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Addressing Vaccine-Related Errors in the COVID-19 Vaccination Programme:

The Impact of Non-Compliance with Standard Operating Procedures

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Dedications

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Abbreviations

AEFI	Adverse events following immunisation
APB	Association Pharmaceutic Belge
ATAGI	Australian Technical Advisory Group of Immunisation
BMI	Body mass index
BNT	Comirnaty®
CDC	Centers for Disease Control and Prevention
ChAd	Vaxzevria®
COVID-19	Coronavirus disease 2019
CSS	Superior Health Council
EMA	European Medicines Agency
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
FPS	Federal Public Service
GCP	Good clinical practice
HAS	Haute Authorité de la Santé
ISMP	Institute for Safe Medication Practices
KCE	Health Care Knowledge Centre
m1273	Spikevax®
MDV	Multi-dose vial
mRNA	Messenger ribonucleic acid
NVX	Nuvaxovid®
PDI	Polydispersity index
PFS	Pre-filled syringe
RCT	Randomised controlled trial
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard operating procedure
UK	United Kingdom
ULT	Ultra-low temperature
VAERS	Vaccine adverse event reporting system
VRE	Vaccine-related error
WHO	World Health Organization

Introduction

In late December 2019, 1,975 cases of an atypical respiratory disease were reported leading to the identification of the novel coronavirus SARS-CoV-2 as the causal agent. Less than two weeks later, on January 10 of 2020, the 29,903 bp genomic sequence of the virus was published. Researchers from all around the world started working on coronavirus disease 2019 (COVID-19) vaccines. Three months later, on March 16 of 2020, Moderna started the Phase I study of 2019-nCov Vaccine (mRNA-1273) for prophylaxis of SARS-CoV-2 infection.

Figure 1: "from sequence to release 42 days" exposed at the Science Museum of London, 2022 (picture made by author)

On May 29 of 2020, mRNA-1273 was among five others undergoing Phase II clinical trial (Wang, Jieliang et al., 2020). Two traditional inactivated vaccines and four new-generation vector-based, including two mRNA vaccine candidates, mRNA-1273 developed by Moderna and NIH, and BNT162b2 produced by Pfizer and BioNTech, received on December 21 of 2020, under the marketing name of Comirnaty®, a conditional marketing authorisation by the European Commission for the prophylaxis of COVID-19.

Less than a year after the first case reported, the pharmaceutical industry, thanks to the incredible work of the scientific community, succeed to develop, produce and manufacture a safe and effective vaccine for the prophylaxis of COVID-19.

This was the beginning of a new challenge: to vaccinate the population the quickest way possible, in the context of a pandemic, with new logistical constraints. At the time, Belgium was significantly impacted by the pandemic, with hospitals overwhelmed and vaccination being

a crucial hope. The Belgian inter-ministerial Conference on Public Health set the objective of eventually vaccinate at least 70% of the population, starting by the most vulnerable.

The crisis context, unusual handling conditions and the desire not to waste any dose can however lead to vaccine-related errors (VREs). Despite this, mass vaccination must be carried out in the safest way possible to ensure safe and effective global immunisation and to prevent vaccine hesitancy.

Methodology

The aim of this work is to assess the impact of vaccine-related errors due to non-compliance with standard operating procedures (SOPs) on the safety and efficacy of the adult COVID-19 vaccination programme in Belgian vaccination centres.

Firstly, in the chapter *1. general concepts* the definition and the prevalence of vaccine-related errors, the way in which vaccination centres are operate and the challenges associated with the use of COVID-19 vaccines are presented. In the chapter *2. Vaccine storage*, the way of presenting vaccines and the challenges associated are exposed.

Secondly, the vaccine-related errors that will be the subject of this work, are described in the chapter *3. Most common vaccine-related errors*. After that, an online survey that I conducted in order to assess the compliance and understanding with SOPs in vaccination centres is discussed in chapter *4. Online survey about vaccination centres.*

Finally, the core of this thesis is secondary research of non-systematic literature analysed with the aim of assessing the impact of these vaccine-related errors on the safety and efficacy on the COVID-19 vaccination programme, which is presented in chapter 5,6,7 and 8.

1. General concepts

1.1 Vaccine-related errors

1.1.1 Definition

Vaccine-related errors are defined as any mistake or malfunction that occurs during any stage of the vaccine process, such as vaccine preparation, handling, storage or administration. Vaccine-related errors are most often routine mistakes (due to the lack of concentration), mistakes related to the failure to apply standard rules or knowledge-related mistakes. (Reason James, 1990)

1.1.2 Prevalence

The prevalence of vaccination errors has been assessed in a systematic review of 17 studies from 2009 to 2018. In this paper the calculated prevalence was 1.15 per 10,000 vaccine doses, moreover vaccination errors were estimated to be responsible of 1.1% to 51.8% of adverse events following immunisation. (Jesse Morse-Brady et al., 2019)
Additionally, a study in a large academic medical centre identified out of 1,431,206 vaccine doses given, 552 vaccine administration errors, which is equal to a prevalence of 4 per 10,000 vaccine doses. (Lauren Reed et al., 2019)
Finally, an increase in the number of reported vaccine-related errors was observed in a descriptive study, indeed, from 2001 to 2016 all vaccine Individual Case Safety Reports (ICSR) increased from 0.4% to 4.0%. (C.E Hoeve et al., 2018)

In both studies the prevalence of VREs was low and very few cases of very severe adverse events (VSERs) were observed. The greatest concern, therefore, was the missed opportunity of vaccination, and the resulting lack of protection.

However, vaccine-related errors may also have dramatic consequences. Indeed, in 2014, 15 Syrian children died following an immunisation with a vaccine reconstituted with the wrong diluent. Likewise, in 2017, 15 children died after receiving a vaccine that was contaminated during reconstitution in South Sudan. (L.M. Hampton, 2020).

These tragic incidents point out the potentially lethal consequences of mistakes, and the necessity of taking actions in order to minimise risks. Although such tragic events are sadly more common in low- and middle-income countries, upper-income countries are also prone to deaths due to maladministration caused by VREs. Indeed, in Japan, two people died following

the administration of Moderna COVID-19 Vaccine (Spikevax®), both vaccines came from the same lot. Investigations reported that black substances were found in syringes and vials. Less than one month later another man died after receiving a vaccine still from the same batch. After further investigations, the official statement stated that the contamination was due to a manufacturing error and from incorrectly inserted needle which caused vial coring. (Wen Han Chooi et al., 2022).

In addition to the low risk of AEFI and potential reduced vaccine efficiency, the risk of fatal adverse event following a VRE is therefore not nil. This has tragic consequences not only on an individual level but also for the community, as these incidents can contribute to vaccine hesitancy and further missed vaccination opportunities. (J. Morse-Brady, A. Marie Hart, 2018) Finally, it has been suggested that VREs are often associated with the use of new vaccines, especially those that require reconstitution. (Lee, Young Hwa et al., 2021).

1.2 Vaccination centres

In most countries, the large-scale COVID-19 vaccination programme started in vaccination centres, we will explore the rationale behind these centres and gain insights into their operational procedures.

Faced with this new challenge of mass vaccination, authorities had to consider various constraints. First of all, Comirnaty® vaccine required at the time a storage at ultra-low temperature (ULT) (-80 °C) which is possible only with special freezers, such equipment is only available in major hospitals. Second of all, people had to be able to get their vaccine in a space that can maintain respect for barrier gestures, and where they can be kept for 15 to 30 min in surveillance. Finally, health products related to COVID-19 crisis were at the time very critical in a security perspective, the delivery and storage had to be monitored by competent authorities. For all these reasons, Belgium decided to lunch vaccination centres for the COVID-19 vaccination programme.

1.2.1 Responsibilities in Belgium

A Task Force Operationalisation of the COVID-19 Vaccination Strategy, composed of pharmacists, doctors and other scientists was created in November 2020. Their biggest missions were to develop a vaccine introduction programme and raise vaccination centres.

The Task Force, in collaboration with the Federal Agency for Medicines and Health Products (FAMHP) and the Federal Public Service (FPS), produced the standards operating procedures related to the use of COVID-19 vaccines in vaccination centres. SOPs are comprehensive procedures explaining in detail, every step of the use of vaccines. These SOPs, written by Belgian authorities, are mainly based on SOPs produced by firms themselves, they are qualified to guarantee a safe and efficient use of the health product involved. It is the responsibility of health care professionals to strictly stick to SOPs and more generally, to follow recommendations of good clinical practices (GCPs), otherwise, any deviation must be justified and documented.

Furthermore, GCPs recommendations can be used in court, to assess the diligence of a health care professional. For example, if citizens decide to take action against a physician, they will have to prove that the doctor did not follow GCPs. In this manner, the Belgian Health Care Knowledge Centre (KCE) argues that health care workers who correctly apply GCPs should be protected to the maximum extent possible in the event of liability claims.

By strictly adhering to standard operating procedures and good clinical practices, patients and health workers are therefore, protected. (Vinck Imgard et al., 2006)

1.2.2 Organisation of vaccination centres

Vaccination centres were distributed in the major cities of the country, most often, in big event centres, or gymnasiums. They were composed of two main zones: individual boxes where people get their injection and a surveillance room, defined as a large space with chairs spaced out from each other where patients freshly vaccinated are kept 15 to 30 min under surveillance, in case of an anaphylactic reaction following their immunisation. (Gianfredi, V et al., 2021)

Very seldom, some patients can indeed have an allergic reaction to a vaccine, in the vast majority of cases, this is triggered within 15 minutes and rapid medical attention is required. In this manner, the Centers for Disease Control and Prevention (CDC), reported that between December 2020 and January 2021 out of 10 cases of anaphylaxis reported (2.5 case per million doses administered) following Moderna COVID-19 vaccine, 9 cases onset occurred within 15 minutes of vaccination. (Sampath et al., 2021).

In addition to those two well-known areas, other spaces were set up for vaccination workers. The pharmacist office where fridges containing vaccines are stored, doctors and administrative staff offices, and finally a separate room where vaccines are prepared.

Vaccination centres were operated by a multidisciplinary team of health care professionals composed of:

A supervising Medical Doctor: who has the responsibility of the centre and deals with administrative tasks such as the online registration of vaccination certificates.

Preparators and vaccinators: they are healthcare professionals such as nurses, pharmacist assistants, or medical, pharmacy, or biomedical sciences students. The preparators' responsibility is to prepare the vaccine doses, ensuring proper handling and preparation of the vaccines. On the other hand, the vaccinators are in charge of administering the intramuscular injections to patients, following appropriate protocols and guidelines.

Pharmacists: their role encompasses the responsibility for vaccine stock management, storage, handling conditions, and preparations. They manage the receipt of vaccines, which may transit from hospital hubs where they are stored at ULT to the centre, and ensure their conformity. More generally, they ensure that the SOPs related to vaccine handling, storage, and utilisation are respected. Pharmacists are most often hospital pharmacists or retail pharmacists trained by the Belgian Pharmaceutic Association (APB) for this specific role. (Maesschalck et al., 2021. Manuel de l'expert pharmaceutique [PDF file].)

2 Vaccines storages

2.1 Containers

There are two main ways of presenting vaccines: pre-filled syringes (PFSs) and multi-dose vials (MDVs). In this section, we will see why COVID-19 vaccines are stored in multi-dose vials and what are the challenges associated to this technology.

