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Safety of vaccines that have been kept outside of recommended temperatures: Reports to the Vaccine Adverse Event Reporting System (VAERS), 2008–2012

Beth F. Hibbs [a,*], Elaine Miller [a], Jing Shi [b,1], Kamesha Smith [c,1], Paige Lewis [a], Tom T. Shimabukuro [a]

[a] Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), United States
[b] HIV Incidence and Case Surveillance Branch, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention (CDC), United States
[c] Flexcare Medical Staffing, Roseville, CA, United States

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ABSTRACT

Background: Vaccines should be stored and handled according to manufacturer specifications. Inadequate cold chain management can affect potency; but, limited data exist on adverse events (AE) following administration of vaccines kept outside of recommended temperatures.
Objective: To describe reports to the Vaccine Adverse Event Reporting System (VAERS) involving vaccines inappropriately stored outside of recommended temperatures and/or exposed to temperatures outside of manufacturer specifications for inappropriate amounts of time.
Methods: We searched the VAERS database (analytic period 2008–2012) for reports describing vaccines kept outside of recommended temperatures. We analyzed reports by vaccine type, length outside of recommended temperature and type of temperature excursion, AE following receipt of potentially compromised vaccine, and reasons for cold chain breakdown.
Results: We identified 476 reports of vaccines kept outside of recommended temperatures; 77% described cluster incidents involving multiple patients. The most commonly reported vaccines were quadrivalent human papillomavirus (n = 146, 30%), 23-valent pneumococcal polysaccharide (n = 51, 11%), and measles, mumps, and rubella (n = 45, 9%). Length of time vaccines were kept outside of recommended temperatures ranged from 15 mins to 6 months (median 51 h). Most (n = 458, 96%) reports involved patients who were administered potentially compromised vaccines; AE were reported in 32 (7%), with local reactions (n = 21) most frequent. Two reports described multiple patients contracting diseases they were vaccinated against, indicating possible influenza vaccine failure. Lack of vigilance, inadequate training, and equipment failure were reasons cited for cold chain management breakdowns.
Conclusions: Our review does not indicate any substantial direct health risk from administration of vaccines kept outside of recommended temperatures. However, there are potential costs and risks, including vaccine wastage, possible decreased protection, and patient and parent inconvenience related to revaccination. Maintaining high vigilance, proper staff training, regular equipment maintenance, and having adequate auxiliary power are important components of comprehensive vaccine cold chain management.
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1. Background

Vaccines should be stored and handled according to manufacturer specifications. Inadequate cold chain management can affect potency, potentially resulting in decreased vaccine effectiveness and suboptimal protection against target diseases [1]. The 2012 Department of Health and Human Services Office of Inspector General report, "Vaccines for Children Program: Vulnerabilities in Vaccine Management," revealed that 76% of sampled healthcare

* Corresponding author at: Immunization Safety Office, Division Of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS D26, Atlanta, GA 30333, United States.
E-mail address: bhibbs@cdc.gov (B.F. Hibbs).
[1] During the time Jing Shi and Kamesha Smith participated in this review both were working in the Immunization Safety Office at CDC.

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providers reported instances when vaccines intended for future use were exposed to inappropriate temperatures for at least 5 cumulative hours during a two-week observation period [2]. Another review of vaccine storage practices indicated that 14–35% of vaccines were subjected to inappropriately cold (i.e., freezing) temperatures [3].

Limited published data exists on adverse health events (AE) following administration of vaccines stored at inappropriate temperatures. In one report, no adverse reactions were observed following an incident involving 19 children that received vaccines potentially stored at temperatures lower than recommended [4]. A study looking at meningococcal group C vaccine stored 6 months at room temperature versus correctly stored vaccine did not detect any differences in safety or immunogenicity [5]. An incident in China involving large-scale distribution and administration of improperly stored vaccines (millions of doses) may have damaged the credibility of immunization programs, but did not appear to be associated with AE [6,7,8].

To further investigate incidents involving vaccines that have been inappropriately stored outside of recommended temperatures, we conducted a review of reports to the Vaccine Adverse Event Reporting System (VAERS). We describe types and frequencies of these reports, characterize any AE documented in reports, and identify reasons for cold chain management breakdown.

