Estimated costs attributable to events of “out-of-temperature” in the stockpiling of hexavalent vaccines occurring in Italy

R. Silvestri*, F. Marchetti**

Key words: hexavalent; vaccines; stockpiling; cold chain
Parole chiave: esavalenti, vaccini, scorte, catena del freddo

Abstract

Background: Antigens contained in vaccines are inherently unstable biologically; such a characteristic is conferred by their three-dimensional structure. Preserving the ability of the vaccines to protect against disease is necessary to ensure the supervision and monitoring of all steps of the cold chain. DTPa-HBV-IPV/Hib vaccine (Infanrix hexa™, GSK Vaccines, Belgium) is designed to prevent disease due to diphtheria, tetanus, pertussis (DTP), hepatitis B virus (HBV), poliomyelitis and Haemophilus influenzae type b (Hib); it was first licensed for use in Europe in 2000 and is currently licensed in at least 95 countries. Since October 2013, more than 102 million doses of GSK’s DTPa-HBV-IPV/Hib vaccine have been distributed globally, with nearly 15 million doses distributed in Italy. DTPa-HBV-IPV/Hib components are stable up to a temperature of 25°C for 72 hours. Lacking of officially approved stability data may generate some concern in case of cold chain accidents.

Methods: An analysis based on collected data was carried out to estimate potential costs attributable to events of “out-of-temperature” in the stockpiling of hexavalent vaccines occurring in Italy in 2014.

Results: The analysis, based on real data, documented that the loss for the National Health Service (NHS) was in the range of 100,000 – 400,000 euros in one year. However, the amount of money that in principle could have been lost would have ranged between nearly half and one million euros/year.

Conclusions: A substantial loss of money was avoided thanks to the availability of officially approved stability data for GSK’s DTPa-HBV-IPV/Hib vaccine.

Introduction

Antigens contained in vaccines are inherently unstable biologically; such a characteristic is conferred by their three-dimensional structure (1). Preserving the ability of the vaccines to protect against disease is necessary to ensure the supervision and monitoring of all steps of the cold chain. This monitoring should take place starting with the batch released by the manufacturer, all the way up to delivery to the end user. A cold chain is the integrated system of equipment (e.g., cold rooms, shipping containers, refrigerators, vehicles), procedures, records, and activities used to handle, store, transport, distribute and monitor temperature-sensitive products.

* Payers and Evidence Solutions Department, GSK Vaccines, Verona, Italy
** Vaccines Medical Department, GSK Vaccines, Verona, Italy
Maintaining the potency of vaccines is important to ensure that an effective product is being used. Vaccine failures caused by administration of a compromised vaccine may result in lack of efficacy of vaccine-preventable disease and may cause loss of public confidence in vaccines and/or the health-care system (1).

A statistically significant correlation between the number of refrigerators with inadequate temperatures and the pertussis rate was reported in the United States (US) (2), which suggested that improper vaccine storage may contribute to an increase in pertussis cases (2). Further, freezing of pertussis vaccine was associated to an outbreak in Canada (3).

Cold chain problems have been documented in all countries where a temperature monitoring study has been conducted (4-10). Indeed, it has been reported that 17-37% of vaccines are stored under inappropriate temperatures in private offices (6). One study involving site visits showed that, while the vaccine should be stored between 2°C and 8°C, 15% of refrigeration units had temperatures of +1°C or lower [6]. A recent report on temperature violations from the US documented that 76% of a selection of 45 service providers stored vaccines under inappropriate temperatures for ≥5 cumulative hours during a period of two weeks (11).

Hexavalent vaccines targeting six diseases are the largest combination vaccines currently available. *Infanrix hexa™* (DTPa-HBV-IPV/Hib, GSK Vaccines, Belgium) is a combined hexavalent vaccine containing 10 antigens (diphtheria toxoid, tetanus toxoid, pertussis toxin [PT], filamentous haemagglutinin [FHA], pertactin [PRN], recombinant hepatitis B surface antigen, inactivated poliovirus [IPV] types 1, 2 and 3, and *Haemophilus influenzae* type b [Hib] polysaccharide polyribosylribitol phosphate [PRP]). DTPa-HBV-IPV/Hib is designed to prevent disease due to diphtheria, tetanus, pertussis (DTP), hepatitis B virus (HBV), poliomyelitis and Hib (12). DTPa-HBV-IPV/Hib vaccine was first licensed for use in Europe in 2000 and is currently licensed in at least 95 countries. Since the end of October 2013, more than 102 million doses of DTPa-HBV-IPV/Hib vaccine have been distributed globally, with nearly 15 million doses distributed in Italy. From 2005 to 2015, DTPa-HBV-IPV/Hib vaccine was the only available hexavalent vaccine on the Italian market; in this time period, the use of DTPa-HBV-IPV/Hib vaccine in Italy has been associated with high rates of vaccine coverage, and with preserved control of the disease among vaccinated children (13). Further to the clinical relevance, complete stability data are available for DTPa-HBV-IPV/Hib vaccine (12). It should be stored in a refrigerator (2°C – 8°C) in the original package, in order to protect from light. Officially approved data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. At the end of this period, *Infanrix hexa™* should be used or discarded. After reconstitution, an immediate use is recommended; however the stability has been demonstrated for 8 hours at 21°C (these data are intended to guide healthcare professionals [HCPs] in case of temporary temperature excursion only) (12).

