 1), we believe that they will not give rise to any viral signal in wastewater since none of these are capable of replication within the vaccinated host. As of September 2022, only non-replicating COVID-19 vaccines have been authorized for use by WHO. (xxxx) As a consequence, the shedding of SARS-CoV-2 vaccine in bodily fluids is highly improbable and, without shedding, there is no possibility of a false positive signal or overestimation in wastewater. However, one plausible way that vaccine-derived viral shedding can happen with currently available vaccines is if there is a reversion of competent-replication vectors from incompetent ones. Vaccine types that have this risk are viral vectored vaccines, such as adenovirus-vectored vaccines. (Sharon and Kamen, 2018; Baldo et al., 2013) Most of the risk of reversion event comes during the production of the vaccines (Kovesdi and Hedley, 2010; Zhu et al., 1999) or when there is a recombination within the vaccinees due to colocalization of wild-type adenoviruses and replication-incompetent adenovirus vectors. (Baldo et al., 2021) It is worth emphasizing that these events are very rare. One review by Schenk-Braat, et al. (Schenk-Braat et al., 2007) collected data from studies of adenovirus vectors used in gene therapies and found that none out of 11 studies that were specifically looking into the reversion of incompetent adenovirus vectors (total study size of 207 patients) actually found it in patients.

While currently available COVID-19 vaccines have a very low probability of generating false positive results in WBS, active research is

Table 3
COVID-19 vaccines authorized/approved for Emergency Use Listing (EUL) by WHO.

Platform	Vaccine name	Manufacturer
mRNA-based vaccine encapsulated in lipid nanoparticles (LNPs)	Spikevax, mRNA-1273, Elasomeran	Moderna
	Comirnaty, BNT162b2	Pfizer / BioNTech
Recombinant ChAdOx1 adenoviral vector encoding the spike (S) protein antigen of the SARS-CoV-2	AZD1222, Vaxzevria	AstraZeneca AB
	Covishield (ChAdOx1-nCoV19)	Serum Institute of India
Recombinant, replication-incompetent, adenovirus type 26(Ad26) vector encoding the spike (S) protein antigen of the SARS-CoV-2	JNJ-78436735, Ad26.COV2.S	Janssen - Cilag International NV (Johnson & Johnson)
Inactivated SARS-CoV-2 (Vero cell)	Covilo, BBIBP-CorV	Sinopharm, Beijing Institute of Biological Products Co., ltd. (BIBP)
	CoronaVac	Sinovac Life Science
	Covaxin	Bharat Biotech India
Recombinant nanoparticle prefusion spike (S) protein formulated with Matrix-M adjuvant	COVOVAX	Serum Institute of India
	Nuvaxovid, NVX-CoV2373	Novavax

ref. WHO, 2 March 2022 (https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_02March.pdf).

being conducted for other types of vaccines that potentially have a higher probability of vaccine-derived viral shedding. For example, two replication-competent vectored vaccines are now in phase 3 trial: 1) the IIBR-100 (VSV-ΔG) vesicular stomatitis virus (VSV) vectored vaccine that produces and presents SARS-CoV-2 spike protein subunit on its viral envelope (Yahalom-Ronen et al., 2020) (NCT04990466), and 2) the influenza virus vectored receptor-binding domain (RBD) peptide vaccine that was based on previous research in developing influenza virus vaccines (ChiCTR2100051391, PACTR202110872285345). (Huang and Yan, 2021; Wang et al., 2019) These vaccines contain the genetic information of specific SARS-CoV-2 peptides (e.g., spike or RBD gene) for eliciting immune responses and can replicate in the host cells. Since they can replicate, shedding of these vaccines can potentially give rise to SARS-CoV-2 signals in wastewater.