2.1.1 Pre-filled syringes

Pre-filled syringes are ready to use drug delivery system for parenteral drugs. The right amount of active substance is already stored in a glass or plastic barrel, the needle can be, depending on the model, already fitted on the barrel or not, the content is protected from the environment.

PFS is an innovative drug delivery system that significantly reduces the risk of overdose or underdose, is it also easier and quicker to use. (Rahul G Ingle, Aayush S Agarwal, 2014)

In a study related to VREs in South Korea, it was expressed by health workers that PFSs could reduce the risk of errors. In addition, in this study, 94.8% of physicians had experienced PFSs for vaccination, and all preferred this delivery system. (Lee, Young Hwa et al., 2021)

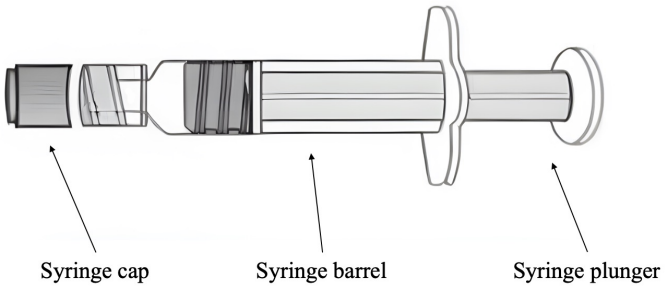


Figure 2 *Schematic view of pre-filled syringe (generated by AI)*

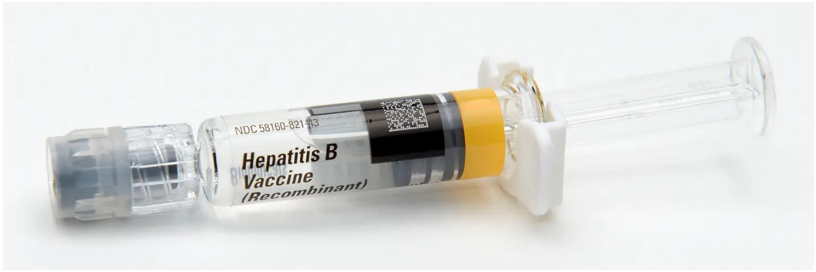


Figure 3 Pre-filled syringe of Hepatitis B vaccine (M.Shields / Alamy Stock Photo)

2.1.2 Multi-dose vials

A multi-dose vial is defined as a vial that contains more than one dose of medication. MDVs are widely used in hospital contexts as primary packaging for parenteral drugs such as propofol or amoxicillin.

Figure 4 Schematic view of a multi-dose vial (adapted from Sashkin / Shutterstock)

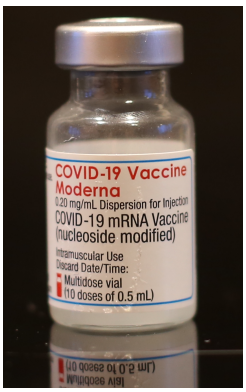


Figure 5 COVID-19 Vaccine Moderna® in a muti-dose vial (picture made by author)

MDVs are available in different sizes, they are composed of a rubber stopper and a glass vial, sealed with an aluminium crimp cap, and on top of that, a plastic flip-off cap. This design prevents the parenteral sterile drug from being contaminated by the environment.
Moreover, the rubber stopper is made to keep its environment-proof properties even after the needle has been inserted in the vial.

The risk of contamination is however not equal to zero and increases each time needles go through the rubber. Medications stored in MDVs most often contain a preservative agent to decrease the risk of contamination. When the medication is in a lyophilised or a concentrated form, the reconstitution is realised by simply injecting the diluent directly into the vial. (Centers for Disease Control and Prevention (2023). Vaccine Storage and Handling Toolkit [PDF file].)

2.1.3 The great use of multi-dose vials for the COVID-19 vaccines

Pre-filled syringes are the safest and easiest delivery system for parenteral drugs. Modern vaccines are most often stored in PFS, and as we will see, many VREs can be prevented by using this delivery system. However, all COVID-19 vaccine manufacturers decided to use MDVs for the storage of their vaccines. Nonetheless, there are many arguments to explain this choice.

First of all, the economic perspective, manufacturing costs are divided in three categories: production (labour and equipment), material packaging and vaccine overfill adjustment percentage, all are cheaper with MDVs. According to a 2003 publication the manufacturing costs were 60% cheaper for a MDV, with an estimated cost of $0.105 per dose for a 10-dose vial versus $0.242 per dose for a pre-filled syringe (Drain Pk et al., 2003).
In more recent studies, the use of MDVs was still associated with cost savings, for example, after implementing a multi-dose vial policy, Egyptian public health authorities reported saving $2,449,079 in one year, representing 0.013% of the annual health budget in Egypt in 2016. (Radwan, Naglaa Fathy et al., 2021)

Beyond the economic benefit, the vaccine distribution is easier with MDVs, vaccine tracking and inventory required less health workers, batches are smaller and lighter for transport. Also, MDVs occupy a less large cold-chain volume per dose. All these arguments are truer in the context of COVID-19 mass vaccination.

Moreover, the use of MDVs reduces medical waste. Indeed, lyophilised or concentrated single-dose vaccines required a second syringe for the reconstitution, which double the amount of sharps waste. As for lyophilised or concentrated MDVs, they only need one syringe dedicated to the reconstitution for 10 doses (in the case of a 10 dose MDV), which causes significantly less medical waste.

However, there are also some challenges with the use of MDVs. Firstly, there are some safety concerns. Indeed, MDVs are much more likely to be contaminated, additionally, MDVs could be affected by a so-called coring phenome, indeed, when the needle passes through the rubber stopper, fragmentation of the stopper may occur, it could get stuck in the needle and be injected into a patient. Finally, there is a risk of overdose or underdose, since health workers have to manually draw a specific quantity of suspension, which can lead to mistakes. Those VREs can range from no clinical reactions to life-threatening adverse events.
A second concern is the vaccine waste rate, which is greater for MDVs. Indeed, when a vial is reconstituted with saline solution and a first dose is withdrawn, there is a limited time to use the rest of the vial, if not used, doses must be discarded.

These issues are two big challenges, vaccines are medications given to people that are not sick, and to a very large population, they must therefore be safe, and COVID-19 vaccines may be safer than ever considering the vaccine hesitancy. Also, considering the very low quantity of vaccines available for the population at the start of the pandemic, wasting doses is unthinkable. (Saurav Basu et Ruchir Rustagi, 2022)

Nevertheless, given the need to reduce costs, reduce storage spaces, facilitate logistics, and reduce medical waste, considering that the risk of contamination is assessed as low if Good Clinical Practices (GCPs) are respected, and considering the vaccine waste rate can be minimised with a good management, especially in vaccination centres, for all those reasons, the use of MDVs is a reasonable choice in the case of COVID-19 vaccination programme in vaccination centres. Health workers must however have those challenges in mind and take actions to minimise the risk of vaccine waste. More importantly they should be aware of the risks of contamination and of vaccine-related errors associated with the use of MDVs.

2.1 Characteristics and challenges with mRNA vaccines

In addition to being stored in multi-dose vials, first available COVID-19 vaccines were innovative in terms of technology platform, these new types of vaccines also pose challenges.

Messenger RNA (mRNA)-based vaccines are composed of nucleoside-modified mRNA sequence stored in nanodelivery system, a lipid nanoparticle. The mRNA sequence codes for the SARS-CoV-2 spike protein, which is normally expressed by the virus and will be detected by the immune system, which will induce a cellular and antibody reaction against it.
The lipid nanoparticle plays a dual function, by protecting the mRNA from enzymatic degradation, and by driving the complex into the cell, where the mRNA should be delivered. (Alfagih, Iman M et al., 2020)

It is known that naked mRNA is unstable and likely to be degraded by RNase. Even if the mRNA is modified in order to minimise this risk, it is very important that the mRNA stay within its delivery vector. Also, the mRNA by itself would not be able to penetrate the cell due to its anionic charge and large molecular weight. (Wadhwa, Abishek et al., 2020)

Vaccines must then be stored and handled, in a way that can prevents mRNA from leaving its lipid vector. Moreover, aggregation is an important concern, indeed, studies conducted by Moderna shown that the lipid nanoparticles should be between 75 nm and 95 nm to allow optimal efficiency (Hassett KJ, Benenato KE, Jacquinet E, et al., 2019).
Additionally, in order to enter the lymphatic system, access to dendritic cells and therefore induce B cell activation which is a vital process for vaccine efficiency, nanoparticles must be in the size range of 10 to 100 nm. (Hajj Ka et al., 2017)
If the molecule is too large, the endocytosis internalisation into the cell will be less effective and impact the vaccine's potency. Aggregation is thus a phenomenon to avoid.

It is with all these considerations that Pfizer-BioNTech and Moderna announced that their vaccines would require special handling and storage conditions. Comirnaty® vaccine will have to be stored at ULT (-80 °C to -60 °C) and Spikevax® vaccine at -20 °C. Once unfrozen, they can respectively stay up for 5 and 30 days, at 2-8 °C.

Formulated mRNA vaccines bring their set of challenges, with these stability and storage conditions. Some scientists blame firms for not working enough to solve those issues.

In the absence of comprehensive stability data, the handling and storage conditions must then be very strict. Public health authorities will have to manage this logistical challenge. (Crommelin, Daan J A et al., 2021)

In the following chapters the most common VREs that may occur in the vaccination centres during the COVID-19 vaccination programme will be discussed. The impact of each of these VREs on the safety and efficacy of the vaccine will then be assessed based on secondary research.

3. Most common vaccine-related errors

3.1 The standard operating procedure for the use of vaccines

The procedure for administering the COVID-19 vaccine to adults in Belgian vaccination centres is described in a comprehensive standard operating procedure.

To begin with, the vaccine preparation process involves several steps. After disinfecting the working surface and preparing the necessary equipment, the healthcare worker carefully inspects the vaccine suspension stored in a multi-dose vial. To ensure uniformity, the suspension is homogenised by performing ten gentle inversions of the MDV. It is important to note that shaking the MDV must be avoided.
Following this, the preparator removes the flip-off cap and disinfects the rubber stopper on the top of the vial using an alcohol swab. A waiting period of 30 seconds is observed to allow the rubber stopper to dry. The required amount of vaccine suspension is then drawn into low dead-volume syringes. In some cases, depending on the vaccine manufacturer, an additional step of vaccine dilution may be necessary prior to this process.
The preparator verifies that the correct quantity of vaccine suspension has been drawn into the syringes and labels it with essential information such as the batch number, time of preparation, and vaccine manufacturer. The drawn syringes are stored at room temperature, protected from the light, and must be administered within a period of six hours.
After this process, an overfill volume of vaccine suspension may be present, the SOP specifies that this overfill suspension must not be pooled with overfills from other MDVs to reconstitute an additional dose.

Vaccines are then transported from the preparation area to the vaccinators area, where vaccines are administered. After placing the patients in individual boxes, vaccinators check the

expiration date and time of the syringe, the manufacturer and perform an intramuscular injection into the patient's upper arm. The SOP specifies that if the patient's skin is clean, the skin disinfection step must not be performed. (Task Force Vaccination (2022). COVID-19 programme de vaccination Standard Operating Procedures Centres de vaccination [PDF file]).

3.2 Deviations from the standard operating procedure

During this process human errors may occur, due to miscommunication, lack of proper training, or desire to keep pace with a high production rate.