Lacking of officially approved stability data may generate some concern in case of cold chain accidents. Recently, a warning on avoiding vaccines stockpiling was published in the Public Health England Bulletin; it was reported an indicative loss of 1,000,000 pounds-worth of stock in 2014 mostly due to fridge misuse (14). Transport and central storage may represent a significant proportion of the end-to-end vaccine system cost framework (15) (Table 1).

Thus, an analysis based on real data was carried out to estimate costs attributable to events of “out-of-temperature” in the stockpiling of hexavalent vaccines occurring in Italy.
Methods

All requests for “out-of-temperature” events received from HCPs at GSK Vaccines, Verona, Italy, in one year were collected and analyzed. The percentage of positive (the vaccine is still usable) and negative (the vaccine should be discarded) feedback provided by GSK Vaccines based on the officially approved stability data of DTPa-HBV-IPV/Hib vaccine (12) was determined. As anticipated, stability data indicate that DTPa-HBV-IPV/Hib components are stable up to a temperature of 25°C for 72 hours; at the end of this period the vaccine should be used or cleared. As the received applications did not contain the amount of vials involved in the event “outside temperature”, a conservative assumption of 100-250 vials was formulated for each HCP request, based on figures collected in some facilities at the time of the analysis. The cost of each vial was fixed at 44.55 euros, which represents by law the maximum tender price to supply the National Healthcare System. Due to the lack of official data, the cost of disposing of the expired doses was not included into the analysis, nor was the time required by medical personnel to handle the event.

Results

In the period April 2013-May 2014, GSK Vaccines received 137 requests for “out-of-temperature” events involving DTPa-HBV-IPV/Hib vaccine. Requests from HCPs were evenly distributed throughout the national territory (data not shown). On the basis of the initial assumption, the total amount of vaccine doses potentially impacted by the cold chain accidents was in the range of 13,700 to 34,250. Nearly three quarters (103/137, 75.2%) of the requests were declared resolved (the vaccine is still usable), leading to 10,300 to 25,750 vaccine doses that were declared still usable. According to the Italian official tender price of DTPa-HBV-IPV/Hib vaccine, the value attributable to the negative feedback (the vaccine should be discarded; 3,400 – 8,500 doses) was in the range of 151,470 – 378,675 euros whilst the value attributable to the positive feedback (the vaccine is still usable; 10,300 – 25,750 doses) was in the range of 458,865 to 1,147,162 euros (Figure 1).
Discussion and Conclusions

Vaccines are sensitive biological products which may become less effective, or even not usable, when exposed to temperatures outside the recommended range. Cold-sensitive vaccines experience an immediate loss of potency following freezing while those exposed to temperatures above the recommended temperature range may irreversibly have lost their potency (1). Thus, to manage a mishandled vaccine, it may be useful to refer to the manufacturer, requesting for officially approved stability data. Vaccines stability data showing no negative impact on vaccine potency for some days outside of the cold chain allows for wastage reduction (15). For the time being, “out-of-temperature” events still represent a major issue in vaccine management. In fact, many different events such as fridge malfunctions or fridge doors left open may result in a vaccine loss; it is therefore crucial to ensure a regular servicing of the fridge (14).

