Deficits of Vaccine Storage in German General Practices and the Effectiveness of a Web-Based Education Program to Improve Vaccine Storage Knowledge of Practice Personnel (Keep Cool)

Dissertation

zur Erlangung des Doktorgrades (Ph.D.) für Versorgungsforschung

der Hohen Medizinischen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität

Bonn

Anika Thielmann, M.Sc., M.A.

aus Remscheid-Lennep

2020

Angefertigt mit der Genehmigung
der Medizinischen Fakultät der Universität Bonn

1. Gutachter: Univ.-Prof. Dr. med. Birgitta Weltermann, MPH(USA)
2. Gutachter: Associate Professor Dr. med. Hans Thulesius
3. Mitglied: Univ.-Prof. Dr. rer. nat. Matthias Schmid
4. Mitglied: Univ.-Prof. Dr. rer. medic. Nicole Ernstmann

Tag der Mündlichen Prüfung: 15.07.2020

Aus dem Institut für Hausarztmedizin

Direktorin: Frau Univ.-Prof. Dr. med. Birgitta Weltermann, MPH(USA)

Table of Contents

List of Abbreviations

C	Celsius
CI	confidence interval
e.g.	exempli gratia; for example
GLMM	Generalised Linear Mixed Models
i.e.	id est; that is
SD	standard deviation
SPSS	Statistical Package for the Social Sciences

1 Short Summary

Maintaining the cold chain of vaccines with a temperature range of 2°C to 8°C is a challenging issue worldwide. Exposure to heat and especially to freezing reduces vaccine effectiveness and tolerability. Prior research revealed cold-chain breaches and heterogeneous vaccine storage practices in German practices but failed to offer broader quantifications or solutions. This PhD project aimed at quantifying vaccine storage deficits (temperature, vaccine storage practices, and personnel's knowledge) and improving vaccine storage conditions by developing an intervention. The intervention is a web-based education program named 'Keep Cool' for general practice teams which was evaluated in teaching practices.

At baseline, 75 refrigerators from 64 practices were analyzed: 68.0% (n=51) had cold-chain breaches with 15% (n=11) showing critically low temperatures (<0°C). On average, only 4.7 (standard deviation (SD) =1.9) of ten predefined quality criteria for vaccine storage practices were fulfilled. Following participation in the web-based education program, knowledge on vaccine storage of 60 participants from 25 practices improved from an average of 5.6 (SD=1.9) to 9.8 (SD=1.2) of 11 correct answers (<0.001) immediately after participation in Keep Cool. The widespread dissemination of Keep Cool promises to solve a highly relevant issue for public health that is currently underestimated by general practices and regulatory bodies.

2 Introduction

Thermostability differs between the various vaccines used for disease prevention (World Health Organization, 2006). The World Health Organization considers protecting vaccines from freeze damage "one of the most poorly addressed problems in vaccine management" that requires attention in order to not jeopardize disease-prevention goals (World Health Organization, 2007). Freeze exposure is especially dangerous to adsorbed vaccines (e.g. hepatitis, tetanus, diphtheria, pertussis), as the aluminum-containing adsorbents form irreversible precipitates, which decrease vaccines' potency and may cause local irritation (Paul-Ehrlich-Institut, 2012; World Health Organization, 2006). The most sensitive vaccines, with a freezing threshold of -0.5°C, are adsorbed hepatitis B vaccines (World Health Organization, 2006). Also, heat exposure has a cumulative negative effect on vaccine potency (World Health Organization, 2006). For instance, pertussis vaccine is stable for two weeks at 20-25°C, for one week at 37°C, and has a loss of potency of 10% or more per day at >45°C (World Health Organization, 2006). The vaccine most sensitive to heat is herpes zoster vaccine, which may be stored for 30 minutes at 20-25°C (GlaxoSmithKline,

personal communication). To ensure vaccine potency, international guidelines stipulate that vaccines are to be maintained within a temperature cold chain between +2°C and +8°C starting from the time of manufacture until patient administration. In a 2014 physician survey on vaccine management, we found that 16% of the surveyed German general practitioners self-reported experiences with cold-chain breaches either as an error or near error. Also, only 51% reported monitoring and documenting temperatures twice a day as recommended (Thielmann et al., 2015a; Weltermann et al., 2014). Thus, we suspected vaccine storage deficits at the end of the cold-chain in general practices. Convenience sample inspections of 21 refrigerators confirmed our suspicions: refrigerators were outside the target range in 10.2% of the time (Thielmann et al., 2015b; Thielmann and Weltermann, 2017a, 2017b). Also, we observed various other vaccine storage deficits which may pose a threat to vaccine potency, e.g. unwrapping of vaccines, contact to outer walls of refrigerators, and wrong temperature probe setups.

