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Turning up the heat: Effect of new vaccine for children's (VFC) program recommendations for use of temperature monitors upon incorrect product storage adverse event reporting

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ABSTRACT

Background: The Centers for Disease Control and Prevention (CDC) coordinates the Vaccines For Children (VFC) program, which provides free vaccines to qualified children in the US. In 2009, the CDC issued Vaccine Storage Requirements, which were later replaced (2012) with an interim guidance and toolkit for vaccine storage and handling. The guidance called for use of Digital Data Loggers (DDL) to monitor vaccine storage temperatures. We describe a change in frequency of Incorrect Product Storage Reports (IPSRs) following issuance of the 2009 CDC guidance.

Methods: Merck & Co., Inc., Kenilworth, NJ, USA, systematically evaluates vaccine safety concerns for all products. The safety database was queried (01-Jan-2004 through 31-December-2016) to identify all IPSRs associated with 10 vaccines. We compared IPSRs received prior to and following the 2009 CDC guidance, comparing reports received from the US with those received from international sources during the same period.

Results: Following the release of the DDL guidance, a progressive increase in IPSRs was identified in the US (1 report received in 2004, 12,993 reports in 2016). In contrast, non-US IPSRs – have not had a similar increase: no reports received in 2004, 216 reports received in 2016. US reports of IPSRs 2004 through 2016 account for 96% of reports worldwide. There were no serious reports found in the database in conjunction with IPSRs, nor were there any additional safety findings in any of the reports with additional events reported.

Conclusion: VFC DDL guidance was followed by an increase in IPSRs. No similar trend was seen outside the US (where no broad change in DDL guidance occurred). Despite the increase in IPSRs, there have been few associated adverse events (AEs) reported; no new safety concerns were identified. These findings suggest that the increase in IPSRs was associated with the introduction of use of DDLs, and suggests the need for further impact assessment.

1. Introduction

Vaccines have been recognized as one of the top ten public health achievements of the 20th century [1]. A 2014 cost-benefit analysis (using 2009 US birth cohort data) predicted that routine childhood immunization would avert 42,000 early deaths and 20 million cases of vaccine-preventable diseases (VPD), and would save $13.5 billion in direct medical costs and $68.8 billion in societal costs, over the lifetimes of 2009 US birth cohort population [2].

In order for society to realize these benefits, systems are required that not only support vaccine development and commercialization, but also the robust public health structures that enable their effective use. Vaccines cannot achieve their public health impact if they are not used properly.

Between 1989 and 1991, a decline in measles vaccination coverage among US preschool children led to a major outbreak, resulting in approximately 55,000 measles cases, including more than 11,000 hospitalizations and 123 deaths [3,4].

The outcome of this outbreak was implementation of the Vaccines for Children's program (VFC, 1994); a federally funded program that provides recommended vaccines at no cost to eligible children (defined as those who are uninsured or underinsured). The VFC receives funding through the Office of Management and Budget

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Nomenclature

Abbreviation/Acronym

DDL	Digital Data Loggers
IPS	Incorrect Product Storage
IPSR's	Incorrect Product Storage Reports
IPSR's-AE	Incorrect Product Storage Reports-Adverse Events
IPSR's-AER's	Incorrect Product Storage Reports-Adverse Event Reports
IPS-AER	Incorrect Product Storage-Adverse Event Report

(OMB), which allocates funding through the Centers for Medicare & Medicaid Services (CMS) to the CDC. CDC purchases the vaccines at a discounted rate, and then distributes them to states and local public health agencies which, in turn, distributes them to recipient organizations, i.e. Federally Qualified Health Centers (FQHC) or Rural Health Clinics (RHC). Finally, these organizations distribute them to VFC providers (qualified private physicians' offices and public health clinics) who offer them at no cost to eligible children. The VFC plays a major role in U.S. childhood immunization. In 2010, an estimated 40 million (48%) of US children received their recommended vaccinations through the VFC program, which was administered through 61 grantees to 44,000 enrolled providers [5,6].

