Health care professionals’ preference for a fully liquid, ready-to-use hexavalent vaccine in Spain

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ABSTRACT

Vaccination is an effective health intervention for the prevention of infectious diseases. This study aims to evaluate the response provided by nurses toward the use of ready-to-use (RTU) formulations of hexavalent vaccines and measures to prevent errors during the vaccination process. This observational, descriptive, cross-sectional study took place from March to May 2018. It included 201 interviews with nurses from health centers in Madrid (70), Murcia (59), and Andalusia (72), who had administered RTU vaccines in the last 12 months. Approximately 91.6% of nurses provided a positive feedback for the use of RTU vaccines. The most significant concerns experienced by nurses were during the preparation and administration of vaccines; 84.1% versus 18.9% of nurses felt that the risk of making mistakes was lower while using RTU vaccines compared with non-reconstituted (lyophilized) vaccines, and 74.1% versus 22.4% of nurses felt ease at preparing RTU vaccines compared with lyophilized vaccines. A total of 66.7% of nurses believed that there were risks associated with the preparation of lyophilized vaccines (administration risk [42.8%] and risk of needle injury [42.3%]). Risk percentages reduced to 4% and 9.5%, respectively, with the use of the RTU vaccines. Therefore, nurses adopted an average of seven steps to reduce the risk of errors. The average time saved during the administration of the vaccines was 1.1 min. In summary, nurses highlighted the need for administering vaccines using RTU formulations for ensuring the safety of the recipients, preventing errors, and saving time during the vaccination process.

1. Introduction

Vaccines are considered one of the most cost-effective public health measures since vaccination programs aid to achieve immunity at the individual level and via herd immunity (Ehreth, 2003, Hansen et al., 2018). Vaccination is used as a preventive measure by all major healthcare systems. The World Health Organization (WHO) stated that vaccination programs prevent 2 to 3 million deaths worldwide annually (Interterritorial Council of the National Health System of Spain, 2019). In Spain, a lifetime vaccination schedule has been in place since 2019 (Interterritorial Council of the National Health System of Spain, 2019). It ensures that vaccines are free and voluntary from the prenatal stage.
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As of 2019, vaccination is no longer considered an intervention strategy reserved exclusively for children in Spain. In November 2019, the vaccination schedule was updated by the Ministry of Health, Consumer Affairs, and Social Welfare via the Interterritorial Council of the National Health System (Fig. 1) (Interterritorial Council of the National Health System of Spain, 2020). It also includes recommendations for individuals belonging to risk groups who require specific vaccines based upon their underlying conditions in both childhood (Interterritorial Council of the National Health System of Spain, 2018a) and adulthood (Interterritorial Council of the National Health System of Spain, 2018b).

Vaccination is one of the most frequently conducted healthcare procedures throughout a person’s life (Kim et al., 2019). To ensure the safety of the individuals receiving the vaccine, vaccination must be performed appropriately. There is a growing concern about human errors during vaccination, specially due to improper storage, handling, and administration of vaccines, possibly leading to higher rates of vaccine-related adverse drug reactions than the vaccine itself (Bundy et al., 2009). Any strategy, mechanism, or system that serves to avoid errors in the administration of vaccines is highly valued by healthcare professionals (HCPs).

Color: Systematic administration; Striped: administration in susceptible individuals or those who are not previously vaccinated.

DTaP, diphtheria, tetanus, and whooping cough (pertussis); HB, hepatitis B; Hib, Haemophilus influenzae type b; HPV, human papillomavirus; IPV, inactivated polio vaccine; MenACWY, meningococcal conjugate vaccine; MenC, meningococcal C vaccine; MM, measles, mumps; MMR, measles, mumps, rubella; PCV, pneumococcal conjugate vaccine; PV, pneumococcal vaccine; Td, tetanus, diphtheria.

