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Increasing vaccine supply with low dead-volume syringes and needles

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ABSTRACT

As global vaccine production capacity is limited, every optimization strategy must be explored to rapidly increase the number of people vaccinated. The objective of this study is to determine which medical devices allow the extraction of the maximum number of doses from different vaccine vials (Pfizer-BioNTech, AstraZeneca, Moderna and Johnson & Johnson vaccines) by analyzing all the factors involved in the preparation of the injected doses. By measuring the dead-volume of 32 syringe-needle combinations, we show that fixed-needle syringe with a dead-volume of less than 5 µL can extract up to 7 doses from Pfizer vials, 13 doses from AstraZeneca vials, 12 doses from Moderna vials and 6 doses from Johnson & Johnson vials. We found that the syringe accuracy is important, and can compromise the chances of extracting additional doses when withdrawing too large a volume. For Pfizer vaccine, particular attention must be paid to the choice of dilution syringe, which may compromise the extraction of the 7th dose. The withdrawal of extra doses from vaccine vials was not operator-dependent. In this unprecedented health context, the medical device considerations presented here could help to optimize every COVID-19 vaccine vial.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has spread worldwide from Hubei province of China in December 2019 leading to an unprecedented epidemic situation (Khan et al., 2020; Priyanka et al., 2020). On July 15, 2021, more than 4.06 million deaths have been attributed to the epidemic situation (Khan et al., 2020; Priyanka et al., 2020). On January 6 and 29, 2021, the COVID-19 vaccines from Moderna and Johnson & Johnson vials. We found that the syringe accuracy is important, and can compromise the chances of extracting additional doses when withdrawing too large a volume. For Pfizer vaccine, particular attention must be paid to the choice of dilution syringe, which may compromise the extraction of the 7th dose. The withdrawal of extra doses from vaccine vials was not operator-dependent. In this unprecedented health context, the medical device considerations presented here could help to optimize every COVID-19 vaccine vial.

Lastly, Johnson & Johnson COVID-19 vaccine has been approved on March 11, 2021, differing from others in that it is a single 0.5 mL in newcomers also consist of two doses (0.5 mL each – 10 doses per vial) administered intramuscularly at 4 or 12 week intervals, respectively. Lastly, Johnson & Johnson COVID-19 vaccine has been approved on March 11, 2021, differing from others in that it is a single 0.5 mL injection (2.5 mL per vial equivalent to 5 doses). To date, no changes to the summaries of product characteristics concerning the extraction of additional doses have been claimed by these 3 laboratories and no study has been carried out to propose recommendations on the use of adapted medical devices. However, the existence of the overfill required by the European Pharmacopoeia could allow the theoretical extraction of additional doses from a single vial using low dead volume syringe-
needle combinations, similarly to Pfizer-BioNTech vaccine vials. The objective of this study is to determine which medical devices allow the extraction of the maximum number of doses from the different vaccine vials by analyzing all the factors involved in the preparation of the injected doses: dependent operator factors, actual quantity of vaccine contained in each vial, characteristics of the syringe-needle combination.

2. Material and methods

To test the quantities of vaccine delivered in mL without knowing the accuracy of the syringe or the exact dead volumes, we chose to perform our measurements by weighing. As a vaccine solution with a density different from 1 could constitute a bias in our results, we aimed to determine the density of the vaccine solutions. All measurements were performed gravimetrically using a Sartorius ME254S-OCE balance, accuracy 0.0001 mg (APAVE certification, July 2020).

2.1. Materials

The Pfizer-BioNTech, AstraZeneca, Moderna and Johnson & Johnson vaccines were delivered by “Santé Public France” to our institution. Four types of syringes were used as well as two types of detachable needles (25G – 16 mm or 25G – 25 mm). The associated pictures and references are detailed in Table 1 and each reference has been assigned a letter for clarification purposes.