Cold-chain breaches are an ongoing issue worldwide (Hanson et al., 2017) and have been linked to disease outbreaks in the past (Boros et al., 2001; Lerman and Gold, 1971; McColloster and Vallbona, 2011; Onoja et al., 1992) or were suspected to be linked (McIntyre et al., 1982). Guidance on vaccine storage in Germany is scarce (Gemeinsamer Bundesausschuss, 2013; Robert Koch-Institut, 2007, 2011; Paul-Ehrlich-Institut, 2012; Robert Koch-Institut, 2013, 2018/2019). However, to establish quality-ensured cold-chain maintenance, compliance with a range of structural and procedural aspects is deemed necessary in practices. Thus, drawing on national recommendations and guidelines from several countries (US (Centers for Disease Control and Prevention, 2014), UK (Salisbury et al., 2006), Australia (Australian Government, 2013), Canada (Public Health Agency of Canada, 2015), Scotland (Health Protection Scotland, 2013)), we identified best practices for the German setting (Thielmann and Weltermann, 2017a). The education program Keep Cool was subsequently designed on the basis of our findings.

3 Objective

The main objective of the Keep Cool study was to quantify vaccine storage deficits and to improve vaccine storage conditions in German general practices. This was operationalized by a succession of three parts: 1) developing an education program to optimize vaccine storage, 2) planning and 3) conducting an outcome evaluation for the education program.

4 Methods (Publications 1 and 4)

4.1 Education Program

The Keep Cool intervention was designed as a web-based education program for physicians and their practice teams. The learning content is presented in five tutorials: temperature (9 subtopics), refrigerator (3 subtopics), storage (4 subtopics), responsibilities (5 subtopics), and monitoring (8 subtopics). The content is based on national (Paul-Ehrlich-Institut, 2012) and international recommendations, guidelines (Australian Government, 2013; Centers for Disease Control and Prevention, 2011, 2014; Health Protection Scotland, 2013; Public Health Agency of Canada, 2015; Salisbury et al., 2006) as well as further scientific literature (Chojnacky et al., 2009; Chojnacky et al., 2010; World Health Organization, 2006).

Participants are given immediate access to basic information and practical tips, and can select expert information for in-depth understanding (see Figure 1). On average, Keep Cool takes 45 minutes to complete and can be done at any time either at home or during the work process (repeated access possible). Upon registering and commencing the education program, participants complete a questionnaire to assess their baseline knowledge. The presentation of the learning content follows three key features: a) content is tailored to an individual's baseline knowledge by providing feedback, b) content is targeted to the occupational group (physicians or medical assistants), and c) the program personally addresses the participants.

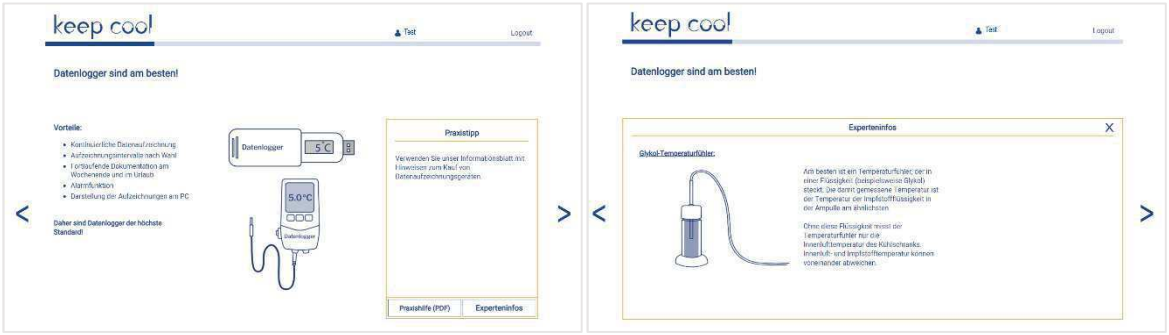

Figure 1: Example of the layout and presentation of the learning content: basic information and practical tip (left), expert information (right).

