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Assessment of preparation time with fully-liquid versus non-fully liquid paediatric hexavalent vaccines. A time and motion study

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ABSTRACT

Background and aims: Simplified vaccine preparation steps would save time and reduce potential immunisation errors. The aim of the study was to assess vaccine preparation time with fully-liquid hexavalent vaccine (DTaP-IPV-HB-PRP-T, Sanofi Pasteur MSD) versus non-fully liquid hexavalent vaccine that needs reconstitution (DTPa-HBV-IPV/Hib, GlaxoSmithKline Biologicals).
Methods: Ninety-six Health Care Professionals (HCPs) participated in a randomised, cross-over, open-label, time and motion study in Belgium (2014). HCPs prepared each vaccine in a cross-over manner with a wash-out period of 3–5 min. An independent nurse assessed preparation time and immunisation errors by systematic review of the videos. HCPs satisfaction and preference were evaluated by a self-administered questionnaire.
Results: Average preparation time was 36 s for the fully-liquid vaccine and 70.5 s for the non-fully liquid vaccine. The time saved using the fully-liquid vaccine was 34.5 s ($p \leq 0.001$). On 192 preparations, 57 immunisation errors occurred: 47 in the non-fully liquid vaccine group (including one missing reconstitution of Hib component), 10 in the fully-liquid vaccine group. 71.9% of HCPs were very or somewhat satisfied with the ease of handling of both vaccines; 66.7% and 67.7% were very or somewhat satisfied with speed of preparation in the fully-liquid vaccine and the non-fully liquid vaccine groups, respectively. Almost all HCPs (97.6%) stated they would prefer the use of the fully-liquid vaccine in their daily practice.
Conclusions: Preparation of a fully-liquid hexavalent vaccine can be completed in half the time necessary to prepare a non-fully liquid vaccine. The simplicity of the fully-liquid hexavalent vaccine preparation helps optimise reduction of immunisation errors.

1. Introduction

Combination vaccines have several benefits for the vaccine, the physician, the society, the healthcare system and public health. By delivering more antigens in fewer injections, combination vaccines can provide better coverage and timeliness of vaccination, improve the efficiency of the programme and reduce costs for the healthcare system [1].

Time spent by Health Care Professionals (HCPs) during vaccine preparation is a component of the overall programmatic cost associated with vaccine administration. Even if limited for one vaccination (approximately 25% of the overall vaccination time [2]), this time can be decreased by adapting devices and may have a larger impact when applied to large populations. For instance, vaccines could be administered 37.3 s quicker using prefilled syringes compared to multidose vials [3] and 46 s quicker using a fully-liquid DTP-HepB-Hib combination vaccine[1] compared to a non-fully liquid combination vaccine comprising of one vial of liquid DTwP–HepB and one vial of lyophilised Hib requiring reconstitution[2] [2]. Another important aspect for success of immunisation programmes is the quality with which vaccines are administered [4]. Proper vaccine handling and preparation is

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[1] Trade name: Easyfive®.
[2] Trade names: Tritanrix® and Hiberix®.

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critical in maintaining the integrity of the vaccine during transfer from the manufacturer's vial to the syringe and ultimately to the patient. Guidelines have been developed to assist HCPs in following up-to-date immunisation standards [5,6]. In Belgium, the National Immunisation Technical Advisory Group (NITAG) provides recommendations for vaccination; based on the NITAG recommendations, Regional Advisory Groups (e.g. the Flemish Vaccination Platform) determine the yearly immunisation vaccination schedule. Practical immunisation trainings are offered in some medical and paramedical curricula. However, in-service training is only offered to the personnel of well-baby clinics and school health centres. Adapting devices can contribute to avoid, reduce or mitigate errors in immunisation and associated impact on safety [7].

A hexavalent vaccine (DTPa-HBV-IPV/Hib, GlaxoSmithKline Biologicals[3]), supplied as powder and suspension for reconstitution and indicated for primary and booster vaccination of infants against diphtheria (D), tetanus (T), pertussis (aP), hepatitis B (Hep B), poliomyelitis (IPV) and disease caused by *Haemophilus influenzae* type b (Hib) has been available in Europe for over a decade. Lyophilised Hib-PRT-T is reconstituted with a syringe containing the D, T, aP, IPV and Hep B components used as a diluent.