Fig. 1. Common lifetime vaccination schedule (recommended schedule for year 2020). Color: Systematic administration; Striped: administration in susceptible individuals or those who are not previously vaccinated. DTaP, diphtheria, tetanus, and whooping cough (pertussis); HB, hepatitis B; Hib, Haemophilus influenza type b; HPV, human papillomavirus; IPV, inactivated polio vaccine; MenACWY, meningococcal conjugate vaccine; MenC, meningococcal C vaccine; MM, measles, mumps; MMR, measles, mumps, rubella; PCV, pneumococcal conjugate vaccine; PV, pneumococcal vaccine; Td, tetanus, diphtheria.

Also, the use of safety and quality mechanisms in the vaccination process promotes adherence and confidence among the general population and HCPs, thus contributing to higher rates of vaccination and ensuring the success of immunization program (Fukushima et al., 2018).

Needles used for parenteral routes of vaccination have protective mechanisms to safeguard the nurses from biological accidents. These needles have biosafety devices incorporated in them to protect against accidental punctures. Use of such devices is recommended to ensure the protection of occupational health (Javadekar et al., 2018, Li et al., 2018).

Another important aspect to be considered is the awareness about the specifications of vaccine before administration (Robertson et al., 2016). It includes methods for safety, product handling instructions, and such other essential information. Before administration, some vaccines need to be reconstituted, while other vaccines come in fully liquid formulations, also named as ready-to-use (RTU) vaccines. The latter are considered useful formulations with respect to the ease of handling and administration (Garcés Sánchez et al., 2010, Lloyd et al., 2015).

Reconstituting a vaccine requires a considerable amount of time before it can be used. It depends upon the presentation of solvent – either a prefilled syringe or a vial. In either situation, the solvent has to be
introduced into the vial consisting of the solute to dissolve the contents before administration. If the reconstitution process is not done appropriately, the composition of vaccines will be incorrect, failing to provide an immunizing and preventative effect for the recipient. Similarly, vials should be handled by taking all the appropriate antiseptic measures to avoid contamination of the final product. Also, given that needles are used to introduce the solvent and to extract the product once it has been reconstituted, the application of measures to avoid accidental punctures is vital to the safety of the person who handles and subsequently administers the vaccine.

RTU vaccines could provide safety in vaccination programs and replace the vaccines that require reconstitution. It is said that reconstitution is one of the leading causes of error during the administration phase (Bundy et al., 2009). This type of error could reduce vaccination efficacy by failing to provide functional immunity to the recipients against several infectious diseases (Interterritorial Council of the National Health System of Spain, 2019).

Research has shown that vaccine-related errors are frequently associated with human errors, especially incorrect dosing during administration (Bundy et al., 2009).

To minimize pragmatic biologic errors, including human errors related to administration and occupational accidents, providers should focus on designing new technologies and safety devices for care delivery. RTU is a safety formulation wherein the reconstitution process is not required (Vesikari et al., 2018). As the name indicates, the vaccine can be used directly without any necessary prior handling. Therefore, it saves time in handling the vaccine, avoids reconstitution errors, and prevents the possibility of accidental contamination and biological accidents by the puncture (Garcés Sánchez et al., 2010).

In infants and children of 6 weeks of age and older, hexavalent vaccines are used as primary as well as booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b (Hib) (Syed, 2019). In Spain, the hexavalent vaccine has a high vaccination coverage due to its inclusion in the systematic schedule vaccination program (Fig. 1). The study results are focused on hexavalent vaccines, which are extremely important for fighting against infectious diseases, such as diphtheria and tetanus. This study aims to evaluate how RTU formulations may improve the Spanish market’s status quo wherein reconstituted vaccines lead the standard of care. One dose of 0.5 mL of RTU formulation of hexavalent vaccine contains diphtheria toxoid (no less than 20 IU), tetanic toxoid (no less than 40 IU), *Bordetella pertussis* antigens, poliovirus (Type 1, 2, and 3), hepatitis B virus surface antigen (10 µg), and Hib polysaccharide (12 µg) conjugated with tetanus protein.