Another family of vaccines that have a higher probability of contributing SARS-CoV-2 RNA into the wastewater is the live attenuated vaccines. This vaccine modality is an exciting development in managing the pandemic because it can potentially confer stronger and longer immune responses. (Okamura and Ebina, 2021) One example vaccine, currently in phase 1 clinical trial, is a live-attenuated nasal vaccine named COVI-VAC, developed by Codagenix (NCT04619628). (Wang et al., 2021) COVI-VAC was developed by de-optimizing codons of the wild-type SARS-CoV-2 genome to be less replicative in human cells, resulting in 283 point mutations. However, the vaccine was reported to retain a perfect amino acid match with circulating wild-type strains, leading to a virus that replicates slower, but perfectly imitates the antigens of wild-type SARS-CoV-2. Clinical trials of this vaccine are still underway and we will only know about their safety and shedding characteristics after the results are published. Additionally, two other live attenuated vaccine candidates have shown to elicit high levels of immune response in hamster models. Intranasal inoculation of these vaccine candidates has shown to induce protection against wild-type viruses, with one of the candidates even reported to prevent close-contact transmission in the hamster animal model. (Li et al., 2022; Yoshida et al., 2022) While the introduction of live-attenuated COVID-19 vaccines to the population is still some ways off, the rapid research and promises of higher benefits mean that this modality will be the focus of future vaccine developments.

However, a higher chance of shedding into wastewater systems does not always entail a positive signal in WBS monitoring as it is also dependent on the molecular methods used. For example, the VSV- and influenza-based COVID-19 vaccines only contain spike (S) gene signals and no other tested genes such as N1 and N2. In this case, wastewater scientists could utilize the possible discrepancy between S and N gene signals to determine where the signals originate. On the other hand, the live-attenuated vaccines might contribute signals for all commonly tested genes (i.e., S, N1, N2, etc.). Future primers that specifically target these live-attenuated SARS-CoV-2 strains could be designed once the sequence is made available to the scientific community.

In conclusion, the analysis of the literature available suggests that none of the currently administered COVID-19 vaccines can cause false positive or overestimation in WBS data. Considering currently available vaccines, only in the very rare chance of adenovirus-vector vaccine reversion will vaccine-derived shedding be possible. However, it is highly recommended that the global wastewater surveillance/monitoring communities take note of the development of new vaccines, in particular live attenuated ones, and to determine from their published safety reports the chance of any vaccine-derived signals in wastewater samples.

3.2. COVID-19 vaccination and interpretation of WBS data

The use of SARS-CoV-2 wastewater data are reliant on prevailing public health strategies. Data can be used as an independent outbreak surveillance tool in scenarios of zero/low cases or as a complement to clinical data in scenarios of high case prevalence. The latter application is more common due to countries adopting policies of mitigating, as opposed to preventing, COVID-19 infections. As such, it is important to understand the dynamics of the relationship between wastewater and clinical data. A potential confounding factor is the mass vaccination campaigns. It can affect both clinical case reports (e.g., by changing healthcare-seeking behaviour due to lower disease severity) and also SARS-CoV-2 wastewater concentration (e.g., by changing viral shedding rates in vaccinees infection cases).

Surveying the literature, we found that vaccination confers a variable boost of immunity in different individuals (Cheng et al., 2022) and viral shedding rate in infected vaccinees is affected by factors such as age, comorbidities, and variant type. (Migueres et al., 2022; Michelena, 2022; Maltezou et al., 2021; Costa et al., 2021) A recent large-scale study conducted in Qatar has shown that nasopharyngeal swabs of breakthrough infections have lower viral concentration than those who are unvaccinated in matched cohorts (i.e., age, sex, and SARS-CoV-2 variant type). (Abu-Raddad et al., 2022) An Israeli group has reached similar conclusions of lower viral concentration by following over 16,000 SARS-CoV-2 infections (via oro-nasopharyngeal swabs), and they noted waning protection with increasing time between vaccination and infection. (Levine-Tiefenbrun et al., 2021) However, some reports concluded oppositely. For example, a large-scale study in The UK followed close contacts of COVID-19 cases for 20 days to determine the person's infectivity. Their results showed that there is no variation of peak viral loads with regard to vaccination status or SARS-CoV-2 variant (Alpha and Delta). (Singanayagam et al., 2022) A preprint by scientists in California has also concluded that there is no difference in virus concentration between vaccinated and unvaccinated individuals when infected with the Delta strain. (Acharya et al., 2021) As of writing this manuscript, the predominant SARS-CoV-2 strain globally is Omicron. Various reports seem to suggest that Omicron infections result in a similar nasopharyngeal viral load as the Delta variant in cases of breakthrough infections (Boucau et al., 2022; Migueres et al., 2022; Puhach et al., 2022), but one study has concluded that Omicron