In the study related to VREs in South Korea, 450 nurses and 250 doctors were asked what they considered to be the main cause of VREs. The complex vaccine preparation process and the lack of time to prepare the vaccines were the two main reasons reported by nurses, while being less careful because of the overall workload was the principal cause of VREs according to the doctors surveyed. (Lee, YH et al., 2021)

Consequently, in a context of pandemic with a very large flow of people to vaccinate, the risk of maladministration following VREs may be increased, which lead to a risk of reduced efficacy and AEFI. However, due to the scarcity of vaccine doses and the desire to avoid wastage, healthcare professionals may be inclined to continue despite deviating from the protocol, considering the mistake to be non-critical. The safety and efficacy of the administered vaccine then depend on the judgement of the vaccinator regarding the significance of the error.

Henceforth, it is essential to be aware of the rationale behind every step of the SOP and to know whether a deviation would have a significant impact on the safety and efficacy of the vaccine, in order to be able to decide if the vaccination should be repeated, or if safety measures should be taken.

3.3 The nine most common vaccine-related errors

Based on case reports and on my personal experience in the Vaccination Centre of Namur, I have identified the most common potential VREs, they are divided into three categories:

a) Errors related to poor vaccine reconstitution: this includes reconstitution with the wrong diluent or insufficient dilution leading to a risk of overdose

b) Errors related to bad handling conditions: this involves shaking the MDV for homogenisation and neglecting to disinfect the rubber stopper.
c) Errors related to administration: this encompasses injecting the wrong medication, administering the wrong vaccine or via an incorrect administration route.

Furthermore, two contentious aspects of the procedure will be discussed: the prohibition of pooling leftovers from different MDVs to reconstitute an additional vaccine dose, and the exclusion of pre-administration skin disinfection.

But prior to that, an online survey conducted at the Vaccination Centre of Namur will be presented.

4. Online survey about vaccination centres

4.1 Introduction

In order to assess vaccination workers' compliance and understanding with SOPs during the COVID-19 vaccination programme in vaccination centres, as well as to evaluate if vaccination centres are run respecting federal directives, I conducted a five-minutes long, online survey for health professionals who have been involved in the vaccination duty.

4.2 Methods

The survey was divided into four parts, in the first one, respondents had to indicate their occupation, place of work, and role within the centre (e.g. administration of vaccines). In the second part, various situations were presented (e.g. vigorously shaking the multi-dose vial), respondents had to give their view about it. The third part looked at the differences between the official protocol and rules that are actually followed in practice within the centre.
Finally, in the last part, people were asked to rate the recurrence of different vaccine-related errors, whether the mistakes were made by themselves or by colleagues.

For all parts, respondents had to choose between the written answers or could write another answer themselves in the 'other' box, they were also able to skip the answer without responding. The survey was sent on Saturday 7th of January 2023 by email to all former and current health workers of the Vaccination Centre of Namur. Between Saturday 7, and Monday 9, 54 people responded to the survey.

4.3 Results

Among the 54 participants responding to the survey, 55.6% (n = 30) were nurses, 16.8% (n = 9) were pharmaceutical, biomedical, or medical sciences students, 14.8% (n = 8) were physicians, and finally, 9.3% (n = 5) and 5.6% (n = 3) were respectively pharmacists and pharmacy assistants. All 54 respondents reported working in a vaccination centre, some of them also did vaccination duty in pharmacy, hospital, nursing home, medical practice or even in prison. 75.9% (n = 41) of respondents were in charge of administering vaccines, 46.3% (n = 25) of vaccine preparation, 11.2% (n = 6) of medical and general supervision, 9.3% (n = 5) of vaccine preparation and storage condition supervision and finally 5.7% (n = 3) were emergency nurses.

For this section multiple selection was available as it is not rare to be in charge of vaccine preparation or vaccine administration on different days. Table of results of the first part of the survey is represented in table 1. Results of second and third part of the questionnaire are presented in table 2 and table 3. All tables are available in appendix

The last part of the survey focused on the recurrence of different vaccine-related errors. For several situations described, respondents had to evaluate the error rate by choosing from: 'never' to 'very frequent'. For certain VREs, many respondents choose 'I have no opinion' response as they were not involved in the preparation of vaccines for example, following results are presented omitting people who declared having no opinion. Full results are however available in appendix.

4.4 Discussion

Results of this survey showed a lack of compliance and understanding with the standard operating procedure, it also shows that health workers do not always see rules as useful, which could explain the low compliance. For example, only 32% (n = 16) of respondents consider that disinfecting the rubber stopper of MDVs is essential to prevent the risk of infection.

Additionally, 35.3% (n = 18) of respondents wrongly think that rubber stoppers are guaranteed to be sterile, 24% (n = 12) of respondents even consider this practice bad as alcohol would interact with the active substance.

More worryingly, although it is mentioned in the SOP that multi-dose vials should be handled with care, and that MDVs must not be shaken but only gently inverted when homogenise the suspension, 34% (*n* = 17) of respondents stated that shaking the MDV vigorously is a good practice as it allows a good homogenisation, additionally, 15.2% (*n* = 5) of respondents rate this behaviour as frequent.
Similarly, in the study conducted by Young Hwa Lee and her team, out of 250 physicians interrogated, 28.0% (*n* = 70) of respondents declared making the mistake of inadequately shaking vaccine vials more than once per 100 vaccinations. (Lee, YH et al., 2021)

About the process of disinfecting a patient's arm prior to administrating the vaccine, as we will see later, it is a controversial practice, this survey revealed that 27.8% (*n* = 15) of participants think it is important to do it, when 33.3% (*n* = 18) of respondents say at the opposite that it is unnecessary.
In the same manner, about the act of pooling different vial left-overs to reconstitute additional doses, health workers are divided with 32.7% (*n* = 17) of respondents saying that this practice should be authorised, 34.6% (*n* = 16) saying that it is reasonable to prohibit this practice and 25% (*n* = 13) reported not being able to say if it should be authorised or not. Additionally, 7.7% (*n* = 4) of participants declared pooling vials even if the protocol prohibits it.

The third part of the survey revealed a relatively good accordance with national guidelines, indeed, 73.5% (*n* = 36) of participants stated that it was customary not to disinfect patient's arm prior to administering vaccines as it is required. In the same manner, 77% (*n* = 30) of respondents declared that pooling vial left-overs was not operated. However, only 54% (*n* = 20) of people said that the process of disinfecting vials' rubber stoppers was in practice carried out. Three people specified that they used to do it, but the rule has changed and now it is not customary any more to process to the disinfection of the rubber stopper, although the official procedure produced by the Task Force Vaccination remains the same.

Furthermore, in this protocol, a special paragraph is devoted to citizens in situation of obesity, in which, it is specified that the use of a longer needle is required in order to assure an effective intramuscular injection. However, it appears that it is not the case in the Vaccination Centre of Namur, as 95.7% (*n* = 45) of participants stated that it was customary to use the same needle as usual when administering a vaccine to an obese person. This situation was then, explained by the fact that the organisation that determines the quantities of vaccines and medical equipment

to be delivered to vaccination centres in Wallonia, AViQ, only provided a very limited stock of 38 mm long needles, which made the correct application of the procedure very complicated.

Initially, the survey was to be sent to health workers from vaccination centres of different Belgian cities in order to be representative of all Belgian centres. Unfortunately, as many centres are now closed and as it was harder than expected to find and contact enough people of different locations, I finally decided to focus my survey on only one vaccination centre, the Vaccination Centre of Namur, capital of Wallonia, this is of course a limitation, however, vaccination centres are supposed to follow the same guidelines and protocols, and if SOPs are not correctly understood and followed at the Vaccination Centre of Namur, it is likely that similar issues will be encountered in other centres.

4.5 Conclusion

Overall, the vaccination centre complies with national guidelines, procedures related to the use of vaccines followed in this centre are those officially given by the Task Force Vaccination, although, due to an insufficient stock of suitable needles, it seems that optimal care for obese citizens is not ensured.

Furthermore, this online survey demonstrates a lack of compliance with certain rules of the SOP by a significant number of health workers. This could be associated with a misunderstanding of those rules. Similarly, with regard to the disinfection of the rubber stopper, responses varied widely between respondents, although the SOP is clear on this, demonstrating little consistency in compliance with the protocol between different health workers.
According to this survey the most frequent vaccine-related error is the inadequate shaking of the vial, which was also found to be a common mistake in a more robust study.

This study has limitations, the main one being that it is focus on only one vaccination centre, nonetheless, issues encountered in this centre are very likely to be similar in other places.

Demonstrating the relevance of different steps of the SOP could improve health worker's compliance with SOPs, as it appears that health workers who do not understand a rule are more likely to break it.
Thus, in the following chapters, the impact of vaccine-related errors will be assessed and the rationale behind specific rules will be described.

5. Errors related to poor vaccine reconstitution

In order to limit the risk of degradation by hydrolysis and thus improve its stability and shelf life, vaccines are sometimes lyophilised (or freeze-dried), this makes them more convenient to use as they can be stored at room temperature. Although Pfizer has indicated working on a freeze-dried form of its COVID-19 vaccine, it is currently only available in a fully-liquid, but concentrated form. Nevertheless, whether in concentrated or lyophilised form, vaccines need to be reconstituted with a specific diluent. To do so, an operator needs to withdraw 1.8 mL of sodium chloride 0.9% solution for injection and directly inject it into the MDV. The SOP then requires to gently inverse the vial ten times, in order to homogenise the suspension.

Even if this process is not complex, mistakes may occur. A potential error is to collect the solution from a poorly homogenised multi-dose vial. Indeed, if the vaccine suspension and saline solution are not well mixed and distributed within the vial, the dose withdrawn could be either under diluted or over diluted. Another potential vaccine-related error would be to reconstitute vaccines with the wrong diluent.

5.1 Reconstitution with the wrong diluent

Reconstitution of vaccines with the wrong diluent is a well-known VRE that has caused deaths, for example in Syria or Samoa, as mentioned earlier. Indeed, a muscle relaxant was used for reconstitution instead of sterile water, tragically resulting in the deaths of 17 children. (L.M. Hampton, 2020)
Typically, such errors occur when diluents are stored in refrigerators with other injectable solutions, creating the potential for confusion.

However, of the COVID-19 vaccines, only Pfizer's vaccine requires reconstitution with 0.9% sodium chloride, and therefore should be the only diluent stored in vaccination centre refrigerators. Thus, although the Institute for Safe Medication Practices (ISMP) stated that one case of reconstitution with sterile water for injection instead of 0.9% sodium chloride, has been reported, reconstitution of vaccines with the wrong diluent are very unlikely during COVID-19 vaccination programme in Belgian vaccination centres since 0.9% sodium chloride is the only diluent stored, consequently, it will not be addressed further.

5.2 Reconstitution with not enough diluent (risk of overdose)

Two VREs related to mistakes in the reconstitution process can result in an overdose of vaccine. The first is withdrawing a shot from an undiluted vial. Indeed, because Comirnaty® vaccine is stored in liquid form and requires only 1.8 mL of diluent, it is in fact, not easy to tell the difference between an undiluted and a diluted MDV. In addition, vaccination centres often have preparators working in pairs, with one health worker handling the dilution and the other taking withdrawing shots. When the bench is full of both diluted and undiluted MDVs, it is sometimes possible to confuse the two. Withdrawing a shot from an undiluted Comirnaty® MDV will then result in six times of the normal dose (180 µg of active substance instead of 30 µg).