After completing the learning content and accessing the download area (e.g., scientific literature and templates for a temperature logbook), participants test their immediate learning success. If completed successfully, participants receive a certificate. Additionally, physicians receive a

continuous medical education point. Further details on the education program are described in Thielmann et al., 2020 (Publication 4).

4.2 Study Design

The evaluation was initially designed as a randomized, controlled trial with one intervention and one waiting-list control group in practices with confirmed cold-chain breaches (see Figure 2 for final study overview) (Thielmann et al., 2015b). For practical reasons during study conduct, we adapted the initially more complex study design. We refrained from randomization due to ethical reasons and offered the program to all practices after baseline temperature analyses showed marked temperature deficits which required immediate briefing of and action on behalf of the practices. This study was thus conducted as a prospective intervention study with two temperature monitoring periods. The primary outcome was the prevalence of refrigerators with temperatures within the target range (2°C to 8°C) for seven days. Improvement in knowledge served as a secondary outcome. Ethical approval was obtained from the Ethic Commission of the Medical Faculty of the University of Duisburg-Essen (14-6118-BO). Participants provided written informed consent.

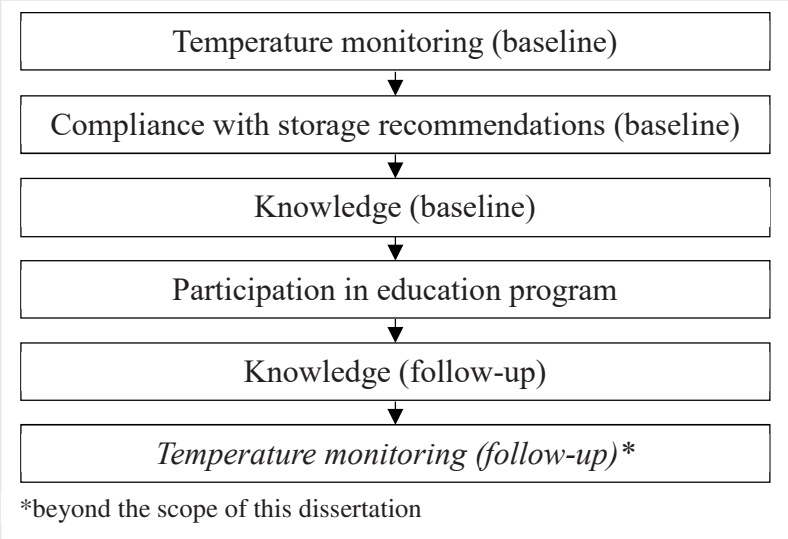

Figure 2: Final study overview.

4.3 Study Population and Recruitment

The study invitation was extended to all general practices of the teaching practice network affiliated with the University of Duisburg-Essen, Germany (N=185). Practices (n=17) that were involved in pre-tests were excluded, yielding a study population of 168 practices. Practices were recruited via email, fax and telephone. Non-participants received a short questionnaire via fax. Recruitment took place between January 2018 and August 2018.

4.4 Primary and Secondary Outcomes

4.4.1 Temperature

Temperature as the primary outcome was measured with a data logger (Testo 175T, accuracy: ±0.4°C) equipped with a standard probe at baseline and during follow-up at seven weeks (note: beyond the scope of this dissertation). Similar to prior studies (Bell et al., 2001; Gazmararian et al., 2002; Gold et al., 1999; Lewis et al., 2001; Page et al., 2008), we used continuous monitoring over seven days with a logging interval of one reading per minute. According to standards (Australian Government, 2013; Chojnacky et al., 2009; Chojnacky et al., 2010; Centers for Disease Control and Prevention, 2014), the data logger was positioned in a plastic bin and placed in the center of the refrigerator (see Figure 3). The data loggers' display was turned off and access to its memory was locked.

Figure 3: Set-up of data logger in plastic bin.