infections had lower peak viral RNA concentrations than Delta infections in subjects normalized by their antibody titers. (Hay et al., 2022) In conclusion, different SARS-CoV-2 variants and the immunological status of the population (unvaccinated, vaccinated, and boosted) affect the shedding in a complex manner. It is worth pointing out that all of these studies were conducted to investigate viral shedding in the upper respiratory tract, not the gastrointestinal tract, which is the main shedding route for wastewater-based surveillance of SARS-CoV-2. Nevertheless, the nasopharyngeal data can be a good proxy of viral shedding in the gastrointestinal tract in the absence of direct evidence.

Few studies have analyzed the impact of vaccination on the relationship of SARS-CoV-2 RNA concentration in wastewater and reported clinical cases. For example, in thirteen small catchment studies reviewed (Wang et al., 2022; Welling et al., 2022; Kitajima et al., 2022; Harris-Lovett et al., 2021; Scott et al., 2021; Wong et al., 2021; Zambrana et al., 2022; Davó et al., 2021; Gibas et al., 2021; Betancourt et al., 2021; Karthikeyan et al., 2021,; Castro-Gutierrez et al., 2022; Bivins and Bibby, 2021), only one was conducted over a timeframe of significant vaccine administration. Bivins and Bibby monitored SARS-CoV-2 RNA concentration in wastewater solids during a massive COVID-19 vaccination campaign in the University of Notre Dame, Indiana, USA. (Bivins and Bibby, 2021) They found a decrease of SARS-CoV-2 RNA in wastewater during and after the second vaccination dose campaign. However, they also noted that the number of clinical cases dropped to zero after the vaccination campaign, making it difficult to interpret the data as a case of lower shedding rates or simply no clinical case in the catchment. A group from Beer-Sheva, Israel, has observed decreasing in SARS-CoV-2 concentration in wastewater as the vaccination rates increased and the number of clinical cases decreased (from February to June 2021). (Yaniv et al., 2021) The two studies above described a concomitant decrease in both virus wastewater concentration and infection following the vaccination campaigns.

On the contrary, other studies have shown different results, where the wastewater viral signal remains higher than expected despite low confirmed cases and high vaccination coverage. Zhan et al. (Zhan et al., 2022) observed that the wastewater concentration continued to increase while the reported COVID-19 cases stabilized during the period of increasing vaccination rates. They also noted that this could also be linked to the switch of the dominant variant. (Zhan et al., 2022) Another study in New York City reported that SARS-CoV-2 signals remained present in wastewater even though confirmed cases fell below the calculated minimum detectable cases in the catchment. (Hoar et al., 2022) Similar observations were published in two studies from Italy (Nattino et al., 2022; Cutrupi et al., 2022) and a study in Spain (Novoa et al., 2022) where by it is hypothesized that there might be a viral circulation in vaccinated populations and that clinical cases underreport infection rates. The disagreeing conclusions above showed that immunity status changes of the population and variant switch might have changed the population's symptom presentation and response to the COVID-19 disease (e.g., case self-reporting).

The mixed conclusions reported are exacerbated by two other factors: 1) lack of established quantitative metric to relate wastewater to clinical data, and 2) mismatch between population under the WBS catchment and population where vaccination records are reported. Our group has recently proposed the ratio of wastewater concentration to reported clinical cases (WC ratio) as a candidate quantitative metric that summarizes the relationship between these two parameters. (Xiao et al., 2022) Utilizing this metric, we analyzed published wastewater and epidemiological data from The Netherlands, as the population used to derive wastewater data (greater than 99 % of the total population) (WHO, 2020) largely matches national vaccination records. (Ministerie van Volksgezondheid, 2022) This type of dataset, where vaccination records can be confidently matched with the population under WBS, could function as a 'model system' in determining the effects of vaccination on wastewater data.