The second mistake that can lead to an overdose, is withdrawing a shot from a poorly homogenised MDV. Indeed, after performing the dilution, the SOP requires to homogenise the suspension. This crucial step may however be forgotten, as well as, be incorrectly performed. If the vaccine suspension and 0.9% sodium chloride are not well distributed in the vial, the shot withdrawn could be, considering the worst-case scenario, only vaccine suspension and thus lead to an overdose.

To assess the impact of this VRE on the safety and efficacy of the Comirnaty® vaccine, three scientific papers will be considered: a research paper about overdoses of vaccines reported from 2007 to 2017, data from clinical trials of Comirnaty® vaccines where 100 µg doses were given, and finally a case report of Comirnaty® overdoses in Taiwan.

5.2.1 Administration of an extra-dose of vaccine from 2007 to 2017

Vaccine Adverse Event Reporting System (VAERS) is a US platform that receives reports of vaccine related adverse events as well as reports of vaccination errors. This surveillance system is co-administered by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC).

In 2019, Pedro Moro and his team searched the VAERS database for reports of excess doses of vaccine administrated from January 1, 2007 to January 26, 2018, in order to evaluate the dangerousness of this vaccination error. Out of 366,815 reports, 5067 reports (1.4%) were related to the administration of an excess dose of vaccine. Interestingly, the analysis found that this kind of report increased from 0.8% in 2007 to 2.4% in 2015. Unfortunately, 90% of reports did not mention the circumstances that led to administration of an excess dose of vaccine.

However, among the other 10%, most of the time, reporters described that errors were due to providers omitting to check the patient's vaccination record, or patients forgetting that they already received a dose, in a minority of reports, an adult dose was given to a child.

In three-fourths of reports (76.9%), no adverse event, sign or symptom was observed and overall, no safety issue was identified (Moro, Pedro L et al., 2019).

This review of the VAERS database demonstrates that the administration of an excess dose of vaccine is a frequent vaccine-related error and tends to increase. However, data are reassuring regarding the dangerousness of this error.

Indeed, unlike drugs with a narrow therapeutic index which can cause serious adverse events at a dose slightly higher than the therapeutic dose, vaccines are known to be much safer. In this study, no serious adverse events were reported when an extra dose of vaccine was administrated.

However, since mRNA vaccines are new medications and administrating an undiluted Comirnaty® vaccine leads to a six-fold higher dose, it may still raise concerns. More specific data are thus needed.

5.2.2 Data from clinical trials

Once preclinical trials are done, comes clinical studies, from phase I to phase IV. The Phase I clinical trial tests the safety and tolerability of the vaccine candidate at escalating doses. The aim is to determine the optimal dose that will be used. At this stage, is it common to have more than one vaccine candidate still in course, Pfizer/BioNTech then conducted their Phase I study on two drug candidates, BNT162b1 and BNT162b2. Additionally, in the specific case of COVID-19 vaccines, clinical trials have been conducted in parallel, explaining why reports also include immunogenicity data. For these clinical trials BioNTech was the regulatory sponsor and Pfizer was responsible or the trial design.

They first conducted the Phase I trial, with BNT162b1 at escalating doses (10 µg, 20 µg, 30 µg and 100 µg), to healthy patients aged of 19 to 54 years old. 45 participants were randomised and received either a placebo or BNT162b1 at 10 µg, 20 µg, 30 µg or 100 µg. After receiving the first dose, only mild and moderate adverse events were reported in groups that received 10

µg to 30 µg. However, severe cases of fatigue, headache, chills muscle pain and joints pain were observed in the group receiving BNT162b1 at 100 µg. Although the 100 µg dosage was associated with an increased reactogenicity, it was not associated with meaningfully increased immunogenicity. For those reasons, participants who received an initial 100 µg dose did not receive a second 100 µg dose. Pfizer then stops to assess the safety and efficacy of BNT161b1 at 100 µg. (Mark J. Mulligan et al., 2020)

Consequently, in the Phase I study of BTN161b2, the vaccine candidate that has been commercialised in the EU under the marketing name of Comirnaty®, the safety and tolerability were assessed at a maximum dose of 30 µg, suggesting that the benefit-risk ratio is less favourable at doses above 30 µg.
Moreover, severe adverse events were observed in the group of healthy adults that received a dose of 100 µg of BNT161b1. It is then very likely that a dose of 180 µg would significantly increase the risk of severe adverse events, without necessarily increasing the immunogenicity. (Edward E. Walsh et al., 2020)

5.2.3 Case report of Comirnaty® overdoses

Although Pfizer did not evaluate their vaccine at doses above 30 µg, the safety and antibody response of Comirnaty® vaccine at dose of 180 µg, has been assessed in an observational study. Indeed, in September 2021 in Taiwan, 25 people unexpectedly received a vaccine injection from an undiluted Comirnaty® multi-dose vial, which is equivalent to receiving a 180 µg dose. The mistake was quickly noticed and all recipients were admitted to the hospital for close monitoring.

Subjects reported mild to moderate adverse events, such as pain at the site of injection ($n = 22$), fever (9), chest tightness (6) or myalgia (5), for the majority of participants (84%) symptoms resolved within seven days. Laboratory abnormalities were evaluated and shown that 4 participants had an elevated liver transaminase level, 4 others suffered from anaemia and finally 3 recipients had an abnormal leukocyte count.

All the laboratory abnormalities were transient and spontaneously recovered within a few weeks. More importantly, no significant changes of left ventricular ejection fraction were observed for all recipients which is also a reassuring fact, given the known risk of vaccine-associated myocarditis. (D. Mevorach, et al., 2021)

Six patients received a second dose of Comirnaty® vaccine with an interval of two months between the prime and booster dose, anti-SARS-CoV-2 spike IgG had a trend of more slowly decay and prompter immunological response even if the second dose were postponed. This result may support the recommendation of delayed inoculation by the CDC.

In conclusion, this observational study provides findings supporting the safety and efficacy of Comirnaty® vaccines at doses up to 180 µg, this is reassuring regarding the impact of an overdose following administration of an undiluted Comirnaty® dose. (W.-H. Sheng et al., 2022)

5.2.4 The impact of vaccine overdose

Given the fact that COVID-19 vaccines are not available in pre-filled syringe dispensers, that some vaccines additionally need to be diluted, and that dosages differ for adult and paediatric use, the risk of overdose is not negligible. Vaccine overdoses in general are known to be well tolerated and serious adverse events related to overdoses are unlikely.

Overdoses of Comirnaty® vaccines were reported in several places, leading in some cases to observational studies. These studies reassured that overdoses are well tolerated, which coincided with non-human primate, and inhuman clinical trials.
However, in these studies, a higher dose, caused severe symptoms although the population tested was healthy adults. It is then plausible that administrating an under-diluted COVID-19 vaccine to a frail person, could cause serious adverse events.

Errors in the dilution process and confusion between diluted and undiluted multi-dose vials must then be avoided to prevent any unnecessary adverse reactions or harm.

6. Errors related to bad handling conditions

As seen before COVID-19 vaccines are particularly critical in term of stability, MDVs containing the vaccines must then be handled with a special care. However, the fact that COVID-19 vaccines are stored in MDVs and for the Comirnaty® vaccine, has to be diluted, inevitably implies that it will be manipulated, potentially incorrectly.

This chapter will focus on two VREs associated with bad handling conditions: shaking the multi-dose vial, and omitting to disinfect the rubber stopper.

6.1 Shaking the multi-dose vial

Whether the vaccine has been diluted or not, for all COVID-19 vaccines SOPs require to homogenising the suspension. The SOP explains that it should be done by 'gently inverse the vial'. Moreover, is it always clearly indicated that the operator should avoid shaking the vial.

Regrettably, this negative habit exists for various reasons, in the study conducted by Young Hwa Lee and her team in South Korea, inadequate shaking of the vaccine was the most common error reported by physicians. Similarly, the act of shaking the MDV was also the most common error reported in the online survey conducted at the Vaccination Centre of Namur.

Some hypotheses could explain the high frequency of this error. First, applying the procedure takes a certain amount of time since the vial has to be inverted ten times with a minimal velocity. Health workers often have to work in line and with an important yield to produce, some of them may then think that shaking the vial would allow a good homogenisation in a reduced time.
In addition, shaking a container for homogenisation is not always forbidden, it is actually recommended for some medications such as Diprivan® (propofol) for example.

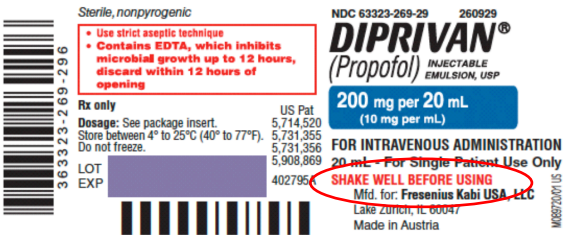


Figure 6 Picture of Diprivan® label with 'SHAKE WELL BEFORE USE' mention (Diprivan-us.com)

Health care workers used to handle such medication could not understand why they would have to inverse the vial instead of simply shaking it as they are used to.
Finally, the inversion of the vial is a process that could engender pain due to repetitive stress to the wrist joint, thus operators may look for alternative methods and lead to shaking the vial in order to avoid this pain.

Furthermore, the online survey conducted at the Vaccination Centre of Namur showed a lack of understanding regarding this step of the procedure, with 34% (n = 17) of respondents stating that shaking the vial is 'a good practice that allows a good homogenisation'.
The prohibition of shaking multi-dose vials raises important questions regarding the potential consequences of this practice. In order to elucidate these concerns, it is then necessary to examine scientific evidence surrounding this issue.

6.1.1 Stability testing of Comirnaty® vaccine: a translational study in UK vaccination centres

In a 2022 study published in the British Medical Journal, drawn syringes of Comirnaty® vaccine were subjected to various stress conditions, including moderate to vigorous shaking or vortexing. Light scattering technology was used to determine the size of the lipid-mRNA nanoparticles, while gel electrophoresis was used to assess mRNA integrity and separation from its lipidic vector.

When samples were inverted according to normal procedure, no significant difference in lipid particle size or polydispersity index (PDI) was observed compared to control samples. However, vigorous shaking led to a significant increase in particle size and PDI. Both values are known to be suboptimal for an effective immunogenic response. More importantly, aggregation due to mRNA release from lipid nanoparticles was demonstrated. The percentage of mRNA release was estimated to be up to 50% for vortexed syringes, indicating that aggregation is proportional to stress intensity. (Laila Kudsiova et al., 2022).

This study succeeded to demonstrate that the physical stability of the vaccine suspension is clearly compromised when subjected to an important stress. More importantly, shaking the suspension caused the release of mRNA from the lipid formulation which is thought to impact the efficacy of the vaccine due to a lack of free mRNA protection and cellular internalisation.

6.1.2 The impact of shaking the vial

This translational study provides evidence that shaking the vaccine suspension has a major impact on the physical stability of Comirnaty® vaccine. In addition, similar results were observed in another study, where massive aggregation of lipid nanoparticles and mRNA degradation were observed when the vaccine suspension was shaken. (Selmin,F et al., 2021)

Although these results need to be confirmed with real-world data, these studies provide evidence that vial agitation is likely to significantly reduce the efficacy of mRNA vaccines. Therefore, health workers should strictly adhere to the SOP and only homogenise the vaccine suspension by gently inverse the vial in order to reduce the risk of aggregation, and mRNA exit from its lipid carrier.