In 2013, a fully-liquid (prefilled syringe), ready-to-use hexavalent vaccine (DTaP-IPV-HB-PRP-T, Sanofi Pasteur MSD[4]) was granted marketing authorisation in Europe. This vaccine is indicated for primary and booster vaccination of infants and toddlers from 6 weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Hib. At the time of this study only the non-fully liquid combination vaccine was available in Belgium.

Time and motion studies (T&M) require an independent and continuous observation and are, as such, a more precise method than self-reporting or work sampling techniques, which collects data at intervals of time. In medical care, T&M studies are efficiently used to determine the timing and duration of tasks or procedures [8]. T&M studies are generally small due to the high resource demands of conducting independent and continuous field observations. This can potentially exacerbate an effect of observer biases and imposes a higher requirement on both subject-selection and subject-observer assignment. Furthermore, a change in subject behaviour may occur following the continuous observation of that subject performing a task. Methods have been developed to limit the potential effect of these biases. Recording HCPs' activities on video has recently been used to prevent the observer effect [9,10] and can also allow the observer to replay each and every task for review and analysis, thus improving the quality of data.

Using a T&M study design, the main objective of this study was to assess vaccine preparation time of fully-liquid hexavalent vaccine versus non-fully liquid hexavalent vaccine that requires reconstitution prior to administration. The study also assessed the risk of immunisation errors, the satisfaction and preference of HCPs in charge of paediatric vaccination when using both vaccines.

2. Methods

2.1. Study design

The study was a cross-over, randomised, open-label study conducted in 4 different cities in Belgium: Brussels, Liège, Charleroi and Namur (Fig. 1).

Study participants were required to prepare consecutively a fully-liquid as well as a non-fully liquid vaccine (or in the opposite order), with at least a 3 to 5 min wash-out period between preparations. Vaccines were displayed on a tray along with an asepsis set to be used at HCPs' discretion in accordance with their usual practice. The first vaccine to be prepared was randomly determined. Randomisation was stratified by site and balanced every two participants.

Both vaccine preparations were recorded using video equipment allowing for time capture. Immediately after preparation of both vaccines, HCPs were asked to complete a self-administered questionnaire on their preference and satisfaction regarding the two vaccines.

2.2. Participants

In order to reflect usual practice in Belgium and different user profiles, HCPs recruited in the study were a combination of General Practitioners (GPs), paediatricians, youth health doctors and nurses. They had to have more than 2 years of experience in paediatric vaccination and to administer or prepare at least 3 childhood vaccines per week, including at least one hexavalent vaccine. Prior specific training on vaccine preparation and administration was collected for analysis purposes but were not a pre-requisite for participation in the study. HCPs having a permanent position within pharmaceutical industry or refusing video capture were excluded.

Phone book lists were used to contact HCPs of different specialties in the geographical area of cities concerned by the study.

2.3. Setting and bias control

Bias prevention steps included:

- Development of standard scripts for study presentation to the participants to decrease selection bias. The sponsor name was systematically concealed until the end of the study procedures.
- A cross-over design to neutralise the effect of video/observer presence between vaccine preparations.
- On-site study personnel trained to avoid any influence on HCPs during vaccine preparation processes.
- Defined start and stop of vaccine preparation time.
- Randomisation of the vaccine preparation sequence and the order of questions on the self-administered questionnaire.
- Study execution outside the usual HCPs working premises, in a central location of each city to provide a neutral unity of place, time and action.
- Vaccine preparation time assessment in a short period of time to prevent time-effect bias.
- Presentation of both vaccines outside their packaging and without leaflet. Thus, avoiding any impact on preparation time due to potential HCP distraction towards packaging leaflets of an unknown vaccine (the fully-liquid vaccine was not yet marketed in Belgium at time of study conduct).

Given the cross-over design of the study and in order to take into account real life conditions of use (including different levels of experience), representativeness or homogeneity of the HCP sample was not required.

2.4. Outcome measures and data collection

2.4.1. Vaccine preparation

An independent HCP (nurse) was trained to assess the time taken for vaccine preparation and immunisation errors by reviewing the videos recorded during each assessment. Training included study methods and video review processes. A physician performed data quality control by reviewing a random sample of 10% of the videos. The quality control concerned preparation time and

[3] Trade name: Infanrix® hexa.
[4] Trade name: Hexaxim®/Hexyon®/Hexacima®.