Based on the analysis of The Netherlands data, multiple factors such as variant emergence and testing capacity seem to contribute to the changes in WC ratio and thus make it difficult to determine the impact of vaccination towards SARS-CoV-2 RNA concentration in wastewater (Fig. 2 Panel C). Nevertheless, the observed WC ratio variations are all within 1 log until the beginning of 2022 (during the vaccination rollout in the country). The WC ratio trends after the early months of 2022 showed sharp increases from previous levels. We hypothesize that this is mainly due to the decrease in clinical testing (and subsequently reported positive cases), coupled with an increase in viral wastewater concentrations. The result is in line with a recent paper where D'Aoust et al. found that the WC ratio increased in the communities across seven cities in Canada. They hypothesized that this was due to insufficient clinical testing. (D'Aoust et al., 2022) A similar study was conducted by Hegazy et al. (Hegazy et al., 2022), and they found a weakened relationship between wastewater signal and COVID-19 incidence under limited clinical testing circumstances. In summary, it is still undetermined whether vaccination programmes significantly impact the interpretation of wastewater data and how it relates with clinical reports. (Hegazy et al., 2022).

It is still difficult to determine the exact impact of the COVID-19 vaccination campaigns on SARS-CoV-2 wastewater concentration as there are conflicting results. Moreover, to the best of our knowledge, there are no direct data on the effects of vaccination on GI shedding rates in breakthrough infections. There is also uncertainty on how vaccination campaigns affect the number of reported cases, as it can be affected by many other factors (in addition to testing capacity).

In this complex landscape, we conclude that WBS continues to be valuable to provide situational awareness of trends across timeframes and spatial areas. We can note that modelling wastewater concentrations as a function of clinical cases has always been subject to large uncertainties (e.g. several orders of magnitude variation in shedding rate). Moreover, changing landscape of vaccines and VOCs will likely increase this uncertainty in the future, complicating comparison of wastewater surveillance signals across long time frames but still supporting robust use of WBS for real-time trends.

4. Conclusion

The highly dynamic and evolving nature of the COVID-19 pandemic - due to vaccine rollouts, emergence of breakthrough variants, and increase in testing capacity - requires the scientific community to constantly adapt and modify its interpretative framework. Based on historical data, clinical studies, and current WBS reports, we identified at least 8 viruses (refer to Table 1 & 2) that are currently or potentially targets for WBS programs that may have wastewater signals from vaccine shedding. However, for SARS-CoV-2, we found no evidence of vaccine-shedding where uninfected, vaccinated individuals contributing to SARS-CoV-2 RNA levels in wastewater. However, if orally administered replicating or attenuated COVID-19 vaccines will be authorized, an analysis of vaccine shedding needs to be re-considered; additionally, the wastewater community may need to update workflows to differentiate the wild-type strains from the vaccine ones in wastewater monitoring. The question of how COVID-19 vaccination campaigns affect the interpretation of WBS data remains difficult to determine due to confounding factors, like changing the shedding dynamics of SARS-CoV-2 variants. However the value of WBS has been well established for revealing trends in viral shedding across time and sewersheds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [Eric J Alm reports a relationship with Biobot Analytics, Inc. that includes: consulting or advisory and equity or stocks.].