Furthermore, pharmacists should re-emphasise that COVID-19 vaccines require special care and should not be handled like any other injectable drug, in order to improve compliance with SOPs, which appeared to be low according to the online survey.

Finally, when syringes are subjected to minimal stress such as being accidentally dropped from a table, operators should be aware that in this case, the physical stability of vaccines has been conserved, the jab should be considered not being discarded.

6.2 Omitting to disinfect the rubber stopper

Once the vaccine is properly mixed, the next step is to withdraw a shot from the multi-dose vial. Prior to inserting the needle through the rubber stopper of the vial, the SOP requires disinfecting it with an alcohol swab.

Unfortunately, the online survey revealed a low level of compliance with this step of the process. In fact, only 32% (n = 16) of respondents considered this practice to be 'essential to limit the risk of contamination' and 24% (n = 12) of respondents even considered it to be a bad practice because the alcohol could interact with the active substance. Finally, only 54% (n = 20) of respondents stated that it was customary to disinfect the rubber stopper at the Vaccination Centre of Namur.

In order to determine the need to disinfecting rubber stoppers, relevant scientific literature will be consulted. A review of previous research will provide insight into the potential risks associated with contamination of such vials. Additionally, an experimental study that examines the consequences of omitting to disinfect the rubber stopper will be considered. And the question of the interaction between alcohol and vaccine active substances will be treated.

6.2.1 Multi-dose vials and the risk of bacterial contamination

It is well known that MDVs are suggested to bacterial contamination, for this reason, medications that are stored in MDVs almost always have a preservative agent in order to decrease this risk. It is however not the case with COVID-19 vaccines. Moreover, a study published in the American Journal of Infection Control, suggests that medications containing lipids are the most subject to contamination, followed by medications without preservative agents. Since COVID-19 vaccines are both lipidic and preservative free, the accumulation of risk factors justifies concerns regarding microbiological contamination. (Mattner F et Gastmeier P, 2004)

The contamination rate of medication stored in MDVs has been assessed in several studies. In 2018, a pilot study in a super-specialty hospital in India has been carried out. Researchers collected without prior intimidation 40 in-use MDVs, the contents of each vial were inoculated into a culture media and incubated at 37 °C for 10 days. Out of 40 MDVs collected, 20 were contaminated (25%) with organisms such as *Staphylococcus aureus*, *Coagulase-negative Staphylococcus sp*p. or *Aspergillus spp.*. (Mohit Bhatia et al., 2018).

Although, *S. aureus* asymptomatically colonises about 30% of the human population, this bacterium can nonetheless cause skin and soft tissue infections, more importantly*, S. aureus* is the most common cause of bacteraemia and infective endocarditis (Tong SY et al. 2015). Bacteria contamination is thus an important concern, especially for people with a poor immune system.

It is however important to note that the contamination rate varies considerably depending on the study. For example, a prevalence study made over 227 used MDVs, in a German hospital, demonstrated only 1 contamination, which is equal to a prevalence of 0.9% (CI_{95} 0.15% - 3%). The identified organism was *Staphylococcus epidermidis*, a Gram-positive bacterium commonly found on the skin, and usually not pathogenic. (Frauke Mattner et al., 2004).

However, once again, patients with a compromised immune system are at risk of serious complications, such as endocarditis or sepsis. Is it important to recall that COVID-19 vaccines are meant to protect these patients in priority.

6.2.2 The rubber stopper is not guaranteed to be sterile

The online survey revealed that many healthcare workers (44%) consider that the rubber stopper should only be disinfected after accidental contact. This could be explained by the misconception that the flip-off cap on the top of the vial hermetically protects the rubber stopper and keeps it sterile. In fact, 35.3% of respondents stated that the rubber stopper is guaranteed to be sterile. This statement is however not true. Indeed, flip-off caps are only considered dustproof and are not expected to maintain sterility. Diaphragms of MDVs are therefore not guaranteed to be sterile, explaining why manufacturers always indicate the necessity of disinfecting it with an alcohol wipe prior to their first use.

In 2004, a seven-month outbreak of nosocomial infections in children resulted of an epidemiological investigation, which has been published in the Journal of Clinical Microbiology. For several months, nosocomial infections due to the *Burkholderia cepacian* bacterium were reported from different wards of the same hospital. All children had clinical signs of septic shock but have been successfully treated with antibiotic therapy. After weeks of investigations, it was found that all patients had one medication in common: Ivelip® a lipid emulsion used for parenteral nutrition, stored in MDVs.

Fifty vials of this medication have been examined, and on 20 of them, drops of condensation were found under flip-off caps covering rubber stoppers. The culture of this condensation revealed that two MDVs were contaminated with *B. cepacian*. Further investigations have been carried out, including at the manufacturing plant of Ivelip®, once again, bacteriological infected drops of condensation were found. The final report stated that it was due to contamination of the autoclave cooling water. All the isolates recovered from the condensation on vials at the hospital, as well as at the manufacturing facility and isolates from infected children, shared the same ribotype, confirming that all cases are due to the external contamination while manufacturing process.

The manufacturer reported that the sterility is guaranteed for the solution itself but not for the outside of the container. Also, flip-off caps are not hermetic and the presence of drop of condensation water is not rare and inherent of the design of the device.
A proper disinfection of the diaphragms of multi-dose vials, would have prevented this outbreak. However, the inquiry revealed inadequate disinfection of rubber stoppers, as the time of antiseptic contact was not respected. (C. Doit et al., 2004)

6.2.3 *Correlation between the lack of disinfection and contaminations*

Although it is clear that bacterial contamination is an important concern, it is not clear if the disinfection of the rubber stopper can decrease this risk.

In the pilot study conducted in India where the contamination rate was very high (25%), it was noticed that the rubber stoppers were never disinfected prior to withdrawal. However, other fatly practices were noted such as the lack of hand hygiene or the practice of keeping the needle inserted in the vial. It is then hard to assess independently the impact of the non-disinfection. (Bhatia M et al., 2018)

Nonetheless, an experimental study has evaluated the impact of several common bad practices on bacterial contamination. Researchers took six series of six most commonly used medications stored in MDVs and simulated six different faulty practices in sterile technique. Out of these six mistakes, three were considered as at high risk and three were considered as at low risk. Low risk mistakes consisted of, deliberately: i) entering the vial without a prior alcohol swab, ii) touching the rubber stopper with skin, iii) wiping the vial diaphragm with a contaminated swab, before withdrawing an aliquot of the solution that went directly into blood agar plates for semi-quantitative bacterial counts and are being incubated for four days at 36 °C.

For each of these three low risk mistakes, agar plate showed a small number of colony growth (< five colonies) in one sample out of six and no growth of colony for other five samples, suggesting that drawing without prior disinfection or touching the rubber stopper with the skin, moderately increased the chance of bacterial contamination. Unfortunately, there is, to this day, no experimental study on a larger scale assessing the correlation between the lack of disinfection and the risk of contamination (Neela K. Sheth et al., 1993).

6.2.4 *Interaction between alcohol and drug substance*

On the online survey 24% (n = 12) of respondents stated that disinfecting the vial is a bad practice as the alcohol could interact with the active substance of the vaccine. Additionally, three respondents mention that the rule of disinfecting the rubber stopper has been removed as preparators usually do not wait for the rubber stopper to be dry after disinfection and directly insert the needle through to withdraw first doses and that this could inactivate the active substance due to interaction with alcohol.

However, although in the UK guidance on best practice in vaccine administration it is quoted that when skin is disinfected using an alcohol swab, it is important to wait until the skin is dry, as alcohol may inactivate live vaccines, I could not find any scientific article documenting interactions between COVID-19 vaccines and isopropyl alcohol use for rubber stopper disinfection. Therefore, as a precaution it seems reasonable to wait for the rubber stopper to be dry, but omitting the disinfection cannot be justified by this argument.

6.2.5 The impact of not disinfecting rubber stoppers

Multi-dose vials have a known risk of bacterial contamination, and outbreaks of infections, sepsis, or even deaths due to contamination of MDVs associated with lapses in aseptic techniques are sporadically reported. The lack of preservative agent and the lipidic formulation of COVID-19 increase this risk. Moreover, vaccines are primarily indicated to protect people with a poor immune system, such as elder adults or immunocompromised individuals, those patients have a greater risk of complications if they receive a vaccine that is microbiologically contaminated.

Additionally, in studies where a high prevalence of bacterial contamination was observed, a lack of compliance with procedures including the non-disinfection of rubber stoppers prior to drawing, was observed as well.

Finally, contrary to belief, rubber stoppers are not guaranteed to be sterile, thus, removing the flip-off cap without touching the diaphragm is not sufficient to exclude the odds of a contamination.

In conclusion, health care professionals must not omit the correct disinfection of the rubber stopper. Additionally, the fact that rubber stoppers are not sterile should be re-emphasise in order to improve compliance with this procedure.

7. Pooling of leftover multi-dose vials

This chapter addresses the practice of pooling the remnants of different multi-dose vials to reconstitute an additional dose. This practice is not exclusive to COVID-19 vaccines, and depending on the drug it may or may not be authorised.

In accordance with the requirements of the European Pharmacopoeia, the Comirnaty® vaccine suspension stored in its MDV has a volume of 2.25 mL after dilution, which allows five doses to be withdrawn. However, only a few days after the first vaccines were reconstituted, health workers found that it was actually possible to withdraw six doses of vaccine using low dead volume syringes. The European Medicines Agency (EMA) quickly reacted by officially authorising the extraction of a sixth dose. Pfizer then changed the summary of product characteristics to state that six doses were available in the vial. They also adjusted the price of the vials retrospectively.

Additionally, in order to permit withdrawal of the labelled number of doses, multi-dose vials always have an overfill volume. This quantity of suspension is not enough to prepare a syringe with a correct volume. However, by pooling two different overfill volumes into one syringe, it is possible to extract an extra dose. (Brendan Le Daré et al. 2021)

7.1 Agencies interdiction

Manufacturers are aware of this potential practice as they all mention it in their SOP that pooling vials is prohibited. This prohibition has not been officially challenged by any health authority, as it seems reasonable for many reasons. In practice, however, it is seen by many health workers as a missed opportunity to vaccinate more people, and some choose not to follow this rule.

7.2 Scientific evidence

The practice of pooling drugs from different vials into a container is accepted for many medications. Nonetheless, many factors explain why it is unauthorised in the case of COVID-19 vaccines.

First of all, as seen before, multi-dose vials are prone to contamination, COVID-19 vaccines do not contain preservative agents, and, the reconstitution is not realised in clean rooms, nor under laminar flow, unlike for drugs that we accept to pool.

Second of all, all COVID-19 vaccines are suspensions that require to be well homogenised in order to permit to active substance to be uniformly distributed. By pooling different vials there is a theoretical risk of combining vaccines that have a slightly varying levels of uniformity. This effect could then be amplified and lead to a subpotent or superpotent dose.

In addition, as seen before, each puncture into the rubber stopper increases the risk of vial coring which can have dramatic consequences, COVID-19 vaccine vials, are only qualified to maintain their integrity for a limited number of punctures. (Kevin N. Hansen, 2021).

There is currently no specific study assessing the impact on safety and efficacy of a COVID-19 vaccine that has been drawn from different vial overfills. However, in Selmin's paper about the stability of pre-drawn syringes, the polydispersity index of the lipid nanoparticles has been measured on its MDV and on a syringe drawn with two different overfills. The experiment showed a variation of 19% of the PDI, demonstrating that mixing vials has a poor influence on the degree of uniformity of size distribution of the particles. Nonetheless the hydrodynamic diameter did not significantly differ. (Selmin et al., 2021).
Also, even with a 19% difference the PDI stays below 0.2 which is considered as good. (M. Danaei et al., 2018).