2. Methods

VAERS is a national vaccine safety monitoring system that is jointly administered by the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) [9]. It is a passive surveillance system that receives spontaneous reports of AE following vaccination from patients, parents, healthcare providers, vaccine manufacturers, and others. The VAERS report form gathers information on the patient, vaccines administered and the AE experienced. Signs and symptoms of AE are coded using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology [10]. An individual VAERS report may be assigned multiple MedDRA Preferred Terms depending on signs and symptoms reported. Although VAERS is intended to monitor adverse health outcomes, it accepts all types of reports regardless of whether an AE is documented, including those involving vaccine storage and handling problems and administration errors. Reports are classified as serious based on the Code of Federal Regulations if one or more of the following is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability [11].

We searched the VAERS database for US reports (foreign reports were excluded) received during the period January 1, 2008, through December 31, 2012, that described incidents of any vaccines stored outside of recommended temperatures. The MedDRA Preferred Terms used in the search included: "incorrect product storage", "incorrect storage of drug", "poor quality drug administered", and "product quality issue." We also conducted a text string search looking for key words and terms in the narrative section of the VAERS report that potentially described situations where vaccines were kept outside of recommended temperatures. The text string search process was validated on a sample of reports prior to applying it to the database. Key text string words and terms included: "refrigerator", "refridgerator" (a common misspelling), "room temp", "below freezing", "above freezing", "improperly stored", "stored improperly", "incorrectly stored", "incorrect storage", "improper storage", "room temperature", "stored incorrectly", "exposed to temp", "exposed to temperature", "stored at", "stored", and "exposed to [numbers 1 through 99 to capture numerical temperatures]".

CDC scientists with clinical nursing backgrounds reviewed all reports from the automated search to identify true cases of vaccines stored outside of recommended temperatures and/or vaccines exposed to temperatures outside of manufacturer specifications for inappropriate amounts of time; only reports that stated vaccines were stored outside of recommended temperatures were included in the final analysis. We analyzed reports by year, vaccine(s) involved, storage or exposure temperature, reporter type, patient age, and whether a patient received potentially compromised vaccine. We compared storage temperatures described in reports to recommended storage temperatures listed in the vaccine manufacturers' package inserts. If specific temperature information was not documented but qualitative information was available (i.e., "too cold," "frozen," "too warm," "left out on counter," etc.), the report was categorized based on reporter description of the incident. We also identified (through the nurse reviews) and analyzed reports of vaccination storage error cluster incidents. A cluster is defined as a discrete incident involving more than one patient affected by the same error, occurring during a defined time period, in a common setting and could be, one report listing the number of patients involved, if known; or multiple reports, one for each patient describing the same incident. Clusters were counted as a single incident regardless of the number of persons involved or reports submitted; however, for the overall analysis each report in a cluster was counted as an individual report.

We classified reports with an AE according to body system categories previously described in the literature [12]. We used SAS version 9.2 (SAS Institute Inc., Cary, NC) for analyses. VAERS is a routine surveillance program conducted as a public health function and does not meet the definition of research; therefore, it is not subject to Institutional Review Board review and informed consent requirements.

3. Results

For the period January 1, 2008, through December 31, 2012, we identified 954 VAERS reports with MedDRA Preferred Terms and text strings consistent with possible vaccine storage temperature control problems. Review of reports resulted in exclusion of 338 that were not related to temperature problems e.g. poor quality drug administered describing vaccine contamination or vaccine failure. An additional 140 reports were excluded after reviewers could not determine if vaccine was stored at or exposed to inappropriate temperatures; these reports described missing temperature monitoring devices in storage units, instances of poor documentation of storage temperature in logbooks, and uncertainty about whether temperature control was compromised.

The final dataset for our analysis included 476 reports (<1% of the 145,760 total VAERS reports during the analytic period) of vaccines stored outside of recommended temperatures and/or exposed to temperatures outside of manufacturer specifications for inappropriate amounts of time (Table 1). We refer to these reports as vaccines "kept outside of recommended temperatures." Vaccine manufacturers submitted most (n = 405, 85%) reports, with one single vaccine manufacturer submitting 333 reports. The length of time vaccines were kept outside of recommended temperatures was documented in 240 (50%) reports and ranged from 15 mins to 6 months (median 51 h). While vaccines were kept on average 2 days outside of recommended temperatures there was a wide range in time, and in half of the reports the length of time vaccines were kept outside of recommended temperatures was unknown or not stated by reporters. A substantial increase in reports was noted in 2012, when 284 reports were submitted compared to the previous 4 years (2008n = 29, 2009n = 76, 2010n = 48, 2011n = 39).

