

Good Practices of Comirnaty[®] Vaccine Injection Using Uncrimped Materials

Laetitia Le (✉ laetitia.le@aphp.fr)

Assistance Publique – Hôpitaux de Paris

Justine Touchard

Assistance Publique – Hôpitaux de Paris

Aymeric Chastel

Assistance Publique – Hôpitaux de Paris

Judith Pineau

Assistance Publique – Hôpitaux de Paris

Nicolas Martelli

Assistance Publique – Hôpitaux de Paris

Marie-Caroline Loustalot

Assistance Publique – Hôpitaux de Paris

David Lebeaux

Assistance Publique – Hôpitaux de Paris

Emmanuel Guerot

Assistance Publique – Hôpitaux de Paris

Patrice Prognon

Assistance Publique – Hôpitaux de Paris

Brigitte Sabatier

Assistance Publique – Hôpitaux de Paris

Eric Caudron

Assistance Publique – Hôpitaux de Paris

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Abstract

Background

In 2020, the first mRNA COVID vaccine was approved by the with six doses from single vial. In the context of material shortages, the aim of the study was to compare different protocols to extract doses using uncrimped materials with good trueness and reproducibility.

Methods

To optimize the extraction of the sixth dose from a single vial with uncrimped materials, alternative protocols of preparation were tested, derived from the drug information.

Results

The repeatability of injected volume was acceptable for all protocols ($CV < 5.3\%$). To prepare six 0.3mL doses using uncrimped materials, protocols with an air bubble were evaluated to offset the high dead volume inherent to uncrimped materials. Regarding the limited doses observed using long intramuscular needle (92.8% of the reference dose), the air bubble protocol with a liquid volume adjustment at 0.27mL was finally validated to respect the administration of full doses.

Conclusion

Results highlighted the necessity to adapt the drug information protocol for the preparation and administration of Cominarty®, due to the use of high dead volume materials. Despite the good reproducibility and accuracy of the air bubble protocols, some precautions have therefore to be taken to maintain the integrity of the vaccine suspension for efficient administration.

Introduction

In December 2019, a new coronavirus called SARS-CoV-2 that causes a severe acute respiratory disease was identified. Initially observed in Wuhan, China, the virus spread rapidly to different countries (1). On 11 March 2020, the World Health Organization (WHO) declared a pandemic (2). In this context, a vaccination race for pharmaceutical industries has begun.

On December 21, 2020, the US Food and Drug Administration and the European Medicines Agency (EMA) approved the mRNA vaccine BNT162b2 Comirnaty® (BioNTech, Mainz, Germany; Pfizer, New York City, NY, USA) as the first vaccine against SARS-CoV-2 (3–5). Comirnaty® from Pfizer is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals aged 16 years or older. The active ingredient of Comirnaty® is a synthetic messenger RNA (mRNA) used by recipient cells to

temporarily produce the SARS-CoV-2 spike protein. mRNA strands in the vaccine are included within lipid and polyethylene glycol (PEG) nanoparticles, to protect them from destruction in the extracellular environment and to facilitate their entry into the host cells. In practice, the handling of Comirnaty® must be done carefully at each step to obtain a diluted vaccine as an off-white dispersion without visible particles. Preparations should be discarded otherwise. According to the available product information, Comirnaty® should be administered intramuscularly after dilution as a course of two doses (0.3 mL each) at least 21 days apart.

In accordance with the standards imposed by the regulatory authorities, an extra volume was foreseen and available in vials to guarantee the extraction of at least five doses of vaccine per vial, with a safety margin. Therefore, a vial initially commercialized for five doses of vaccines virtually contains a sufficient extra volume representing a sixth dose. Leveraging this observation, the EMA's human medicines committee has recommended updating the product characteristics of Comirnaty® to authorize the preparation of six doses of the vaccine for each vial since the 8 January 2021.

To secure a bona fide immunization procedure, numerous protocols of preparation were implemented to reproducibly obtain a sixth dose, using the commonly available medical devices. This study provides feedback on the use of unsuitable medical devices for the preparation of vaccines in the context of a health crisis and supply shortage or tension. The aim of this study was to compare different protocols applied by our vaccination center to extract and inject six 0,3mL doses from a single vial of Comirnaty®.

Material And Method

Briefly, according to the summary product characteristics, the thawed vaccine was diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques. After dilution, the vial contains 2.25 mL. Using low dead-volume syringes and/or needles (0.5 mm x 25 mm needles combined with syringe (HUNAN22012021, Hunan Pingan Medical Device Technology) having dead-volume less than 35 microlitres) to extract doses from a single vial, six syringes can be withdrawn with 0.3 mL. This protocol was considered as reference protocol (protocol P1) to compare the use of standard medical devices presenting higher dead-volume in the vaccine extraction and administration.

Depending on body shape, different uncrimped medical devices were tested to administer vaccine: tuberculin syringes of 1.0 mL (ref. 002022140, Penta®) combined to needles for intramuscular administration of 0.5 mm x 25 mm (25 gauges, ref. 402558, Smiths Medical®) or 0.6 mm x 30 mm (23 gauges, ref. 402558, Smiths Medical®). Using these devices, different volumes and techniques of extraction were tested.