This paper suggests that the pooling of vials has a negligible impact on those parameters. In spite of that, bacteriological concerns remain.

7.3 This impact of pooling left-overs

The practice of pooling overfills from different vials, represents a good opportunity to increase the number of available doses and thus the number of citizens vaccinated. However, in the absence of solid scientific data, assessing the safety and efficacy of this process, health workers should keep following national and international recommendations and do not pool vials. The quality must not be sacrificed over the quality and vaccine optimisation should only be done by using low-dead space volume syringes. Moreover, in Belgium, vaccine's stock is not critical any more.

Nonetheless, in view of the reassuring data regarding the efficacy, the EMA should consider conducting further studies, especially about the safety of this process, to potentially allow this practice, which could be beneficial in certain areas, especially where vaccine's stock is critical.

8. Errors related to administration

This chapter covers VREs associated with vaccine administration. First, the usefulness of skin disinfection prior to administration will be discussed, then the error of administering the wrong vaccine and the error of injecting the drug by the wrong route of administration will be explored.

8.1 Skin disinfection

Historically, it has been customary, to clean the site of injection with alcohol swabs, using 70% isopropyl alcohol wipes prior administrating the vaccine in order to decrease the risk of skin infection, this practice is however increasingly being questioned.

In this section the major studies that have been conducted on the usefulness of this practice will be presented, and the costs associated with this process will be examined. Furthermore, the guidelines of various countries regarding this practice will be analysed.

8.1.1 Scientific evidence

The main argument against systematic cleaning prior to injection is the lack of scientific evidence demonstrating the utility of this process. In 2018, a double blind, randomised controlled trial (RCT) has been publish on Human Vaccines & Immunotherapeutics.
Participants were healthy children aged 0-18 years old who were eligible for vaccination, they were separated into two groups, the first one got an alcohol swab prior to the administration of vaccine, the second group got an alcohol swab but adjacent to the site of injection. The incidence of several outcomes such as local skin reactions, skin infections, redness, swelling, warmth, or spontaneous drainage has been evaluated. No significant differences were found in the incidence of local skin reactions, redness, pain or swelling.
Additionally, in a post-hoc analysis, it was found that the duration of redness in the alcohol swab group was significantly longer. Unfortunately, this study is underpowered to detect a difference in the incidence of skin infection since no case has been reported in either group.
Nonetheless, this research paper is the first RCT assessing the utility of this process, and it is demonstrating that cleansing the skin with an alcohol swab may be unnecessary. (Wong, Horace et al., 2018)

Moreover, a study published on The Lancet, points out that there is no experimental evidence that skin bacteria are introduced into the deeper tissues when an injection is given. In this study,

5000 unselected patients received injectable medications by all routes (intradermal, intravenous …) without any kind of skin disinfection, over 6 years. This result of no single case of infection, either local or systemic. (T.C. Dann, 1969)

8.1.2 Cost of disinfection

In addition to having no data supporting the usefulness of systematic disinfection, some researchers have been interested in the cost of this practice. Indeed, the protocol for skin disinfection requires wiping an alcohol swab for 30 seconds and waiting for the skin to dry for another 30 seconds. Researchers estimate that skin disinfection add 90 seconds to each injection, assuming that every US resident would receive two doses of vaccines, this operation would take ~16.5 million hours.
In the US, the median nursing wage is $37.24 per hour, the projected cost of this process is then estimated at $615 million USD. To that amount we should add the cost of alcohol swab estimated at $13 million USD, ($0.02 for each wipe). (E.G. Poland et al., 2021)
In Belgium almost 30 million doses have been administrated, only taking into account the cost of isopropyl alcohol swabs, the estimated cost of this practice is around €900,000.

8.1.3 Disparities between national guidelines

For all these reasons, omitting the skin-disinfection step before vaccination is recommended by several national health authorities such as the UK Health Security Agency or the Australian Digital Health Agency, but also by the World Health Organization (WHO), which bases its recommendation on a systematic review showing no evidence of infection, when subcutaneous injections of insulin were performed without prior cleansing of the skin. (Hutin Y et al., 2003)

The Centers for Disease Control and Prevention (CDC), although, continues to recommend the use of an alcohol wipe on the skin prior to immunisation.

In Belgium, the Task Force Vaccination has chosen to follow WHO's guidelines and indicate that skin cleansing prior immunisation is unnecessary if the patient's skin does not appear to be soiled.

However, this recommendation was not always accepted, it even created outcries from some health care providers, saying that skin cleansing is essential, Sabine Stordeur (member of the Task Force) says. This statement is supported by the online survey, since only 33.3% (n = 18)

of respondents said that skin disinfection is unnecessary if the skin is clean. In fact, in many Belgian vaccination centres, health care workers still systematically disinfect patients' skin prior administrating vaccines.

Additionally, the non-disinfection of skin, is also not always accepted by patients, omitting to disinfect the patient's arm is therefore likely to create tensions in vaccination centres, and may increase fear and reluctance of vaccination.

8.1.4 Necessity of skin disinfection

In the absence of data supporting the relevance of skin cleansing prior immunisation, and face to the cost of this process, vaccination workers should adhere to the national guideline and no longer clean patients' skin, except when skin appears to be dirty. Moreover, health workers should consider taking time to explain to patients why skin disinfection is not applicable any more, in order to increase compliance.

8.2 Injection of the wrong medication

In this section the impact on safety and efficacy of two VREs will be assessed: injecting a product that is not a vaccine, and injecting a COVID-19 vaccine but not from the right manufacturer.

Among immunisation related errors, injecting the wrong vaccine is, according to J. Morse-Bardy's study the most frequently reported vaccine-related error. Most of the time errors involve vaccines with a similar name or acronym, for example, diphtheria, tetanus and acellular pertussis vaccines named 'DtaP vaccine' are sometimes mix-up with 'Tdap vaccine', both target the same disease but while Tdap is recommended for older children and adults, DTaP is indicated for infants.
In the other hand, injection of a medicine that is not a vaccine is much less likely, but still possible.

8.2.1 Injection of another health product

The Institute for Safe Medication Practices (ISMP) revealed that during the COVID-19 vaccination programme two patients received an epinephrine injection instead of their Spikevax® dose. This mistake was explained as pre-drawn syringes of epinephrine were prepared in case of anaphylactic reaction and stored in light-protecting bags, close to pre-drawn

Spikevax® syringes, the nurse took syringes from the wrong bag and administered epinephrine to her first two patients, she realised her mistake when she noticed that there were two extra doses of Spikevax® vaccine left.

In the same manner, in a West Virginia clinic, 44 patients received an injection of casirivimab, a monoclonal antibody instead of Spikevax® vaccine. Two health workers were asked to pick up vaccine supplies and did not notice that they were given a box of casirivimab vials instead of COVID-19 Moderna vaccine, this mistake was explained as both medications were stored in 5 mL multi-dose vials with identical red caps. Also, the barcode on the box was not functional. No serious adverse events were reported and manufacturer declared that they will manufacture a new version of vial, with another colour and a functional bare code.
Despite those events, mix-ups between vaccines and other type of medications are still very rare, most of the time, errors of administration involved two different vaccines. In fact, during the COVID-19 vaccination programme, mix-ups between different manufacturers are a common mistake that leads to inadvertent heterologous vaccination.

8.2.2 Heterologous COVID-19 vaccination

Heterologous vaccination refers to the use of vaccines developed with different platforms for the first and second dose. Heterologous vaccination can be voluntary, for example if the first dose caused an allergic reaction, or involuntary, due to human error.
In this section, reasons that might lead to heterologous vaccination will be outlined and the impact of this VRE on the safety and efficacy of the vaccine will be assessed by referring to two scientific papers.

I) <u>Heterologous vaccination due to human error</u>

COVID-19 vaccines are likely to get mixed up, indeed, although multi-dose vials from different manufacturers are easily distinguishable, once vaccines are reconstituted, they are stored in standard syringes, with the only distinguishing feature being a little paper label stick on the pre-drawn syringe. To mitigate the risk of mix-ups, in most vaccination centres, different vaccines are usually separated from each other, for example nurses in lines one to four operate Spikevax® vaccination while Comirnaty® vaccine is given in lines five to seven. In the same manner, some preparators reconstitute only Spikevax® vaccines while other health workers reconstitute Comirnaty® vaccine at a separate work station. Nonetheless, even when following those recommendations, in view of the number of doses administrated every day, errors are

almost inevitable, and administration of the wrong vaccine is often reported. If the mistake occurs for the patient's second dose, it leads to an inadvertent heterologous vaccination.

II) Immunogenicity, safety and reactogenicity of heterologous COVID-19 vaccination

In March 2021, following several cases of potentially vaccine-related thrombolytic events in the young population, the use of AstraZeneca vaccine (Vaxzevria®) has been prohibited in Belgium for the younger population. This led to a dilemma for those who received a first dose of Vaxzevria® vaccine but were now ineligible for it: which vaccine should they receive for their second dose. Since these questions were raised, many scientific studies have been conducted to assess the feasibility of a mixed vaccine strategy.

A single-blind, randomised, controlled trial was conducted to evaluate the immunogenicity, safety and reactogenicity of different COVID-19 vaccine combinations, including Comirnaty® (BNT), Nuvaxovid® (NVX), Vaxzevria® (ChAd) and Spikevax® (m1273) vaccines.

1072 adults aged of 50 years old and older, previously vaccinated with a prime dose of Comirnaty® or Vaxzevria® vaccine were enrolled in this trial and randomly received a second dose of one of the four vaccines mentioned above, making six different combinations of vaccines. The primary outcome assessed was the non-inferiority of serum SARS-CoV-2 anti-spike IgG concentration at 28 days, in comparison with the homologous group. Secondary outcomes evaluate the safety and reactogenicity of the vaccination up to three months after the second dose.

Among patients that received a prime dose of Vaxzevria® vaccine (ChAd), the mean SARS-CoV-2 anti-spike IgG concentration was higher for heterologous schedules (ChAd/m1273 and ChAd/NVX) compared to homologous schedules. The mean IgG concentration was even 10 times higher in ChAd/m1273 group than in the ChAd/ChAd group. Similar results were observed for patients that received a prime dose of Comirnaty® vaccine (BNT) with a slight increase in the BNT/m1273 group compared to BNT/BNT group.

Cellular responses and live virus neutralising antibody titres followed the same trend, as heterologous schedules were always superior compared to homologous schedules with the exception of the BNT/NVX group. Once again, combination of two mRNA vaccines (BNT/m1273) induced a slight increase compared to the BTN/BNT schedule, whereas the combination of an adenoviral-vectored vaccine and an mRNA vaccine (ChAd/m1273) induced a larger increase compared to ChAd/ChAd.

However, heterologous vaccination appears to result in more frequent local or systemic reactions. Indeed, feverishness was for example, reported by 33% of participants in the ChAd/m1273 group and only 5% of participants in the m1273/m1273 group (difference 28% CI_{95} 20-36). Similarly, 22% of recipient in the BNT/m1273 group reported this symptom compared to only 9% for BNT/BNT group. Similar observations have been noticed for other common symptoms such as chills, headaches, nausea, joint pain … Nonetheless, none of the combinations raised any safety concerns, and according to this experiment, heterologous vaccination is safe.