Table 1
Reports of vaccines kept outside of recommended temperatures in the Vaccine Adverse Event Reporting System (VAERS), 2008–2012.

Report characteristics	N (%)
Total reports[a]	*476*
Administered to patients	458 (96)
Involved cluster incidents[b]	366 (77)
Included description of reason for storage error	68 (14)
Adverse health event in vaccine recipient reported[c]	32 (7)
Type of reporter	
Vaccine manufacturer	405 (85)
Healthcare provider	21 (4)
Patient or parent	2 (<1)
Other	48 (10)
Unknown	0
Patient age	
0–1 years	23 (5)
2–5 years	9 (2)
6–18 years	63 (13)
19–64 years	83 (17)
≥65 years	10 (2)
Not reported or unknown	288 (61)
Types of adverse health events[c]	*33*
Local reaction	21(66)
Gastrointestinal	4 (13)
Other noninfectious (anemia and dermatological)	3 (9)
Other infectious	2 (6)
Neurologic	1 (3)
Respiratory, (influenza-like illness, pneumonia)	1 (3)
Death (infection)	1 (3)

[a] Reports received by year: 2008 (n = 29), 2009 (n = 76), 2010 (n = 48), 2011 (n = 39), 2012 (n = 284).
[b] A cluster is defined as a discrete incident involving more than one patient affected by the same error, occurring during a defined time period, in a common setting.
[c] There were 32 total reports documenting 33 adverse health events (categorized by the body system classification) with one of these reports documenting two adverse health events.

3.1. Vaccines involved and temperature excursions

The specific vaccines kept outside of recommended temperatures were documented in all but 4 reports. Of the 476 reports, 6 reported two vaccines concomitantly kept outside of recommended temperatures, yielding a total of 482 vaccines specified in reports. The most commonly reported vaccines involved in temperature excursions were quadrivalent human papillomavirus (4vHPV) (n = 146, 30%), followed by 23-valent pneumococcal polysaccharide (PPSV23) (n = 51, 11%), and measles, mumps, and rubella (MMR) (n = 45, 9%) (Table 2). 4vHPV was the most frequently reported vaccine kept too cold (n = 85/210, 40%), while MMR was the most frequently reported vaccine kept too warm (n = 44/180, 24%). Twenty reports documented vaccines kept both too cold and too warm; data sources cited included automatic monitors and temperature logbooks documenting fluctuating storage unit temperatures. There was one report of a vaccine diluent for herpes zoster (shingles) vaccine (HZV) that had been kept in the freezer instead of at room temperature or refrigerated. The diluent was thawed and used to reconstitute the frozen vaccine.

3.2. Adverse health events (AE) following vaccination with vaccines kept outside of recommended temperatures

Of the 476 total reports, 458 (96%) involved patients who were administered potentially compromised vaccines. In the remaining 18 reports, vaccine was either not administered or it was unknown if vaccine was administered. Thirty-three AEs were documented in 32 (7%) of the 458 reports where patients received compromised vaccine – more than one AE can occur in a report (Table 1). The most common vaccine where an AE was reported was PPSV23 (n = 16), followed by varicella vaccine (n = 2). The most frequently reported AE was local reaction (n = 21, 66%) followed by the gastrointestinal symptoms, e.g. nausea, diarrhea (n = 4, 13%). Among the 21 reports with local reaction, 20 documented that vaccine had been kept above recommended temperatures and one described vaccine kept below the recommended temperature. Local reactions were most frequently reported following PPSV23 (n = 16); 15 of these reports were derived from a single cluster incident where vaccine was left on a counter overnight and for "half the next day."

Four of the 32 reports (13%) that documented an AE were classified as serious. Two of these serious reports described two persons who contracted influenza disease in a single cluster incident involving multiple vaccine recipients that had been previously published in the literature [13]. The incident involved possible influenza vaccine failure during an outbreak of severe influenza disease at a residential facility that provided services for children and young adults with neurological and neurodevelopmental conditions. In this incident, the inactivated influenza vaccine was stored below the manufacturer recommended temperature for an unspecified period of time. Several months following vaccination at the facility, 76 residents had acute onset of respiratory illness, 13 residents became severely ill with confirmed (n = 7) or suspected (n = 6) influenza, resulting in ten hospitalizations and seven deaths. The other two reports classified as serious included a report of syncope that was believed to be disabling and a neurologic event resulting in hospitalization.