As recommended by the drug information, single vial was used to extract six doses (one vial per protocol). Vaccine solution was diluted by 1.8 mL sodium chloride 9 mg/mL (0.9 %) solution using 3 mL syringe (307727, Becton Dickinson France®) combined with a 0.8 mm x 38 mm needle (21 gauges, ref. 402115, Smiths Medical®). The 3 mL syringe was then disconnected and tuberculin syringes withdrawn

with 0.30 mL (protocol P2) or 0.35 mL (protocol P3) one after the other using the same 0.8 mm x 38 mm needle. The filled syringes were then connected to 0.5 mm x 25 mm or 0.6 mm x 30 mm needle for administration.

In order to facilitate the extraction of the sixth dose, an alternative strategy of vaccine dose preparation with an air bubble was explored. The air bubble was used to flush the vaccine solution from the dead space of the system to limit lost of vaccine. The vial is taken from a work surface with a 0.8 mm x 38 mm needle to withdraw the vaccine from the bottom of the vial. An air bubble from 0.9 mL corresponding to the dead volume of the system was formed near the plunger of the syringe. On contrary to the current practices, this air bubble was preserved in the syringe and the vaccine solution was withdrawn at different volumes: 0.30 mL (protocol P4), 0.27 (protocols P5 and P6) and 0.25 mL (protocol P7 and P8).

For each protocol tested, empty vials of Comirnaty® of vaccine which were pre-filled in by 0.45 mL of 0.9% sodium chloride solution (Freeflex, Fresenius Kabi France®) to mimic vaccine solution, were used. Each solution was then diluted by 1.8 mL of 0.9% of chloride sodium solution (n=8, CV = 0.96%) according to drug information. Using aseptic technique, vaccine doses defined by the protocol were withdrawn of the vial. If the amount of vaccine remaining in vial cannot provide a full dose, the vial was discarded.

After syringes preparation, vaccine administration was miming for each syringe. The injected volume (repeatability and trueness) was evaluated by weighing after correction by the bulk density of 0.9% sodium chloride solution. The protocol 1 corresponding to Comirnaty® drug information was considered as the reference to compare other protocols.

Experimental Results

Results are exposed in Table 1, the repeatability of injected volumes was acceptable for all protocols (CV <5.3%). The reference protocol proposed in the drug information (protocol P1) allow the extraction of sixth and more over seven doses using crimped materials. Using uncrimped syringes and needles, none other protocol allowed the extraction of seven doses. The protocol P2 allowed the extraction of six doses but the underfill was around 13.1% due to the needle change. To extract the correct dose volume with a needle change, an overfilling of the syringe to include the purge of the system to 0.3 mL is necessary (protocol P3). This protocol is incompatible with the extraction of the sixth dose.

The standard preparation does not allow the preparation of six doses per vial, with the adequate injected volume and with the good practice of administration including the change of needle before each administration. In order to prepare six doses of 0.3mL per vial and in accordance with the good practice of administration, protocols with air bubble in syringes were evaluated in response of large dead volume inherent to the available material.

We decided to use a long needle (0.8 mm x 28 mm) to reach the bottom of the vial to extract all the diluted vaccine solution in Figure1. In protocols 4 to 8, after vaccine dilution (step 1, figure 1), an air

bubble was generated by the dead volume of the needle and syringe (step 2, figure 1). During vaccine injection, the bubble has to stay near the plunger of the syringe to finally flush the vaccine solution. These four protocols allow the extraction of a full sixth doses in accordance with the good practices of administration. Results highlighted therefore variation on the volume injected. The protocol P4 was associated with an overfilling of around 15% of the injected vaccine volume due to the injection of the dead volume. Therefore, the extracted volume was reduced to respect the recommendation of drug information. By contrast, protocols with volume adjustment at 0.27 mL and 0.25 mL shown doses close to the reference protocol using a standard 0,5 mm x 25 mm needle for intramuscular administration. Regarding the limited doses observed with a 0.6 mm x 30 mm needle (92.8% of the reference dose according to the protocol P8), the protocol with 0.27 mL was selected to respect the administration of full doses with the two needles.

Discussion And Conclusion

In the context of the COVID-19 pandemic, shortages of medicines and medical supplies prevent the rapid implementation of public health measures aiming to protect the most vulnerable segments of the populations. The limited access to the vaccine has led public health deciders to first recommend the extraction of six and thereafter seven doses per Comirnaty® vial. In order to guarantee the administration of 0.3mL of vaccine to each patient, the results of the present work highlighted the necessity to adapt the drug information protocol when standard syringe and needle are available in routine practice. Indeed, using standard syringes and needles (dead-volume larger than 35 microliters) and routine practices, the extraction of six doses and moreover seven doses of 0.3mL each from a single vial of Comirnaty® cannot be guaranteed. Thus, in our view, only the combination of a syringe and a needle with a low dead volume (less than 35 microlitres) should be employed. In this context, preparation protocols including the introduction of an air bubble in medical device offer an interesting alternative when standard devices are used. This procedure enables the flushing of the vaccine solution from the dead space of the system, limiting the loss of vaccine solution and thus, optimizes the number of vaccine doses injected with good reproducibility and accuracy. These protocols need however some precautions: syringes have to be vertically withdrawn from vials at the bottom using a long needle of 21 gauges to fill syringes. Subsequently, syringes have to be transferred vertically with the head down and handled carefully thereafter to maintain the air-bubble near the plunger. Like some pre-filled syringes marketed by the pharmaceutical industry, the air bubble in the syringe ensures that the entire contents of the dose will be injected accurately and reproducibly with inexpensive equipment. Finally, as the volume of the bubble is small, corresponding to the dead volume of the delivery device, it does not present a clinical risk to the patient.