In Spain, three hexavalent vaccines with different types of formulations from different manufacturers are currently available in the market;
two of them have an RTU approach (injectable suspension in pre-filled syringe which does not require to be reconstituted), whereas the other vaccine needs to be reconstituted before administration, requiring additional administration steps that increase the risk of biological errors and the time required for the HCP (powder and suspension for injectable suspension, diphtheria-tetanus-acellular pertussis-hepatitis B recombinant (adsorbed)-inactivated poliomyelitis-adsorbed conjugated Haemophilus influenzae type b vaccine (DTPa HBV-IPV) is a white cloudy suspension. The freeze-dried Hib component is a white powder) (Fig. 2).

Although clinically there is no difference between these vaccines, the administration process of RTU vaccines is perceived as quite easier and intuitive compared with others due to its pharmaceutical form.

2. Materials and methods

2.1. Design and population

This is an observational, cross-sectional, descriptive study conducted between March 2018 and May 2018 via 201 interviews with nurses working in public health centers in the autonomous communities of Madrid, Murcia, and Andalusia who had administered RTU hexavalent vaccines in the last 12 months. The results compared RTU formulation and other vaccines that required prior reconstitution before their use (powder and suspension for injectable suspension, DTPa HBV-IPV is a white cloudy suspension, and the freeze-dried Hib component is a white powder). All nurses met the inclusion/exclusion criteria and provided their written informed consent before participation. There were two exclusion criteria defined per protocol – nurses who had not vaccinated any recipient with a biosafety device in the last 12 months were excluded from the study (Appendix A. Supplementary materials, questions 8 and 9). The confidentiality of the collected answers was maintained. The data were used for only statistical analysis, in accordance to the Organic Law 5/1992 on the Regulation of the Automated Treatment of Personal Data and the Organic Law 15/1999 on the Protection of Personal Data, of the Spanish government.

A 17-question questionnaire was designed for the study (Appendix A. Supplementary materials) by an analysis and research consultant (Grupo Análisis e Investigación), which the nurses completed via in-person interviews or an interview submitted through mail or email. For the collection of data, two different phases were followed. In the first phase, the questionnaires were sent to the health centers by post, and in the second phase, on-line interview and in-person interview methods were used for collecting the data.

2.2. Statistical analysis

The error for an infinite universe and a confidence level of 95.5% was used in this study, with a coefficient of determination of (p = q = 0.5) ±7.05% for the sample total. Under the same assumptions, the standard error was ±12.00% for Madrid sample; ±13.02% for Murcia sample; and ±11.80% for Andalusia sample.

The questionnaire has two types of questions, the ones with nominal variables, which have been analyzed through tables of distribution of margins, and the scale questions, which have been analyzed through averages as a measure of central tendency. Also, bivariate tabulations have been used to determine possible differences between groups or correlations between questions.

2.3. Anonymity and confidentiality

The absolute anonymity of the interviewed nurses’ responses was ensured, which were used only in the calculation of statistic charts.

| Type of vaccine | Ready-to-use | Reconstituted |
|-----------------|--------------|---------------|
| Less risk of making mistakes in preparation (overall) | 84.1% | 18.9% |
| Madrid           | 91.4%        | 28.6%        |
| Murcia            | 91.5%        | 33.6%        |
| Andalusia        | 70.8%        | 23.9%        |
| Quickier and simpler to prepare (overall)     | 74.1%        | 22.4%        |
| Madrid           | 75.7%        | 28.6%        |
| Murcia            | 84.7%        | 23.6%        |
| Andalusia        | 63.9%        | 26.3%        |
| Risks of errors when preparing vaccines (overall) | 4.0% | 66.7% |
| Madrid           | 2.9%         | 60.0%        |
| Murcia            | 6.8%         | 83.1%        |
| Andalusia        | 2.8%         | 59.7%        |
| Potential risk of biological accident for needle lesions (overall) | 9.5% | 42.3% |
| Madrid           | 11.4%        | 42.9%        |
| Murcia            | 8.5%         | 55.9%        |
| Andalusia        | 8.3%         | 30.6%        |
| Decrease in time spent performing the vaccination process (overall) | 8.08 min | 9.16 min |
| Madrid           | 8.7 min      | 9.84 min     |
| Murcia            | 10.60 min    | 12.06 min    |
| Andalusia        | 5.41 min     | 6.11 min     |