4.4.2 Vaccine Storage Practices

To assess vaccine storage practices other than cold-chain maintenance, we developed a checklist to be completed after each practice visit. We derived quality criteria from the international literature for the five core issues of the previously determined best practices for the German setting, i.e., refrigerator, temperature, storage, monitoring, and responsibilities (Thielmann and Weltermann, 2017a). The criteria were subsequently used to develop a 10-item checklist which was developed and refined using checklists from previous studies (Bell et al., 2001; Bishai et al., 1992; Gazmararian et al., 2002; Grasso et al., 1999; Haworth et al., 1993; Lee et al., 2012; Lewis et al., 2001; Woodyard et al., 1995; Yuan et al., 1995).

4.4.3 Knowledge

Knowledge was measured with a self-developed questionnaire consisting of 11 items with five answer options of which one was correct. The content was based on previous studies (Bell et al., 2001; Bishai et al., 1992; Chojnacky et al., 2009; Gazmararian et al., 2002; Gold et al., 1999; Kassenärztliche Bundesvereinigung, 2013; Lee et al., 2012; Page et al., 2008; Thakker and Woods, 1992; Woodyard et al., 1995; Yuan et al., 1995), German (Paul-Ehrlich-Institut, 2012; Robert

Koch-Institut, 2018/2019) as well as national recommendations/guidelines of other countries (Australian Government, 2013; Centers for Disease Control and Prevention, 2011, 2014, 2015; Public Health Agency of Canada, 2015; Salisbury et al., 2006), and also on scientific literature on the temperature sensitivity of vaccines and the performance of different refrigerator types (Chojnacky et al., 2009; Chojnacky et al., 2010; World Health Organization, 2006).

4.5 Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (Armonk, NY: IBM Corp.) and R, version 3.5.1. Descriptive statistics were used to describe participating and non-participating practices for each part of the study, i.e., the temperature monitoring and the intervention. Percentages and mean values are reported for valid cases. χ^2 test was used for categorical data, Student's t-test for continuous data.

Temperature: Temperature readings of a 7-day monitoring period were analyzed. The first 120 minutes after setting up each data logger were excluded to allow the probe to acclimatize. The primary outcome was the prevalence of refrigerators with temperatures within the target range (2°C to 8°C) for seven days. Secondary outcomes included reaching different cut-offs, e.g. ≤0°C (Hanson et al., 2017; Matthias et al., 2007; World Health Organization, 2006). For a better indication of unacceptable temperature exposure, we calculated the cumulative and consecutive time (in hours) beyond the target range and different cut-offs. A further secondary outcome addressed the refrigerators' capacity to maintain the target temperature range, considering cycling ranges >5.0°C as unacceptable. Refrigerators were categorized in acceptable and unacceptable types based on scientific literature (Chojnacky et al., 2009; Chojnacky et al., 2010; Centers for Disease Control and Prevention, 2014). To estimate the relationship between practice characteristics and 'within temperature range (2-8°C) versus outside target range' and 'reaching critically low temperatures (0°C) versus within target range', we used hierarchical generalized linear mixed models (GLMM) for binomial responses with random practice-specific intercepts (to account for practices with more than one refrigerator).

Vaccine storage practices: Descriptive statistics were performed at item level for all checklist items, including the quality criteria and the sum score of quality criteria. The latter was described for a) the total sample, b) refrigerators that continuously maintained the cold chain (2°C to 8°C),

and c) refrigerators that reached critically low temperatures (≤0°C). Associations between reaching more than half (6+) of the ten quality criteria and temperature data were analyzed using GLMM.

Knowledge: The frequency of all knowledge items and the learning effectiveness was calculated collectively for all participants and separately by professional group as well as per practice (at least one person with 8/11 or 11/11 correct). The outcome 'good vaccine storage knowledge' was defined as answering at least 8 of 11 of the questions correctly. For participants with data at both collection times, the level of improvement after program participation within the groups was compared using McNemar's test for categorical and the Wilcoxon signed-rank test for continuous variables. GLMM were used to assess the relationship between practice characteristics and 'optimal vaccine storage knowledge'.

5 Results

5.1 Temperature (Publication 2)

Of the 168 practices invited, 64 (38.1%) practices with 75 refrigerators participated in the baseline monitoring (Table 1).