3.3. Cluster incidents

Three hundred and sixty-six of the 476 reports (77%) described clusters where multiple patients received vaccines kept outside of recommended temperatures. These 366 reports involved 142 separate cluster incidents in a specific setting. In 93 cluster incidents, the number of patients affected could not be determined from information provided in the reports; these reports contained non-specific information such as "several" or "multiple" persons affected. In the 47 incidents where reports did specify numbers of patients affected, clusters ranged in size from two to 60 patients. Thirteen clusters involved 10 or more patients. The most common vaccines involved in the 142 cluster incidents included 4vHPV (n = 47, 33%), MMR (n = 17, 12%), Hepatitis B (n = 15, 11%), PPSV23 (n = 13, 9%).

3.4. Reasons for vaccines kept outside of recommended storage temperatures

Sixty-eight reports included descriptions of reasons why and how vaccines were kept outside of recommended temperatures. Explanations included: incorrect storage of vaccine during shipping from the manufacturer or during local transport between clinics or pharmacies; storage equipment failure/fluctuations/power outages causing vaccines to become too warm or too cold; failure of staff to properly store vaccine; inadequate temperature monitoring; confusion about where to find storage temperature information (e.g., vial does not contain storage instructions, boxes thrown out); inadequate training on vaccine storage resulting in failure to recognize, report or act on compromised vaccine before it is administered to patients (Table 3).

4. Discussion

From 2008 through 2012, we found 476 VAERS reports involving vaccines kept outside of recommended temperatures. Most

Table 2
Most commonly reported vaccines kept outside of recommended temperatures[a] in the Vaccine Adverse Event Reporting System (VAERS), 2008–2012.

Vaccine	Vaccines N (%)	Kept too cold N (%)	Kept too warm N (%)	Kept too warm and too cold N (%)	Temperature excursions not specified[a] N (%)
Human papillomavirus (quadrivalent)	146 (30)	85 (40)	10 (6)	0	51 (72)
Pneumococcal polysaccharide (23-valent)	51 (11)	9 (4)	21 (12)	19 (95)	2 (3)
Measles, mumps, and rubella	45 (9)	0 (0)	44 (24)	0	1 (1)
Herpes zoster (shingles)	41 (9)	13 (6)	24 (13)	0	4 (6)
Hepatitis B	35 (7)	28 (13)	4 (2)	0	3 (4)
Monovalent inactivated H1N1 influenza	25 (5)	23 (11)	2 (1)	0	0 (0)
Varicella	22 (5)	3 (1)	16 (9)	0	3 (4)
Hepatitis A	17 (4)	10 (5)	6 (3)	0	1 (1)
Rotavirus (pentavalent)	17 (4)	5 (2)	10 (6)	1 (5)	1 (1)
Anthrax	16 (3)	0 (0)	16 (9)	0	0 (0)
Meningococcal conjugate (quadrivalent)	14 (3)	10 (5)	1 (1)	0	3 (4)
Trivalent inactivated influenza	14 (3)	10 (5)	3 (2)	0	1 (1)
Live attenuated influenza (trivalent)	14 (3)	2 (1)	11 (6)	0	1 (1)
Other vaccines[b]	25 (5)	12 (6)	12 (7)	0	1 (1)
Total vaccines[c]	482	210	180	20	72

[a] Direction of excursion was determined by the documented temperature or qualitative description of excursions in the VAERS report.
[b] Other vaccines included: combination diphtheria and tetanus toxoid and acellular pertussis adsorbed with hepatitis B and inactivated poliovirus vaccine (n = 2), live attenuated monovalent H1N1 influenza vaccine (n = 1), Haemophilus influenzae type b conjugate vaccine (n = 8), combination measles, mumps, rubella, and varicella vaccine (n = 2), pneumococcal 7-valent conjugate vaccine (n = 5), pneumococcal 13-valent conjugate vaccine (n = 3), tetanus toxoid, reduced diphtheria toxoid with acellular pertussis vaccine, adsorbed (n = 3), typhoid vaccine (n = 1).
[c] Of the 476 total reports, six reports documented more than one vaccine for a total of 482 vaccines reported to be kept outside of recommended storage temperatures. Four reports did not specify the vaccine(s) involved in temperature excursions.