Based on question 15 (Appendix A. Supplementary material), What do you like most about the different vaccine formats for vaccinating infants younger than 2 years of age? (For each type of vaccine you can tick as many answers as you consider)

2.4. Quality control

Quality control was conducted per the criteria of the ISO 20252 standard and the International Chamber of Commerce/European Society for Opinion and Market Research (ICC/ESOMAR) Code of Conduct.

3. Results

In autonomous community of Madrid, 70 interviews were carried out, accounting for 34.8% of the total sample. In Murcia, 59 interviews were conducted, corresponding to 29.4% of the total sample. In Andalusia, 72 interviews were conducted, corresponding to 35.8% of the total sample.

A total of 76.6% of the nurses were female, and 23.4% of them were male. The average age of the nurses surveyed was 50 years; approximately 10.4% of nurses were up to 35 years of age, 19.4% of nurses were between 36 and 45 years of age and 32.3% between 46 and 55 years of age, and 37.8% of nurses were ≥55 years of age. The sample population had an average of 15 years of professional experience in the administration of vaccines. A total of 22.4% of nurses reported having 5 years’ experience, 34.3% reported having between 6 and 15 years of experience, and 43.3% reported having over 15 years of experience.

The average number of vaccines the sample population was administered weekly was 52. Approximately, 32.3% of nurses administered 25 vaccines weekly, 35.8% of nurses administered 50 vaccines weekly, and 31.8% of nurses administered >50 vaccines weekly.

Irrespective of the autonomous communities analyzed, it was observed that the nurses positively appraised the inclusion of fully liquid vaccines. On a scale from 0 to 10, 0 being the least favourable and 10 the best, the average overall rating was 8.84 points (question 9 of Appendix A. Supplementary materials). A total of 91.4% of nurses agreed that usage of biosafety devices in vaccination positively aid in the prevention of biological accidents, such as accidental needle punctures during the handling and administration.

Regarding routine vaccination processes, on a scale from 0 to 5, 5 being the highest rating, nurses polled independently from the
autonomous community to which they belonged. Parent appreciation of being informed about the vaccine administered to their children was rated as 4.8. At the same time, they expressed concern about making mistakes during vaccine preparation and administration (4.0 on a scale from 0 to 5).

A majority (87.6%) of nurses, independent of the autonomous community they belonged to, were concerned about the use of lyophilized vaccines, while 12.4% of nurses stated that they had no cause for concern. Among the concerns for the lyophilized vaccine, over the other aspects valued, 52.2% of nurses raised concern regarding the risk of making errors in administration, 44.8% of nurses noted limited flexibility once the vaccine is prepared, and 44.8% of nurses were concerned about the risk of needle contamination.

It is worth highlighting that the nurses who participated in the study had a much better appraisal for RTU formulations compared with lyophilized formulations of vaccines. The greatest differences were associated to the lower risk of making errors in preparation, lesser time invested in preparing the vaccine, and the overall time saved throughout the vaccination process. A total of 84.1% of nurses expressed a lower risk and were more confident when using RTU vaccines compared with 18.9% of nurses who were inclined toward vaccines requiring reconstitution (Table 1).

Regarding preparation of RTU vaccines, 74.1% of nurses stated that they are quicker and simpler to prepare compared with 22.4% of nurses who expressed the same sentiment for vaccines that require prior reconstitution (Table 1).

Approximately 66.7% of nurses in the study believed that there was a risk of errors during the preparation of lyophilized vaccines compared with 4.0% of nurses who had the same perception of RTU vaccines (Table 1).