Table 1: Characteristics of participating practices (N=64).

	n	%*
Number of physicians in practice, mean ± SD [10]	2.1±1.2	
Number of medical assistants, mean ± SD [11]	5.3±3.3	
Number of vaccines in practices (vaccine spectrum), mean ± SD [10]	17.9±1.8	
Practice type: Group	38	59.4
Patients with statutory health insurance: > 85% [8]	37	66.1
Certified quality management [15]	14	28.6
Physician qualifications: Travel medicine [10]	12	22.2
Physician qualifications: Tropical medicine and/or yellow fever license [10]	7	13.0
Services offered: Pediatric preventive services and/or adolescent medicine [10]	22	40.7
Services offered: Adolescent preventive services [10]	44	81.5
Refrigerator type (n=75)		
Pharmaceutical grade	9	12.0

Household model	66	88.0
Freezerless refrigerator	30	47.0
Refrigerator with internal ice compartment (one exterior door)[#]	31	45.5
Refrigerator with internal non-insulated ice compartment (one exterior door)[#]	2	3.0
Full-size dual-zone refrigerator/freezer (separate exterior doors)	2	3.0
Unclear	1	1.5

[*]valid percentages [missing values] SD = standard deviation [#]unacceptable refrigerator types

The prevalence of refrigerators with temperatures within the target range was 32.0% (n=24 of 75), i.e. 68.0% of refrigerators had temperature deficits: 14.7% (n=11) reached critically low temperatures <0°C, while 44.0% (n=33) showed temperatures >8°C and 28.0% reached temperatures (n=21) <2°C. See Figure 4 for an overview of temperatures for all refrigerators.

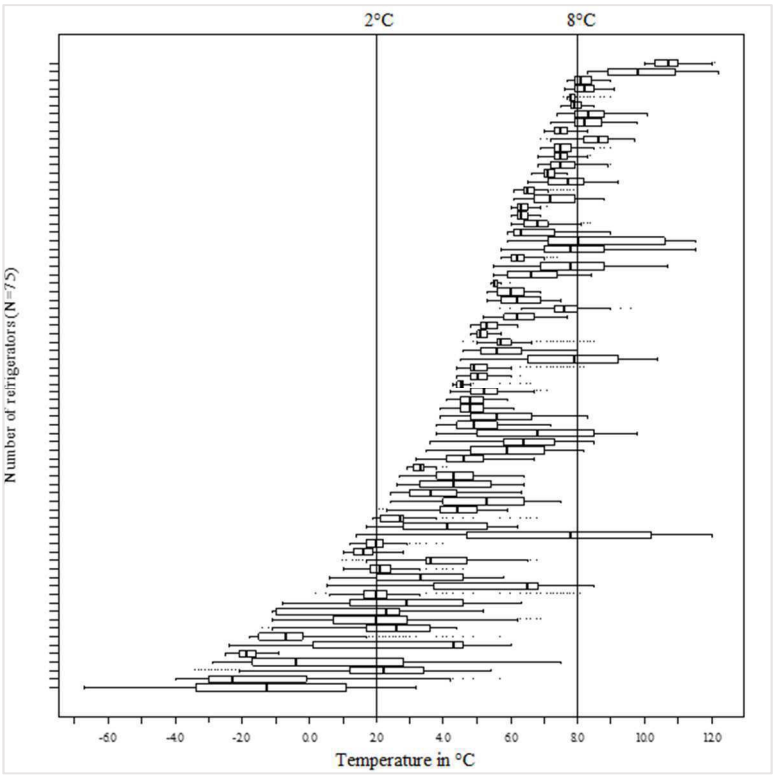

Figure 4: Temperature ranges by refrigerator (N=75).

Of the 168 hours recorded per refrigerator, the average cumulative time >8°C was 49 hours, <2°C 75 hours and ≤0°C 74 hours. The longest consecutive period of critically low temperatures was 168 hours (mean: 39±53). The temperature inside the refrigerators does not remain constant due to the design of the cooling mechanism. It can best be described as cyclic. The prevalence of

refrigerators with a cycling range of >5°C was 29.3%. Figure 5 shows typical temperature recordings encountered.