Table 3
Direct and paraphrased quotes of selected comments from reports that included descriptive information about vaccine kept outside of recommended storage temperatures (n = 68) in the Vaccine Adverse Event Reporting System (VAERS), 2008–2012.

Key area or factor[a]	Selected direct and paraphrased quotes from VAERS reports describing reasons for vaccines stored outside of proper temperatures
Product packaging	• "Storage temp information not on vial, box thrown out" • "Differentiate inside packaging of products since outer box not used in hospital settings when automated dispensing cabinets are utilized"
Shipping	• "When shipment of vaccine arrived, 4–5 days after it was shipped, the medical assistant stated that the cold packs felt hot" • "The nurse stated that it was stored in a truck over the weekend, and she does not know the temperature"
Local transport	• "They transported the vaccine to a clinic packed with cold packs in a cooler without a thermometer", • "Using dry ice to transport vaccines which froze"
Handling of vaccine at the clinic, failure to follow proper vaccine storage procedures	• Placed into wrong storage temp upon receipt of the vaccines from pharmacy • "After delivery vaccine left out on counter all night and next morning" • "Gardasil stored at room temperature for a three week period" • "Vaccine and its diluent stored together at room temperature" • "Vial of Varivax had been stored in the refrigerator rather than the freezer for the past 2 months" • "Gardasil was inadvertently stored in freezer for 2 weeks" • "new nurse left refrig left open for extended periods of time which caused the inappropriate storage temp"
Patient education	• "Patient did not store the typhoid vaccine in the refrigerator even though instructed in writing to do so" • "Flumist purchased at pharmacy and stored at room temp for 20 days by patient"
Temperature monitoring	• "Refrigerator and Freezer temperatures not monitored" • "The cup for the temperature gauge was placed too close to the vent for a couple of hours" • "TempTale alarmed but vaccine was administered anyway"
Storage unit failure to maintain proper temperatures	• "Refrigerator not holding temperature", "Inconsistent fridge temp found through temperature monitors", "Freezer malfunctioned" • Vaccine was stored both too hot and too cold: to 47–48F for 72 h and 32F for 24 h • "It was reported that the patient received above vaccine during time of refrigerator failure. Temps found to be <32°" • Inconsistent temps- was exposed to 68F for 9 h and then on Wednesday last week "on 15-AUG-2012", the temperature went to 48F for 1 h
Power outage	• "Power outage and not noticed until after vaccination" • "Stored outside of temp due to hurricane sandy" • "Refrigerator was turned off over 11 days during spring break"

[a] Key area or factor was determined through a reviewer interpretation of the initial or primary comments included in the description of the error.

(96%) reports indicated that potentially compromised vaccine was administered. However, adverse health events were reported in only a small minority (7%) and these events tended to be mild and self-limited. Injection site reactions were most common, which is consistent with what is observed in VAERS reports in general, indicating that administration of vaccines kept outside of recommended temperatures likely does not pose a substantial or common direct health risk. However, we were not able to assess risk of disease from lack of (or reduced) immunological protection in recipients who may have received compromised vaccines [14] or AE risks associated with revaccination. An exception was one cluster incident, also described in the literature, involving influenza disease among high risk institutionalized patients that was temporally associated with receipt of improperly stored vaccine, which investigators interpreted as vaccine failure [13].

Three hundred and sixty-six of the 476 total reports (77%) involved cluster incidents concerning more than one patient. Often, specific counts were not available and included subjective descriptions like "many or unknown" numbers of patients affected. In some reports the length of time of improper vaccine storage was stated as "unknown." In others vaccine storage problems were retrospectively documented to have occurred over several months. This indicates a need for improvement in vaccine storage temperature deviation identification, communication and management by clinic staff to avoid the error impacting large numbers of patients.