Table 1
Different types of syringes and needles used in the experiments.

| Classification                        | Syringe (reference) | Needles (if provided or stamp fixed onto the syringe) | Manufacturing location                                      | Pictures |
|---------------------------------------|---------------------|--------------------------------------------------------|------------------------------------------------------------|----------|
| High dead-volume syringe and needle   | A PENTAFERTE        | PENTAFERTE ITALIA s.r.l. Loc. Nocella S.P. 262 64012 CAMPLI (TE)- ITALY |                                                            |          |
|                                       | B BD PLASTIPAK      | Becton Dickinson S.A., Camino de Valdeoliva, s/n, 28750 San Augustin del Guadarrma, Madrid, Spain |                                                            |          |
|                                       | F PENTAFERTE        | PENTAFERTE ITALIA s.r.l. Viale Piane Nocella, 23 64012 CAMPLI (TE)- ITALY |                                                            |          |
| Reduced dead-volume modified syringe with plungers molded to the luer cone | C BBRAUN INJEKT-F  | B. BRAUN Melsungen AG. Carl-Braun-Straße 1, 34212 Melsungen, Germany. |                                                            |          |
|                                       | D DOVILAB           | Jiangsu Jichun Medical Devices CO., Ltd, Zhenglu Town, Tianjin 212111, Jiaojia, China |                                                            |          |
|                                       | E DOVILAB           | Jiangsu Jichun Medical Devices CO., Ltd No. 98, Bajiang Bridge, Zhenglu Town, Tianjin 213111, Jiaojia, China |                                                            |          |
|                                       | G SOL-M             | Sol-Millennium Medical, Inc. 1735 North Brown Road, Suite 120, Lawrenceville, GA 30043, USA 404-973-2200 |                                                            |          |
|                                       | H Not specified     | Zhejiang Haifu Medical Equipment Co., Ltd 668 Xueding 1 ST RD, 314200 Pinghu |                                                            |          |
2.2. Measurement of vaccine solution density

Vaccine density was determined by weighing 100 µL of vaccine collected with a 200 µL micropipette (Sartorius, Göttingen, Germany) from the remainder contained in 5 vials of the different vaccines returned by the vaccination centers.

2.3. Determination of the vaccine vial filling volumes

Vials were numbered and weighed before being delivered to the vaccination centers. Once the vials were returned to the pharmacy after extraction and administration of the doses, they were opened, emptied, oven-dried and weighed. The difference in weight between the full vial and the same empty vial, taking into account the density of the vaccine solution, gives the filling volume of the vaccine vial.

2.4. Accuracy of graduations

The accuracy of the 1 mL and 3 mL syringe graduations was determined by sampling 0.3 mL, 0.5 mL and 1.8 mL of distilled water and weighing the expelled volume. This test was performed blindly by 5 operators on 10 samples for each syringe. The results were compared to the “tolerances on graduated capacities” of the NF EN ISO 7886-1 standard.

2.5. Inter and intra-operator repeatability

Repeatability of syringe filling was assessed at volumes of 1.8 mL (3 mL DOVILAB syringe reference 13103LL), 0.3 mL (1 mL PLASTIPAK syringe reference 303,172 BD) and 0.5 mL (1 mL B.BRAUN INJEKT-F syringe reference BBR_9166017V) by weighing the expelled volume. Tests were performed blindly by 10 operators on 10 samples (5 operators for the 0.5 mL volume).

2.6. Dead volumes of the different syringe/needle combinations

The dead volumes of the different syringe/needle combinations were performed in accordance with NF-EN ISO 7886-1 Annex C. Each syringe/needle combination was weighed before and after sampling and expelling a volume of 0.3 mL of distilled water. The volume of distilled water remaining in the syringe/needle combinations after emptying the syringe is the dead volume. Tests were performed on 5 samples per syringe.

2.7. Number of extractable doses

In order to avoid wasting vaccine doses to perform the extractable volume test in our laboratory, the number of extractable doses was calculated theoretically from the volume contained in each vial and the volume collected for each syringe (injected volume + dead volume). This value was confirmed by the operators of the vaccination center regarding the syringe-needle combinations used in our center. For the syringes not distributed at the center, the number of extractable doses was determined on expired vials that had suffered a break in the cold chain. These vials were also used to perform the extractable volume test for parenteral preparations of the European Pharmacopoeia, which specifies the use of a syringe whose capacity does not exceed three times the volume to be measured, fitted with a 21G needle with a minimum length of 2.5 cm (European Pharmacopoeia (Ph. Eur.) 10th Edition | EDQM · European Directorate for the Quality of Medicines).

2.8. Statistical analysis

Data were expressed as the mean ± standard error of the mean (SEM). Inter-operator differences were probed in a one-way analysis of variance (ANOVA). The significance of intergroup differences in the overfilling bias experiment was determined using a Mann-Whitney test. All analyses were performed using Prism software (version 5.0, GraphPad Software, La Jolla, CA, USA). All tests were two-sided, and the threshold for statistical significance was set to p < 0.05.