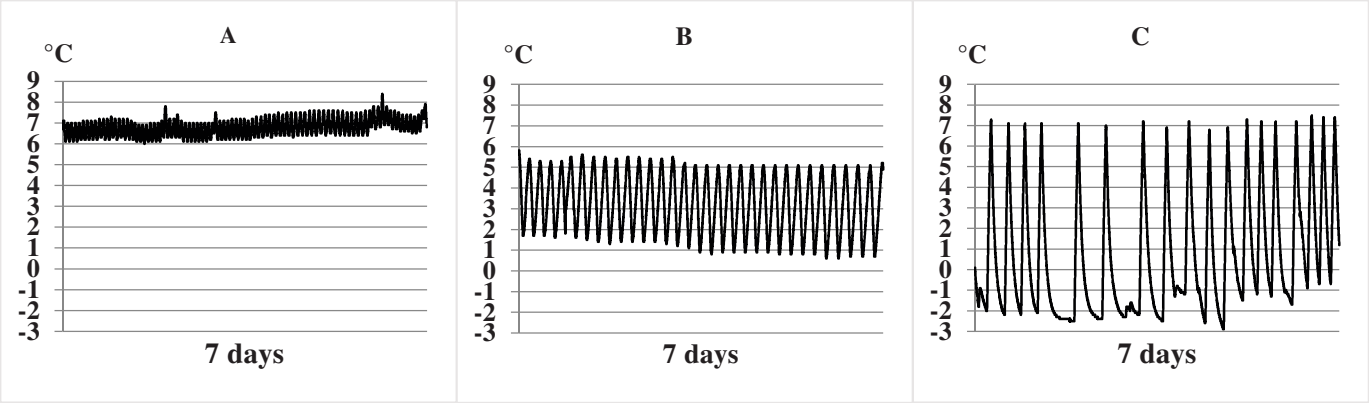

Figure 5: Examples of typical temperature recordings.

5.2 Vaccine Storage Practices (Publication 3)

Of the refrigerators described in 5.1, no practice/refrigerator had 'good refrigerator management' defined as reaching all ten predefined quality criteria. For details on criteria see Figure 6. On average, refrigerators met 4.7 (SD=1.9) criteria.

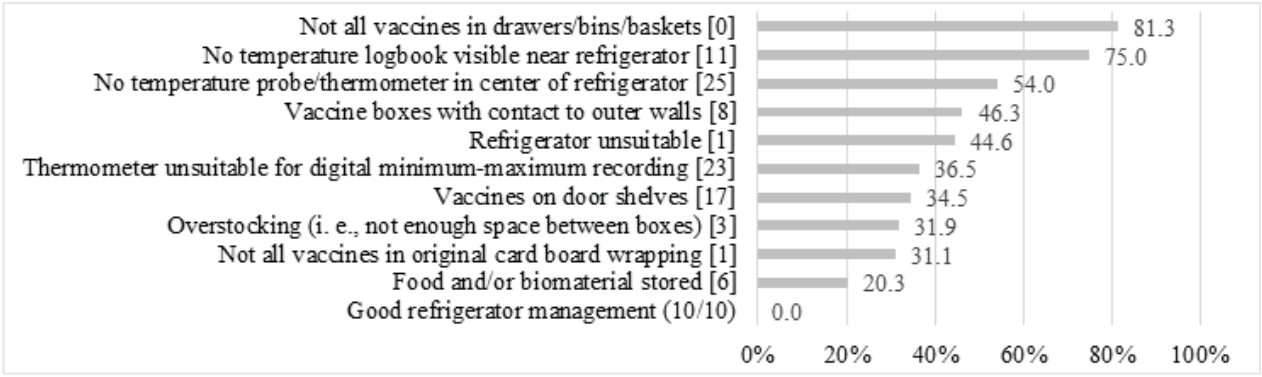

Figure 6. Frequencies of the ten quality criteria for 'good refrigerator management' (N=75) [missing values].

5.3 Knowledge (Publication 4)

Of the 64 practices that took part in the two-week temperature monitoring, 25 practices completed the learning program (response rate: 39.1%) with a total of 60 participants (mean 2.4 ±0.8). Information on personnel's knowledge is available for 16 physicians and 44 medical assistants. For details on participating and non-participating practices see Table 2.

Table 2: Comparison of participating (n=25) and non-participating (n=39) practices.