Proper storage and handling of vaccines, including maintaining temperature control according to manufacturer specifications, is an important component of vaccination practices at the manufacturer, distributor and healthcare provider levels. Excursions of temperature (both too warm and too cold) have the potential to affect vaccine potency [3,15,16] and by extension, effectiveness in the vaccine recipient. According to vaccine package inserts, most vaccines requiring refrigeration should be stored between 2 °C and 8 °C (35°/36°F and 46°F), and those requiring freezer storage should be stored between −50 °C and −15 °C (−58°F and 5°F) [17]. In our review, vaccines kept below recommended temperatures were found in 44% of reports where specific (i.e., actual temperature readings) or descriptive (e.g., "too cold") temperatures were documented. Freezing temperatures can irreversibly reduce the potency of vaccines that are recommended to be stored above 34°F [18,19,20]. Certain freeze-sensitive vaccines contain an aluminum adjuvant that can precipitate when exposed to freezing temperatures, resulting in a loss of potency [21,22]. Conversely, vaccines kept above recommended temperatures were found in 38% of reports where temperature excursions were documented. Some live attenuated vaccines are especially vulnerable to potency loss when stored too warm [23] CDC recommends digital data loggers for monitoring vaccine storage temperatures [17].

Risk factors for improper vaccine storage practices have been identified in the literature and include inadequate staff training, lack of temperature logs or thermometers, and storage unit problems including improper maintenance, and equipment failure [24,25,26]. Additionally, inadequate procedures for receipt and handling of vaccine deliveries can pose a risk to proper cold chain management [27]. In our review, reporters commented on key risk factors including: poor monitoring and response procedures (e.g., recording temperatures without acting on excursions); failure to retain or check manufacturer storage instructions (e.g., discarding vaccine packaging information containing storage instructions); inadequate backup systems to respond to power failures; and simple failure to adhere to manufacturer storage and handling specifications (e.g., comment in report: "Vial of Varivax had been stored in the refrigerator rather than the freezer for the past 2 months").

An increased number of reports of vaccines kept outside of recommended temperatures was observed during 2012 compared to prior years. Reasons for the increase are not clear, but the observation coincides with a 2012 Department of Health and Human Services Office of Inspector General report [2] on vaccine storage errors. Also, in 2012 CDC released interim guidance and early in 2013 a vaccine storage and handling tool kit that included recommendations for vaccine providers to use digital data loggers which monitor temperature automatically and more frequently than manual methods. Healthcare providers were also directed to report storage temperature excursions to vaccine manufacturers. Guidance on reporting vaccination errors [28] was first posted on the VAERS website in 2013.

Our study has several limitations. VAERS is a spontaneous (or passive) reporting system with under-reporting, inconsistent data quality and completeness, and a general inability to assess cause and effect. Decisions to report possible vaccine storage errors are made in the context of the reporter's perspective on what constitutes an error. Some reports of vaccines kept outside of recommended temperatures for short periods of time may not have been actual violations of cold chain protocol. However, more likely, vaccine storage errors are underreported, especially if no recognized AE occurs in a patient receiving potentially compromised vaccine. Cluster incidents were inconsistently reported. In some cases, multiple individual VAERS reports were submitted for a single cluster and in other cases only one report was submitted documenting the cluster and providing non-specific information on total numbers of patients involved. One vaccine manufacturer, for reasons that are unclear, submitted the majority of reports, which may have biased the frequency of specific types of vaccines involved, producing results that are not representative of storage errors in general. Most reports documented only one vaccine kept outside of recommended temperatures; however, many of these reports described problems with temperature regulation in storage units which would likely contain multiple vaccines. In these cases reporters may have been focused on reporting a specific vaccine that patients received versus all vaccines that were affected by the temperature excursion.

5. Conclusions

Proper vaccine storage and handling is a collective responsibility requiring attentive management from the point of manufacturing until vaccine is administered to an individual patient. Storage errors that go unrecognized can ultimately involve multiple patients, as in the case of cluster incidents. While our review does not indicate any substantial direct health risk from vaccine storage errors, vaccine storage errors can result in lack of protection from vaccine preventable disease. Additionally, there are potential costs and risks in terms of vaccine wastage, possible lack of protection in patients receiving potentially compromised vaccines, costs of revaccination – to include direct costs and patient and parent inconvenience, and loss of confidence in the healthcare delivery system. Healthcare workers involved in giving vaccinations should be educated in the importance of following instructions on vaccine package inserts [29] and CDC recommendations and guidelines on vaccine storage and handling [17].

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Rebel Jackson, Public Health Analyst, National Center for Immunization and Respiratory Disease, Centers for Disease Control and Prevention (CDC).

Cameron B. Noblit, MPH, Public Health Analyst, National Center for Immunization and Respiratory Disease, Centers for Disease Control and Prevention (CDC).

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