Public attention on the VFC tends to focus on access to recommended vaccines and increasing national coverage rates; however, the success of the program depends as well upon the integrity of vaccine distribution, storage and delivery systems. To avoid losing potency and ensure vaccine safety, CDC recommends that refrigerated vaccines are stored within the temperature range of 2–8 °C (36–46° F), and frozen vaccines are stored between −50 °C and −15 ° C (−58° F and +5° F) to avoid risk of losing potency [7]. To strengthen vaccine storage, decrease handling errors, and preserve the nation's vaccine supply, the CDC issued Vaccine Storage Requirements (2009). These were later replaced (2012) with an interim guidance and toolkit for vaccine storage and handling [8], which called for the use of Digital Data Loggers (DDLs). DDLs are digital thermometers that are combined with a device to continuously record ambient temperature. For VFC purposes, DDLs are used to continuously monitor and record (at preset intervals, at least once every 30 min, per CDC guidance) the temperature of the refrigerator (or freezer) in which a vaccine is stored. In the guidance, CDC specifically recommended the use of DDLs that have buffered temperature probes, in which the temperature gauge is contained within a material that protects it from transient temperature fluctuations (e.g. associated with momentarily opening and closing a refrigerator door). The DDL's data logger component is intended to provide medical staff with an efficient means of determining whether the stored vaccines have been exposed to temperatures outside of the recommended range. Such instances of temperature excursions are defined as cases of incorrect product storage (IPS). When an IPS case occurs, affected doses are to be withheld from use until advice has been solicited and provided from the state/local immunization program and/or the vaccine manufacturer(s) [7]. At this manufacturer, IPSRs are recorded and evaluated on a case-by-case basis, with recommendations to the reporting health care provider (HCP) based upon the product characteristics and the particular circumstances. A key source of information designed to mitigate risk is contained in the storage and handling section of the product label.

The objective of this report is to describe a change in the frequency of IPSRs received following issuance of the 2009 CDC guidance for DDL use, explore domestic vs. international trends in IPSRs, review the temporal trend of adverse events that are reported with the IPSRs, evaluate the association between incorrect product storage and associated clinical adverse events and provide suggestions regarding vaccine storage practice.

2. Methods

In addition to the Vaccine Adverse Event Reporting System (VAERS) that is maintained by the FDA [9], vaccine manufacturers with licensed vaccines in the US are required to maintain a post-marketing reporting system for Adverse Events (AEs) to receive, analyze, and report AE reports that they receive. Regulatory requirements define "an adverse event as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. [10]" As the name suggests, incorrect product storage (IPS) occurs when a product is not stored under recommended conditions. An incorrect product storage adverse event report IPS-AER) is defined as an adverse event that was reported in association with incorrect product storage, without judgment on whether the adverse event was caused by exposure to the incorrectly stored product. Much of the data contained in a manufacturer's adverse event database derives from reports submitted by the public. Such voluntary, passive data collection systems are well known to be imperfect, as they rely upon reporters to reliably identify and accurately report all cases as they occur [11]. The Merck Sharp and Dohme (MSD) global safety AE reporting database contains records of AEs spontaneously reported to the company by consumers, health care professionals and case reports from published literature. Descriptions of AEs are coded using standard Medical Dictionary for Regulatory Activities (MedDRA) nomenclature.

We queried this database for all IPSRs and IPSRs-AERs associated with 10 MSD vaccine products that had been recommended for use by the Advisory Committee on Immunization Practices (ACIP) and distributed through the VFC program during the period 01-January-2004 through 31-December-2016 (Table 1).

Analyses were based on the post-marketed AEs that were temporally associated with the vaccine reviewed by MSD. Descriptive analyses were performed to assess temporal trends by geographic region, product, and clinical events associated with IPSRs-AERs.

3. Results

From 01-January-04 through 31-December-16 a total of 32,989 IPSRs were received for vaccines that had been distributed to VFC providers. Issuance of the 2009 and 2013 Vaccine Storage and Handling Guidance were temporally associated with a progressive increase in IPSRs. In 2004, the manufacturer received a single IPSR; in 2016, MSD received 12,993 such reports. During the five years prior to publication of the first CDC Vaccine Storage Guidance, there was a progressive yet modest increase in IPSRs. Beginning one year following that Guidance, a noticeable increase in the frequency of reports was observed, and has continued to the present. The majority of the reports have been received since 2013 (one year following the most recent guidance), accounting for 87.6% of reports received during the study period (Fig. 1). The frequency of IPSRs has varied among the states. The top 10 reporting states (Pennsylvania, California, Texas, Michigan, Florida, Virginia, New York, Ohio, Kentucky, and Massachusetts) accounted for 70% of the IPSRs between 2004 through 2016 (Fig. 2).