3. Results

3.1. Vaccine fill volume

The density of the four vaccines was measured at 1, allowing the weight of the samples to be equated with their volume. The volume of vaccine contained in each vial is shown in Table 2:

3.2. Dilution volume of Pfizer vaccine

Only Pfizer should be diluted with 1.8 mL of 0.9% sodium chloride, resulting in an actual vaccine volume of 2.27 mL (Fig. 1-A). The accuracy of the DOVILAB 3 mL syringe (1.7984 ± 0.0120 mL) at the 1.8 mL graduation, measured blindly by 10 operators on 10 samples each, was better than that of the BD PLASTIPAK 3 mL syringe reference 309,658 (1.7585 mL ± 0.0078 mL) (Fig. 1-D). On this experiment, the first trial of each operator also showed that 9 out of 10 operators reflexively re-injected the volume of liquid (dead volume of the needle) arising in the syringe when the plunger was raised for pressure equalization (Pfizer BioNTech procedure). The tests were therefore performed with or without re-injection of this dead volume. The average injected volume with or without injection of this dead volume was 1.826 ± 0.003 mL and 1.790 ± 0.002 mL respectively (Fig. 1-B). In contrast, these experiments revealed no inter- and intra-operator differences on the injection of the dilution volume (Fig. 1-C).

3.3. European Pharmacopoeia extractable volume

The European Pharmacopoeia extractable volume test, performed with a BD Plastipak 1 mL syringe (reference 303172) and a 21G/40 mm B.BRAUN Sterican needle (reference 4670045S-01) on 5 Pfizer BioNTech vials only allows for the extraction of 5 syringes of 0.3 mL.

3.4. Repeatability and reproducibility of the injected volume

As with the dilution syringes, the repeatability and reproducibility tests performed at the 0.3 mL (Fig. 2-A) or 0.5 mL (Fig. 2-B) graduation did not show inter- and intra-operator variability.

3.5. Dead volume of syringe/needle combinations

The dead volumes of the 32 different syringe/needle combinations evaluated are shown in Fig. 3 with the number of extractable doses associated for each vaccine. The high dead volume syringes PENTA-FERTE (A) and BD PLASTIPAK (B) with dead volumes varying from 75 to 100 µL depending on the needle associated with them did not allow the extraction of additional doses from PfizerBioNTech and Johnson & Johnson vaccine vials. A first improvement was made with molded plunger syringes that fit into the Luer cone, B.BRAUN (C) and DOVILAB (D and E), with a reduction of the dead volume to 50 µL. Again, the dead volume was directly related to the associated needle (Table 3) and this variation can be attributed to different volume bases and/or a greater or smaller volume.

| Volume measured | Theoretical volume |
|-----------------|--------------------|
| 0.472 ± 0.003 mL | 0.45 mL |
| 6.318 ± 0.042 mL | 5 mL |
| 6.653 ± 0.043 mL | 5 mL |
| 3.194 ± 0.003 mL | 2.5 mL |

Table 2

Actual volume contained in the COVID-19 vaccine vials.
lesser insertion of the syringe tip into the needle base. With the exception of BD Flu syringes, which are less efficient (dead volume of about 20 \( \mu \)L), syringes with a fixed-needle and a dead volume of less than or equal to 5 \( \mu \)L (syringe I to Q) allowed the extraction of the maximum number of doses: 7 doses for Pfizer, 13 for AstraZeneca, 12 Moderna and 6 Johnson & Johnson.

3.6. Accuracy of graduation of injection syringes

The graduation accuracy is variable according to the syringe references. At the 0.5 mL graduation (Fig. 4-C) some syringes withdrawn more than 0.51 mL (syringes A, F, N, R, S, T) or less than 0.49 mL (syringes I, L, M, O). Two syringes (R and T) did not meet the specifications of “NF-EN ISO 7886-1: Tolerance on graduated capacities - Table 1” as the volume injected exceeded the tolerances (Fig. 4). Interestingly, syringe J is the only one with a nominal volume of 0.3 mL (compared to the others which have a nominal volume of 1 mL) (Table 1). Therefore, the tolerance values calculated according to the NF-EN ISO 7886-1 standard formula (Fig. 4A) are different: 0.3 ± 0.021 mL for the 1 mL syringes and 0.3 ± 0.0105 mL for the 0.3 mL syringes. Although the syringes tested were NF-EN ISO 7886-1 compliant at the 0.3 mL graduation, similar results were found with syringe I withdrawing less than 0.29 mL. No difference were found in withdrawal volume between the operators.