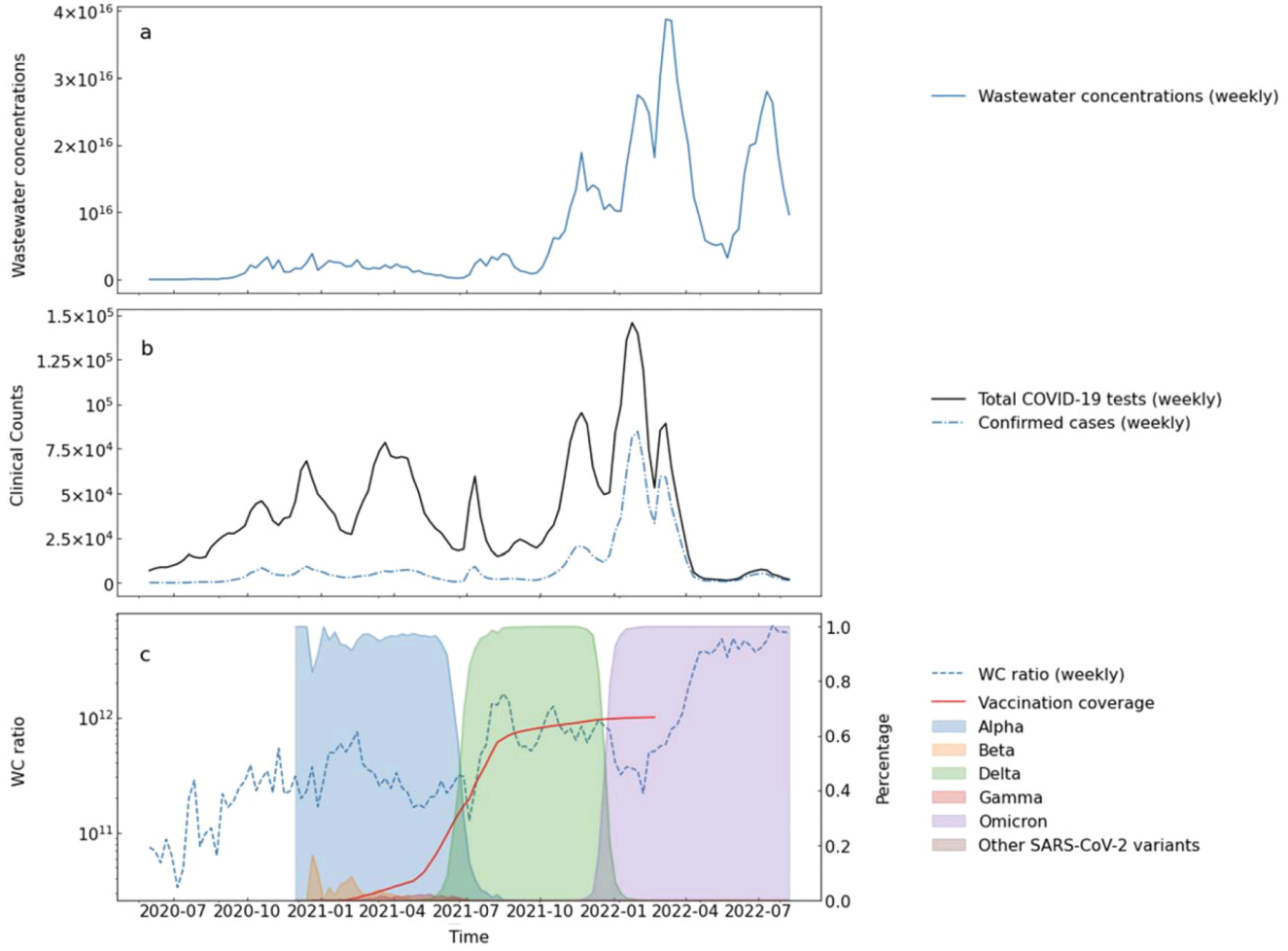

Fig. 2. SARS-CoV-2 wastewater concentration, COVID-19 clinical cases and their ratio for the population of The Netherlands from mid-2020 to mid-2022. To analyze the effect of vaccination coverage on wastewater data, we downloaded publicly available data from The Netherlands (RIVM, accessed 8 August 2022) and plotted the ratio between the number of clinical case and the SARS-CoV-2 wastewater concentration from June 2020 to August 2022. Panel a: SARS-CoV-2 7-day-average wastewater viral RNA per 100,000 inhabitants over time. Panel b: Total testing conducted and positive clinical cases data (weekly) over time. The number of tests conducted with known results (dark blue) and the number of positive results (dash-dotted light blue). Panel c: Ratio between 7-day-average wastewater viral RNA and weekly new cases (WC ratio; dashed blue line) with the percentage of vaccination coverage (red line). Percentages of circulating SARS-CoV-2 variants over time are shown as shaded areas. The population vaccination coverage is reported until 21 February 2022. Results were analyzed and visualized using Python version 3.6, with the code available on GitHub at https://github.com/XiaoqiongGu/Armas_Chandra_2022_CovidVaccine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Data availability

Data will be made available on request.

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