Some limitations are therefore to be noted, the main one being that the prime dose of vaccine was not randomised, as patients were recruited afterward. Since Comirnaty® vaccine was considered safer and more efficient, recipients that got Comirnaty® vaccine are thus more likely to have a higher rate of comorbidity compared to recipients that got Vaxzevria® vaccine as their prime dose. More importantly, the age range of the cohort was 50-78 years and over 90% of participants considered themselves white. The generalisability of the reactogenicity and immunology results to a younger population and to non-white individuals is therefore limited.

As a conclusion, this experimental study succeeded to demonstrate that heterologous vaccination, especially mixed adenoviral-vectored and mRNA vaccines combination is safe, tolerable and induces a good immunogenetic response. Furthermore, although this study has some limitations, it confirms previous evidence, including data from a real-world observational study (n = 12,121) published in Nature, which suggested that the ChAd/BNT schedule confers a better protection as well as being safe and well tolerated. (Stuart ASV et al. 2022; Pozzetto B et al., 2021)

III) Safety and efficacy of heterologous vaccination

Heterologous vaccination has now been evaluated in many scientific studies, including RCTs, and large real-world observational studies. Although the incidence and severity of local and systemic reactions appeared to be greater, these researches provide reassurance that heterologous vaccination is safe and effective.

Moreover, mixing adenoviral-vectored vaccine and mRNA vaccine has shown a complementarity as one vaccine induces a stronger T cell response and the other a stronger IgG response, together, they confer a stronger immunity than homologous schedules, which could be suitable for immunocompromised individuals.

Finally, the mixing vaccine strategy could speed immunisation process and facilitate rapid vaccine deployment especially in lower-income countries where vaccine supply is inconsistent. (M.M. Alshahrani et al., 2022)

8.2.3 The impact of administration of the wrong product

Since COVID-19 vaccines are almost the only injectable suspension stored in vaccination centres, inadvertent injection of another medication is very implausible. Nonetheless, cases of unintended administration of adrenaline or monoclonal antibodies have been reported, showing that zero risk does not exist. Such an event, could lead to vaccine hesitancy and induce a loss of trust in health care providers, but it is unlikely to provoke serious adverse events.

Mix-ups between different COVID-19 vaccines are, on the other hand, almost inevitable, fortunately, studies have shown that heterologous COVID-19 vaccination is safe and effective, in some cases, it may even confer a better protection against SARS-CoV-2. Recipients must however be informed of the increased risk of common adverse events.

8.3 Wrong administration route

The final VRE associated with vaccine injection that will be discussed is administration of the vaccine by the wrong route of administration.

Although some vaccines, namely Rotavirus or Typhoid vaccines are administered orally, the vast majority of protein medications are administrated parenterally because of their vulnerability to the gastric system. Depending on the localisation of application, parenteral administration can be either, intramuscular, subcutaneous, intravenous or intradermal. The injection angle and needle size are key parameters in order to achieve the desired technique.
COVID-19 vaccines like most other vaccines are indicated to be given by intramuscular route, inadvertent subcutaneous injections are however a common mistake.

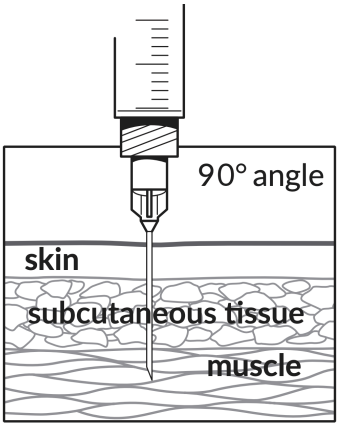
According to the EudraVigilance database, between 2001 and 2016, incorrect routes of drug administration represented 12.5% of vaccination errors reported. (C.E Hoeve et al., 2018)

After presenting the key parameters that can lead to an intramuscular or subcutaneous injection, and explaining how errors can occur in vaccination centres, the impact of this error will be

assessed based on a narrative paper about the difference in immunogenicity and reactogenicity between subcutaneous and intramuscular vaccination, and on two case reports of COVID-19 vaccines mistakenly administered via the subcutaneous route.

8.3.1 Subcutaneous versus intramuscular administration

To perform an intramuscular injection into the deltoid muscle, health care professionals should use a 22–25-gauge, 25 mm long length needle, and insert it at a 90° angle. The use of a shorter needle and/or the insertion of the needle at the wrong angle may result in an inadvertent subcutaneous injection.



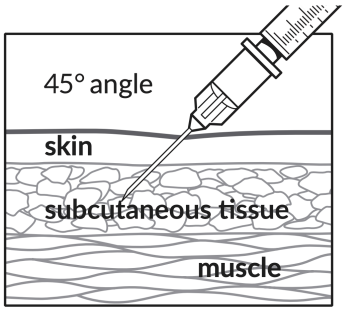


Figure 7 intramuscular injection (NCIRD) *Figure 8 subcutaneous injection (NCIRD)*

Furthermore, the CDC recommends the use of up to 38 mm long length needles for patients who weigh between 70 and 118 kg, due to the greater thickness of their deltoid fat pad (NCIRD, 2022).

Consequently, in Belgian vaccination centres in addition to regular 23/25G - 25,4 mm needles, 23G - 30 mm needles should be available according to national guidelines. (Task Force Vaccination (2022). COVID-19 programme de vaccination Standard Operating Procedures Centres de vaccination [PDF file].)

However, the online survey revealed that at the Vaccination Centre of Namur, only 23/25G were available making it impossible to correctly apply the procedure. Additionally, since syringes are drawn and prepared in advance, being able to adapt to the patient requires special organisation which is difficult especially in busy periods. Health care workers may also feel uncomfortable asking patients for their BMI. Finally, some practices such as pinching the skin, as well as simply getting the wrong needle may lead to unintentional subcutaneous injection.

(WHO (1984). Immunisation in practice (a guide for health workers who give vaccines [PDF file].)

8.3.2 Clinical consequences

In 2020, an extensive narrative review paper has been published in Human Vaccines & Immunotherapeutics. Ian F. Cook, analysed a total of 58 studies, using the PICO model as P = human vaccine recipients, I = intramuscular route of injection, C = subcutaneous route of injection and O = reactogenicity and immunogenicity of vaccines. The objective of this review paper was thus to assess the differences in immunogenicity and local reactogenicity following immunisation by intramuscular versus subcutaneous injections.

Dr. Cook, divided articles into two study design groups (randomised and observational studies) according to GRADE guidelines. Randomised trials can provide moderate to high-grade evidence, while observational studies are only able to give very low to low-grade evidence.

This extensive review succeeded in providing high-grade evidence that subcutaneous injections significantly increase the risk of local reactogenicity compared to intramuscular injections. Additionally, this review provides moderate grade evidence that intramuscular significantly improves the immunogenicity of vaccines. This study therefore permits to strongly recommend intramuscular injections for vaccine immunisations (Ian F. Cook, 2021).

It should however be noted, that the author conducted this review on all vaccine types, excluding mRNA vaccines, since at the time there were no clinical studies available.

Those results are not surprising, indeed, subcutaneous fat is known to be poorly vascularised which is likely to result in slow mobilisation and processing of antigen, and thus, vaccine failure. Moreover, subcutaneous fat contains an insufficient number of antigen-presenting and phagocytic cells, leading to a decreased immune response. Additionally, antigens may also take longer to reach the general circulation, resulting in a delayed immune response. Finally, antigens are more likely to be denatured by enzymes as they remain in fat longer. These phenomena explain the findings that patients with thicker skinfolds are associated with a lowered antibody response (Poland GA et al., 1997).

Subcutaneous injections are also subject to abscesses, cellulitis or granulomas, which are less common in muscles, probably due to their abundant blood supply, and better drainage of channels which favour the elimination of potential toxic material making this tissue less susceptible to adverse effects (Michaels L et al., 1970).

8.3.3 Case reports of subcutaneous COVID-19 vaccine injections

Although BNT162b2 shown an equivalent immunological response when administrated either via intramuscular or intradermal route, in a nonhuman primate trial, Pfizer/BioNTech among other COVID-19 vaccine manufactures conducted clinical trials using intramuscular injection as the only route of administration, this method is thus the only one indicated. Nonetheless, several cases of inadvertent subcutaneous injections of COVID-19 vaccines have been reported in published case reports.

In January 2021, 790 military personnel accidentally received their Comirnaty® first dose, administered with a 27-gauge needle, intended for subcutaneous injections. Following this mistake, qualitative and quantitative IgC antibodies of 719 military personnel were assessed. 706 subjects (98.2%) demonstrated seroconversion which was defined as IgC levels above 50 Au/mL. In comparison, 514 healthcare workers (92%) in an Israeli hospital had detectable IgC antibodies after an intramuscular first dose of Comirnaty®. Additionally, in this study, the amount of subcutaneous fat was not correlate with the seroconversion rates. Adverse events, including local skin reactions were however not assessed in this paper (L. Friedensohn et al., 2021).

In late 2021, a 60-year-old woman reported a depressed lesion on her left arm following an inadvertent subcutaneous Vaxzevria® vaccine immunisation. The wrong route of administration was explained by the use of a 16 mm needle, and the fact that the recipient had a BMI of 31.2 kg/m^2. The lesion was diagnosed as a localised lipoatrophy, ultrasound analysis revealed a necrosis in the area of subcutaneous fat and further investigations such as blood tests looking for autoimmune disease and skin biopsy permit to differentiate this case from a localised involutional lipoatrophy. The author reports that this pathology is therefore likely due to subcutaneous injection of Vaxzevria® vaccine. Moreover, woman who received her second dose using a 25 mm long needle did not report similar reaction (Ian F. Cook, 2022).

Other cases of local skin reactions following incorrect injection of COVID-19 vaccines have been reported by Jia Yu Ng and Gyldenlove and his team, once again health care workers diligently omitted to use a longer needle for patients that suffer from obesity. (Ng JY, 2022; Gyldenlove M et al., 2021)

8.3.4 The impact of subcutaneous injection of COVID-19 vaccine

The management of an immunisation operated via an incorrect route of administration differs depending on the country. Indeed, while the CDC or the Australian Technical Advisory Group of Immunisation (ATAGI) both recommend not to repeat doses, and only inform recipients of an increased risk of local adverse reactions, Canadian Public Health Agency, considers the dose invalid and thus recommends directly repeating the dose.

In the absence of solid studies assessing the safety and efficacy of COVID-19 immunisation via subcutaneous route, it is not surprising to see that recommendations can vary.

Nonetheless, existing data regarding the immunological response of COVID-19 vaccines administrated subcutaneously are reassuring, which could justify considering the vaccination valid.
However, to maximise the chances of a successful immunisation and limit the risk of local adverse events, health workers must be aware of the importance of a correct injection technique, as well as, the choice of the right needle. Additionally, improvements could be implemented in vaccination centres such as asking for people's BMI in forms that patients have to fill out.

8 Conclusion

The COVID-19 vaccination programme must be carried out in the safest and most efficient way possible. For this purpose, it is essential to ensure that the standard operating procedure related to the use of COVID-19 vaccines is strictly followed.

Unfortunately, the online survey revealed that the SOP is not always well understood and followed at the Vaccination Centre of Namur, resulting in VREs. Although, because this was done with a small sample size and only in one centre, results should be interpreted with caution and cannot be widely generalised.