The analysis presented here is affected by some limitations as it encompasses only 1 year follow-up, is based on some assumptions and was carried out on the sole requests received by the vaccine manufacturer (GSK Vaccines). However, to our knowledge, this is the first attempt to quantify the vaccine and money loss that might be caused by “out-of-temperature” events in Italy. DTPa-HBV-IPV/Hib vaccine is on the market since 2001 (and the only one between 2005 and 2015 in Italy) and since then, many data were generated and made available on the vaccine profile including safety, tolerability, co-administration, effectiveness and technical data such as stability into and outside of the fridge (12). The analysis estimated in Italy a loss for the National Health Service (NHS) in the range of 100,000 – 400,000 euros in one year. However, the amount of money potentially lost could have ranged between nearly half and one million euros/year, only taking into consideration the hexavalent vaccine costs. Such a huge loss of money was
avoided thanks to the availability of officially approved stability data for DTPa-HBV-IPV/Hib vaccine. Further, it is worth noting that the analysis did not take into account the cost of disposing the no-more-usable vials nor the time requested to HCPs to manage the event (vaccine discard, stock refill, management of scheduled office visits and new appointments). A recent study carried out among vaccination nurses in the United Kingdom valued 4 minutes 47 seconds of saved working time in syringe preparation, for an amount of 7.91 pounds (16). In general, healthcare worker time is among the main driver of vaccine framework costs, reaching 16% of the total distribution framework (15). On the basis of these figures, it can be readily understood the huge amount of indirect costs related to the “out-of-temperature” events that can be postulated and that were not included in the present analysis.

According to Karp et al, the full thermostability of vaccines should be defined and included in the label, and the thermostability aims of new vaccines (including both heath and freezing stability) should be defined at the level of the target product profile (15). In the future, it can be expected that cold chains will be based on new technologies (insulated and passive storage systems) and better temperature controls (17).

In conclusion, despite being very conservative, financial figures obtained in the analysis were consistent. The estimated costs related to the “out-of-temperature” events were reduced by the availability of officially approved stability data for DTPa-HBV-IPV/Hib vaccine, and, at least in 2014, a potential consistent loss for the NHS was prevented. Thus, the combination of the high immunogenicity profile and inherent stability of DTPa-HBV-IPV/Hib vaccine along with efforts to prevent “out-of-temperature” events are required to best ensure reduced wastage and improve vaccination rates and protection among Italian babies.

Trademark

*Infanrix hexa*™ is a trade mark of the GSK group of companies.

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Conflicts of Interest

RS and FM are employees of the GSK group of companies.

**Riassunto**

*Stima dei costi attribuibili ad eventi di “fuori temperatura” nella conservazione dei vaccini esavalenti che si verificano in Italia*

**Background:** Gli antigeni contenuti nei vaccini sono biologicamente instabili; tale caratteristica è conferita dalla loro struttura tridimensionale. Per mantenere integra la capacità dei vaccini di proteggere contro le malattie è necessario assicurare la supervisione ed il monitoraggio di tutti i passaggi della catena del freddo. Il vaccino DTPa-HBV-IPV/Hib (*Infanrix hexa*™, GSK Vaccines, Belgium) è stato progettato per prevenire difterite, tetano, pertosse (DTP), epatite B virus (HBV), poliomielite ed *Haemophilus influenzae* di tipo b (Hib); è stato registrato in Europa nel 2000 ed è attualmente autorizzato in almeno 95 paesi. Da ottobre 2013, più di 102 milioni di dosi di vaccino DTPa-HBV-IPV/Hib sono state distribuite da GSK a
livello globale, delle quali 15 milioni di dosi soltanto in Italia. Il vaccino DTPa-HBV-IPV/Hib è stabile fino ad una temperatura di 25°C per 72 ore. In mancanza di dati di stabilità ufficialmente approvati può essere difficoltoso gestire eventuali incidenti nella catena del freddo.

**Metodi:** È stata condotta un’analisi, basata su dati reali, per stimare i potenziali costi imputabili ad eventi di “fuori-temperatura” nella gestione di scorte di vaccini esavalenti che si sono verificate in Italia nel 2014.

**Risultati:** L’analisi ha documentato che la perdita economica per il Servizio Sanitario Nazionale (SSN) è stata pari a circa 100.000-400.000 euro in un anno. Tuttavia, in caso di mancanza di dati di stabilità ufficiali tale perdita avrebbe oscillato tra circa la metà e un milione di euro all’anno, prendendo in considerazione soltanto il costo del vaccino esavalente.

**Conclusioni:** È stata evitata una consistente perdita di denaro da parte del SSN grazie alla disponibilità di dati ufficiali sulla stabilità del GSK vaccino DTPa-HBV-IPV/Hib.

**References**

4. Burgess MA, McIntyre PB. Vaccines and the cold chain: is it too hot ... or too cold? Med J Aust 1999; 171(2): 82.

Corresponding author: Dr. Federico Marchetti, GSK Vaccines, Via A. Fleming 2, 37135 Verona, Italy
e-mail: federico.e.marchetti@gsk.com