In the current context, vaccination is an essential part of the fight against the Covid-19 pandemic (6). Results from studies of candidate vaccines show that vaccination significantly reduces severe disease and mortality due to the virus. Combined with barrier measures, the vaccine helps to control the current impact of the epidemic and will generate the expected herd immunity in the long term. Despite vaccination was deployed progressively in different countries and following different vaccinal strategies,

respect for recommended injected vaccine dose is essential to ensure the proper immunization of the populations. Administration of the correct dose will both prevent the development of novel escape variants of the virus and oppose the apparition of clinically severe forms of the disease that might result from a suboptimal immunization. In a period of quota, the use of extra doses of vaccine such as the sixth or even seventh dose, depending on the material used, is a real public health issue. In this regard, our work shed useful light on readily implementable improvements of immunization practices.

Declarations

Author contribution

LL and EC wrote the main manuscript text. JT, AC, JP, NM, MCL, DL, EG and PP contribute to implement the vaccination campaign in the hospital. All authors reviewed the manuscript.

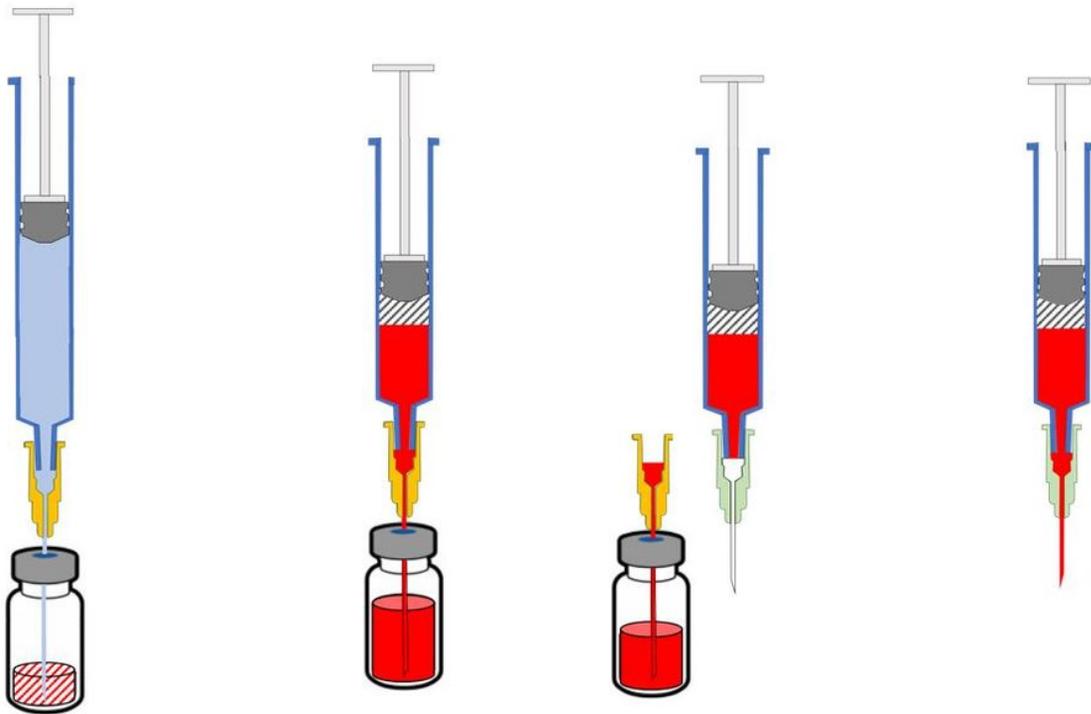
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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures



1) Add 1.8 mL of aqueous solution of NaCl 0.9% (blue) with a 2 mL syringe and a 0.8 x 38mm needle (21 G) in the vial containing 0.45 mL of concentrated vaccine suspension (red striped)

2) Withdraw an air bubble (grey striped) equivalent to the dead volume of the syringe and withdraw the vaccin diluted suspension (red) dose by adjusting the piston at 0.27 mL using a 1 mL tuberculine syringe and a 0.8 x 38 mm needle (21 G)

3) Change the needle for 0.5 x 25 mm (25 G) or 0.6 x 30 mm (23 G) needle

4) Before injection, purge the needle untill seeing a small drop of liquid coming out

Figure 1

Protocol of preparation and administration for six doses per Comirnaty® vial with uncrimped syringes corresponding to protocols P5 and P6

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.jpg](#)