Approximately 42.3% of nurses surveyed expressed that vaccines needing reconstitution have a potential risk of biological accidents for needle lesions, compared with 9.5% of nurses who expressed the same sentiment for RTU vaccines. Further details regarding data evidence per regions are presented in Table 1.

In terms of overall safety, nurses surveyed used an average of seven quality measures to reduce the risk of making mistakes during the vaccination process. The following measures were of the highest priority:

- The vaccine should not be prepared before the recipient’s visit, but instead during the visit of the person to be vaccinated;
- Verify and check the recipient’s entire vaccination history;
- Review the expiration date before preparing the vaccine.

Another important advantage perceived by the nurses who participated in the study was the flexibility to use RTU formulations, allowing them to store the vaccine in case the appointment with their recipient is postponed. In contrast, vaccines that require reconstitution must be used immediately after reconstitution (Fig. 3).

In all autonomous communities, nurses stated that when they used RTU vaccines, they required less time than lyophilized vaccines.

|   | Ready to use                      |
|---|-----------------------------------|
| 1 | Easy to prepare                   |
| 2 | Quick preparation of the vaccine before the injection |
| 3 | There is no need to reconstitute it |
| 4 | No risk of incomplete dissolution |
| 5 | Stability of the vaccine in case of problems in the cold chain |
| 6 | Flexibility in using the vaccine for another recipient in case the appointment is postponed |

Fig. 3. Valuation of ready-to-use vaccines.
Therefore, RTU vaccines exhibit a decrease in time spent performing the vaccination process; overall, nurses save an average of 1.1 min. Regional data are available in Table 1.

4. Discussion

In terms of vaccine preference, the results of this study are aligned with previous publications in other European countries (Bakhache et al., 2019, De Coster et al., 2015, Laurence et al., 2015, Lloyd et al., 2015). HCPs prefer to use RTU vaccines over vaccines that need to be reconstituted before administration.

The nurses surveyed acknowledged the need to administer vaccines with biosafety devices to avoid biological accidents through accidental contamination with the needles used in the preparation and administration of the vaccines.

It is also important to emphasize that both nurses and parents stated the importance of being well informed about the vaccination schedule and the possible adverse events associated with vaccines administered to the children. There is a controversial anti-vaccine movement led by parents who do not want to vaccinate their children. Therefore, HCPs must dedicate enough time during the consultation to explain and resolve all doubts of the parents.

Nurses had concerns with lyophilized vaccines in three fundamental aspects: the possibility of errors in administration, poor flexibility, and time available for usage after reconstitution, and the possibility of needle contamination when handling the vaccine during the preparation process.

Vaccines in the RTU formulations constitute an essential improvement and innovation for the administration of vaccines by nurses. They contribute to greater safety and quality during the vaccination process, avoiding errors in vaccine preparation, and therefore improving the safety of the recipient.

The nurses expressed that the time saved by using RTU vaccines during the vaccination process could be invested in the implementation of other activities, such as informing and educating the recipient to clarify vaccine-related questions and strengthening adherence in general, thus improving vaccine coverage.

5. Conclusion

In summary, HCPs had a very positive view about the properties of RTU vaccines. These properties included its RTU nature, ease of use, and time saved compared with vaccines that require a reconstitution process. Furthermore, HCPs highlighted flexibility as one of the positive attributes of this pharmaceutical form, compared with vaccines that need to be reconstituted and cannot be used with another recipient in case of a postponed appointment.

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Declaration of Competing Interest
Immaculada Cuesta Esteve, Pilar Fernández Fernández, Sonia López Palacios, María José Menor Rodríguez, Hosanna Parra Vino, and Begona Reyero Ortega have no conflicts of interest to declare outside the submitted work for which they have received fees for their participation. Maria Luz Nieto Nevot, Georgina Dragó Manchón, and Juan Luis López-Belmonte are employees of Sanofi Pasteur Inc., Spain.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data statement

Qualified researchers may request access to recipient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Recipient-level data will be anonymized, and study documents will be redacted to protect the privacy of study participants. Further details on Sanofi’s data-sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2021.101376.

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