4. Discussion

In this study, we determined that obtaining additional doses from COVID-19 vaccine vials is not operator dependent and that the medical device used is the most important parameter for this purpose.

Of the various characteristics of collection and injection medical devices, the dead-volume of syringe-needle combinations was found to be of utmost importance. As the fixed-needles syringes did not have a hub, they emerged as those with the lowest dead volume (references I to T). Among them, the combinations I to Q allowed the extraction of seven doses instead of five for the Pfizer vaccine, 13 doses instead of 10 for the AstraZeneca vaccine, 12 doses instead of 10 for the Moderna vaccine and six doses instead of five for the Johnson & Johnson vaccine. Conversely, the needles to be inserted on the syringe had the highest dead volumes and the same syringe on different needles did not give the same dead volume. Accordingly, the use of syringe-needle combinations cannot be decided at random, from an evidence-based dose optimization perspective. These data suggest that the I to Q syringes should be prioritized for the AstraZeneca vaccine since they provide 13 doses from a single vial. The other fixed-needle syringes should be prioritized for the Moderna vaccine since only a maximum of 12 doses can be obtained. Interestingly, the European Pharmacopoeia’s parenteral preparations extractable volume test did not allow the extraction of a 6th dose from Pfizer-BioNTech vaccine vials. Thus, the modification of the summary of product characteristics officially allowing the possibility of extracting 6 doses from one vial makes this vaccine non-compliant with the European Pharmacopoeia.

The accuracy variations of the syringes according to the references also appeared important in the optimization of the doses of vaccines, as exemplified by the accuracy of the syringes at the 0.5 mL graduation in this study. Recent evidence suggest that administration of fractional doses of vaccine (e.g. half a dose) would be sufficient to generate immune responses associated with high vaccine efficacy, so that injecting a
A slightly smaller amount would not make any appreciable difference (Cowling et al., 2021; Więcek et al., 2021). However, while withdrawing a larger volume than indicated by the syringe at each collection is unlikely to result in an overdose, it may compromise the chances of extracting additional doses from a vial. In a previous report, we found similar results at the 0.3 mL graduation, taking all its importance for the optimization of the Pfizer-BioNTech vaccine extra doses (Le Daré et al., 2021). Regarding these issues, the thinner syringes appeared to be the most accurate because a larger syringe body diameter increases the margin of error. Moreover, we have shown that the accuracy of the syringe is also critical to the dilution of the Pfizer-BioNTech vials, as a syringe injecting less than 1.8 mL is likely to compromise the withdrawal of additional vaccine doses. The experience of the vaccination centers confirms that this significant difference between BD PLASTIPAK 3 mL and DOVILAB 3 mL syringes accuracy (p < 0.0001) is likely to compromise the extraction of the 7th dose of Pfizer BioNTech vaccine. Loewenstein et al. showed that the use of a prefilled syringe was associated with improved accuracy compared to using a 1.0 mL syringe to withdraw and expel a volume (Loewenstein et al., 2019). However, the use of prefilled syringes, which requires a longer manufacturing process, does not seem achievable in the short term because of the urgent need for COVID-19 vaccines (Feinmann, 2021). Interestingly, the differences in the characteristics of the medical devices used for the vaccination campaign, which appear insignificant in current practice, take on their full importance in the context of the current shortage.

On the operator’s side, we have shown that there were no significant differences, either for the vaccine dilution in the case of Pfizer vials, or for the collection of doses. However, it seems pragmatic that an experienced vaccinator will perform these preparations more efficiently. Although overfilling bias has been investigated for the Pfizer-BioNTech vaccine, it seems unlikely that the small amount of extra dilution volume will affect the ability to extract additional doses.