Among VREs, shaking the MDV appears to be the most frequent mistake, as 15.2% (n = 5) of respondents rated this behaviour as 'frequent'. This observation is further supported by the finding that 34% (n = 17) of respondents mistakenly believe that shaking the MDV is a good practice as it allows a good homogenisation.
Likewise, similar observations have been found in more robust studies. For instance, in a study conducted in South Korea, out of 250 physicians surveyed, 28.0% (n = 70) admitted making the mistake of inadequately shaking vaccine vials more than once per 100 vaccinations. (Lee, YH et al., 2021)
Additionally, the survey revealed that only 54% (n = 20) of respondents stated that it was customary to disinfect the rubber stopper of MDVs. This low rate of compliance could be attributed to misconceptions. Indeed, 35.3% (n = 18) of respondents mistakenly believe that the rubber stopper is guaranteed to be sterile and only 32% (n = 16) of respondents consider that disinfecting the rubber stopper of MDVs is essential to prevent the risk of infection.
These data align with similar observations in hospital contexts where a low rate of compliance for this particular process was also noted. (Mohit Bhatia et al., 2018)
Lastly, despite the need to use a longer needle to administer correct intramuscular injections for patients with obesity, 95.7% (n = 45) of respondents reported using the same needle for all patients. This situation was explained by the insufficient supply of 38 mm long needles provided by AViQ, which makes the correct application of the procedure impossible.

Fortunately, VREs do not always have a significant impact on the safety and efficacy of vaccines. For example, vaccine overdoses are known to carry a low risk of serious complications. Indeed, between 2007 and 2017, out of 5067 reports of vaccine overdoses, no safety issues were observed. (Pedro Moro et al., 2019)

Existing data from clinical trials and case reports are reassuring and the risk of complications following COVID-19 vaccine overdoses, also appears to be low. (W.-H. Sheng et al., 2022)
In the same manner, data from case reports are reassuring regarding the efficacy of COVID-19 vaccines that have been administrated subcutaneously. However, clinical studies conducted on non-COVID-19 vaccines, and case reports about COVID-19 vaccines, suggest that there is a high probability that it would significantly increase the risk of local reactogenicity. (Ian Cook, 2022; Ng JY, 2022; Gyldenlove M et al., 2021)

Finally, some VREs can be beneficial, indeed, real-world observational studies and RCTs have shown that heterologous vaccination, especially the combination of adenoviral and mRNA vaccines, provides better protection and is safe and well tolerated. (Stuart ASV et al. 2022; Pozzetto B et al., 2021)

On the other hand, some VREs are more worrying. Indeed, although there are not enough robust studies on the omission of disinfection of rubber stoppers to clearly demonstrate the impact of this VRE, available data allow us to confirm that this step is essential to prevent bacterial contamination and should not be omitted. The low rate of compliance with this process at the Vaccination Centre of Namur is therefore concerning.
Furthermore, although it would need to be confirmed with real-world data, two robust experimental studies have provided high quality evidence that shaking the MDV has a significant impact on the integrity and preservation of the mRNA within its lipidic vector and is therefore very likely to reduce vaccine efficacy. Vial shaking is the VRE that has both the greatest negative impact and appears to be the most frequent according to the online survey. (Kudsiova, L et al., 2022; Selmin, F et al., 2021)

It is the responsibility of the pharmacist to emphasise to vaccinators that MDV must be handled with special care and to ensure that the rule of not shaking the vials is understood and followed.

In general, in addition to the high workload and complexity of vaccine preparation leading to VREs, a lack of understanding of the procedure appears to be associated with a lack of compliance and therefore an increased risk of VREs. Therefore, the rationale behind each step of the procedure should be explained in order to address VREs and thus enable a safe and effective vaccination programme.

Appendix

Results of the online survey conducted at the Vaccination Centre of Namur

Table 1. Occupation of participants

Characteristics	*n* = 54
Occupation, *n* (%)	
Nurse	30 (55.6)
Pharmacist	5 (9.3)
Pharmacy assistant	3 (5.6)
Medical doctor	8 (14.8)
Student (medicine, pharmacy, biomedical sciences)	9 (16,8)
Place of work, *n* (%) (multiple selections)	
Vaccination centre	54 (100)
Hospital	2 (3.7)
Nursing home	4 (7.4)
Pharmacy	4 (7.4)
Medical practice	3 (5.6)
Prison	1 (1,9)
Role, *n* (%) (multiple selections)	
Medical and general supervision	6 (11.2)
Vaccine preparation supervision (Pharmacist)	5 (9.3)
Vaccine preparation (preparator)	25 (46.3)
Vaccine administration (vaccinator)	41 (75.9)
Emergency nurses	3 (5.7)

Table 2. Opinion on different situations presented. Respondents had to choose between proposed responses or write an answer in the 'other' box.

Situation	*n* = 54
Vigorously shake the multi-dose vial containing the vaccine, n (%)	*n* = 50
This is a good practice, it allows a good homogenisation	17 (34)
As a precautionary measure, it should not be done, but it is probably not very serious	10 (20)
This is bad practice and may damage the active substance	23 (46)
Disinfect the rubber stopper of the vial with an alcohol wipe, n (%)	*n* = 50
It is essential to do so in order to limit the risk of contamination	16 (32)
This is only useful if the rubber stopper is accidentally touched	22 (44)
Disinfecting the rubber stopper is a bad practice, as the alcohol will interact with the active substance	12 (24)
About the rubber stopper, covered by a plastic cap: do you think it is guaranteed as sterile?, n (%)	*n* = 51
Yes, I do	18 (35.3)
No, I do not	20 (39.2)
I don't know	13 (25.5)
Disinfect patient's arm with alcohol before administering the vaccine, n (%)	*n* = 54
It is important to do this to avoid the risk of infection	15 (27.8)
This is unnecessary, it should not be done if the skin is clean	18 (33.3)
It is not very useful but should be done as a precaution	17 (31.5)
Other: it should not be done, as alcohol could interact with the vaccine	4 (7.4)
Pooling two vials left-overs to reconstitute an additional dose, n (%)	*n* = 52
This allows to gain a dose, I do it even if the protocol forbids it	4 (7.7)
The protocol prohibits it, so I don't do it, but consider that it should be allowed	17 (32.7)
The protocol prohibits it, so I don't do it, I consider it reasonable to prohibit this practice	18 (34.6)
The protocol forbids it, so I don't do it, I wouldn't be able to say whether or not it's something bad	13 (25)

Table 3. About rules that are followed in practice in the Vaccination Centre. Respondents had to choose between proposed responses or write an answer in the 'other' box. Participants who weren't involved were tell to skip the question.

Rules	***n* = 54**
About the disinfection of rubber stoppers, n (%)	*n* = 37
It was customary to disinfect it	20 (54)
It was customary not to disinfect it	8 (21.6)
There were no clear instructions, it was at the discretion of the preparator	6 (16.2)
Other: the rule has changed, we use to do it, but we don't do it anymore	3 (8.1)
Pooling several vial left-overs to reconstitute an additional dose, n (%)	*n* = 39
It was customary not to do so	30 (77)
It was customary to do so	4 (10.3)
The rule could vary depending on who was present	5 (12.8)
About the disinfection of the patient's arm prior administering the vaccine, n (%)	*n* = 49
It was customary to disinfect the patient's skin	6 (12.2)
It was customary not to disinfect the patient's skin	36 (73.5)
There was no position taken, it was at the discretion of the vaccinator	4 (8.2)
Other: the rule has changed, we use to do it, but we don't do it anymore	1 (2)
Other: I worked in different vaccination centres and the rule varies between centres	1 (2)
Other: yes or not, depending of the material available	1 (2)
About vaccination of an obese person, n (%)	*n* = 47
It was customary to use a longer needle	2 (4.3)
It was customary to use the same needles as usual	45 (95.7)

Table 4. Assessment of the frequency of different vaccine-related errors. Respondents were asked to choose between the proposed answers. In the right-hand column, the percentage was calculated without taking into account respondents who did not have an opinion

Situation	$n = 54$	
Mistake in dilution process (incomplete homogenisation), *n (%)*	$n = 54$	$n = 39$
Never	24 (44.4)	24 (61.5)
Very rarely	12 (22.2)	12 (30.8)
Rarely	3 (5.6)	3 (7.7)
Frequently	0 (0)	0 (0)
Very frequently	0 (0)	0 (0)
I have no opinion	15 (27.8)	n/a
Mistake when handling the vial (shaking the vial), *n (%)*	$n = 54$	$n = 33$
Never	15 (27.8)	15 (45.4)
Very rarely	8 (14.8)	8 (24.2)
Rarely	4 (7.4)	4 (12.1)
Frequently	5 (9.3)	5 (15.2)
Very frequently	1 (1.9)	1 (3.0)
I have no opinion	21 (38.9)	n/a
Mistake when handling the vial (touching the rubber stopper), *n (%)*	$n = 54$	$n = 34$
Never	16 (29.6)	16 (47.0)
Very rarely	13 (24.1)	13 (38.2)
Rarely	3 (5.6)	3 (8.8)
Frequently	2 (3.7)	2 (5.9)
Very frequently	0 (0)	0 (0)
I have no opinion	20 (37)	n/a
Wrong labelling of the syringe, *n (%)*	$n = 54$	$n = 46$
Never	27 (50)	27 (58.7)
Very rarely	16 (29.6)	16 (34.8)
Rarely	3 (5.6.)	3 (6.5)
Frequently	0 (0)	0 (0)
Very frequently	0 (0)	0 (0)
I have no opinion	8 (14.8)	n/a
Administration of the wrong vaccine, *n (%)*	$n = 53$	$n = 48$
Never	30 (56.6)	30 (62.5)
Very rarely	14 (26.4)	14 (29.1)
Rarely	4 (7.5)	4 (8.3)
Frequently	0 (0)	0 (0)
Very frequently	0 (0)	0 (0)
I have no opinion	5 (9.4)	n/a

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The COVID-19 vaccination programme in Belgian vaccination centres must be carried out in the safest and most efficient way possible. To this end, Standard Operating Procedures (SOPs) for the use of COVID-19 vaccines have been written and should be strictly followed.

However, an online survey conducted at the Vaccination Centre of Namur showed that the SOPs are not always followed and understood, some steps of the procedure are even being questioned. Furthermore, case reports available in the scientific literature have described many cases of vaccine-related errors (VREs) during the COVID-19 vaccination programme.

Therefore, the aim of this thesis is to assess the impact of the most common VREs on the safety and efficacy of the COVID-19 vaccination programme. For this purpose, a secondary research of non-systematic literature will be conducted.

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Le programme de vaccination COVID-19 dans les centres de vaccination belges doit être mené de la manière la plus sûre et la plus efficace possible. À cette fin, des procédures pour l'utilisation des vaccins COVID-19 ont été rédigées et doivent être suivies à la lettre.

Cependant, une enquête en ligne menée au Centre de Vaccination de Namur a montré que ces procédures ne sont pas toujours suivies et comprises, certaines étapes de la procédure sont même parfois remises en question. De plus, des case reports disponibles dans la littérature scientifique ont décrit de nombreux cas d'erreurs liées à la vaccination pendant le programme de vaccination COVID-19.

L'objectif de ce mémoire est donc d'évaluer l'impact des erreurs liées à la vaccination les plus fréquentes sur la sécurité et l'efficacité du programme de vaccination COVID-19. Dans ce but, une recherche secondaire de la littérature non systématique va être menée.

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