Overall, these data were used to optimize the vaccination campaigns managed by our hospital and could be generalized to all current global COVID-19 vaccination campaigns. On July 15, 2021, at least 1.96 billion people have received a first dose of COVID-19 vaccine worldwide, representing around 25.2% of the world population (OurWorldInData, 2021). As global vaccine production capacity is limited from two to four billion doses per year according to the coalition for epidemic preparedness innovations estimates, optimization of COVID-19 vaccine doses through medical devices might be a valuable strategy (CEPI survey assesses potential COVID-19 vaccine manufacturing capacity). Surprisingly, apart from journalistic articles on the subject, scientific publications dedicated to vaccine campaign optimization issues do not mention this possibility, hindering the generalization of simple and easily achievable solutions (Buckner et al., 2020; Kim et al., 2021; Matrajt et al., 2021). Since the herd immunity to SARS-CoV-2 can be achieved only via vaccination, global efforts should consider every evidence-based data allowing to administer additional vaccine doses. We argue that uses of extra doses using fixed-needle syringes for the administration of COVID-19 vaccines must be integrated into public health policy decisions to fully optimize these limited resources as suggested by Priyanka and colleagues (Priyanka et al., 2021b, 2021a). The margin for improvement, which consists in obtaining material with a low dead volume and the best possible accuracy, is very dependent on the vaccination centers since they may have different syringes and needles. Consequently, along with this consideration, what is needed is the development of production capacities for fixed-needle syringes with high accuracy in parallel with the vaccine production. More importantly, in the event that fractionated doses of vaccine are used, a larger number of doses will be collected from each vial. Therefore, the rational use of needle-syringe combinations that collect the lowest possible dead

![Fig. 2. Determination of withdrawal volumes according to the operators. (A) Measurement of the 0.3 mL withdrawal volume by 10 operators using BD Plastipak 1 mL syringe (reference 303172). (B) Measurement of the 0.5 mL withdrawal volume by 5 operators using BBRAUN INJEKT-F syringe (reference BBR_9166017V). The data are quoted as the mean ± SEM from at least 5 independent and blind measurements. N.S: not significant; OP: operator.](image-url)
volume with the greatest accuracy, consistent with the data presented here, could allow for unprecedented optimization of vaccine strategies. These results must be interpreted according to several limitations. Firstly, no AstraZeneca, Moderna or Johnson & Johnson vial has been returned whole to the pharmacy, making it impossible to perform the European Pharmacopeia extractable volume tests. The data presented here for these three vaccines are therefore only theoretical, although the vaccination centers confirmed our data. Secondly, although we show that the extraction of additional doses can be achieved with several fixed-needle syringe references, this does not preclude other references from also allowing this maximization of the number of doses extracted from multidose COVID-19 vaccines.

Table 3

| Syringe – 1 mL | Needle 25G, 25 mm | Dead Volume |
|----------------|-------------------|-------------|
| DOVILAB 13101LS Medtronic Monject | 0.0495 ± 0.0055 mL |
| DOVILAB 13101LS Terumo Neolus NN2525R | 0.0767 ± 0.0085 mL |
| DOVILAB 13101LS B Braun Sterican | 0.0653 ± 0.0053 mL |
| DOVILAB + needle 25G (ref 13111LS) | 0.0469 ± 0.0127 mL |

Fig. 3. Extra doses from COVID-19 vaccines vials according to syringe-needle combinations. Actual volume of (A) Pfizer-BioNTech, (B) AstraZeneca, (C) Moderna, (D) Johnson & Johnson vaccine vials associated with number of doses extractable from a single vial according to different syringe/needle combinations. (E) References of syringe and needles. The data are quoted as the mean ± SEM from at least five measurement per syringe-needle combination. The background colors represent the number of doses achievable compared to the data in the summary of product characteristics (SPC): red (one dose less than indicated by the SPC), pale pink (number of doses according to the SPC), blue (one dose more than indicated by the SPC), green (two doses more than indicated by the SPC), yellow (three doses more than indicated by the SPC).
5. Conclusion

In the face of this immense challenge that has been the COVID-19 pandemic for more than a year and a half now, it seems pragmatic that we should put together every effort in an evidence-based approach in order to bring this unprecedented health context under control. For this purpose, the reasoned choice of medical devices remains crucial. The dead volume of the syringe/needle combinations appears to be the determining factor for the extraction of additional doses from the vaccine vials, with fixed-needle syringes making the best use of vial overfill. For Pfizer vaccine, particular attention must be paid to the choice of dilution syringe, which also may compromise the extraction of the 7th dose. In this context, this work shows which parameters are important to consider for syringe/needle combination sourcing, either when setting up a vaccination center or when looking for alternatives in case of shortages.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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