	Participating practices (n=25)		Non-participants (n=39)	
	n	**%***	**N**	**%***
Practice type: Group	13	52.0	25	64.1
Number of physicians in practice, mean ± SD [10]	2.0±1.4		2.2±1.1	
Number of medical assistants, mean ± SD [11]	4.4±3.1		5.8±3.3	
Certified quality management [15]	2	10.5	12	40.0
Physician qualifications: Travel medicine [10]	4	20.0	8	23.5
Physician qualifications: Tropical medicine and/or yellow fever license [10]	1	5.0	6	17.6
Number of vaccines in practices (vaccine spectrum), mean ± SD [10]	17.7±2.0		18.0±1.6	
Number of refrigerators	33		42	
Temperature				
Always within target range (2-8°C)	7	21.2	17	40.5
Within target range but at least once >8°C	10	30.3	18	42.9
Within target range but at least once <2°C	12	36.4	5	11.9
Always >8°C	1	3.0	1	2.4
<2°, in target range, >8°C	2	6.1	1	2.4
Always <2°C	1	3.0	0	0.0
Type of refrigerator used, household	32	97.0	34	81.0

*valid percentages [missing values] SD = standard deviation

The mean knowledge score at baseline was 5.6 correct answers (SD=1.9), which increased to 9.8 (SD=1.2) after program participation ($p<0.001$) (see Figure 7). The item with the highest net change addressed the need for twice-daily documentation of temperatures (+76.7%). Knowledge of the lower and upper temperature targets improved from 58% (medical assistants) and 63% (physicians) to 100% in each group. Optimal vaccine storage knowledge after participation (38% of participants) was associated neither with age, gender, occupational group, nor practice type.

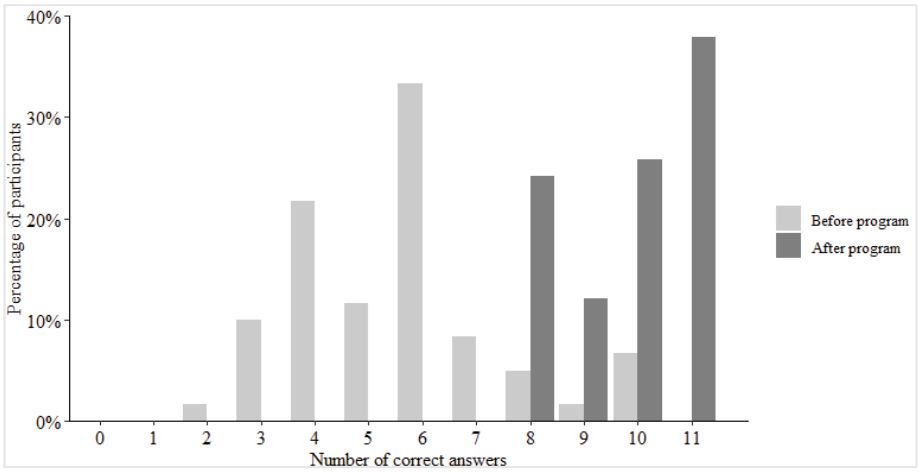

Figure 7: Knowledge on vaccine storage: Number of correct answers per participant (maximum 11 items) before and after program participation (before program N=60/ after program N=58).

6 Discussion

This dissertation project on vaccine management in general practices provides added value for public health for the following four reasons: 1) it offers the first quantification of cold-chain breaches in vaccine storage in German general practices (Publication 2); 2) it describes the status quo of vaccine storage practices and quantified deficits judged by international standards (Publication 3); 3) it quantifies knowledge deficits in practice personnel (Publication 4); and 4) it includes the development of a web-based education program that was tested successfully in the target group (Publications 1 and 4).

The cold-chain breaches in two thirds and the critically low temperatures in 15% of the refrigerators are similar to reports from other wealthier countries worldwide (Hanson et al., 2017). Comparing the other encountered deficits in vaccine storage practices (e.g. temperature probe/thermometer in center of refrigerator) to the literature is difficult due to the existing methodological variety. Overall, practices lacked adequate temperature monitoring rigor (i.e., a suitable thermometer, at least twice-daily monitoring), which is a significant prerequisite for identifying critical temperatures (Matthias et al., 2007). Keep Cool was effective in improving the poor knowledge levels encountered at baseline (Publication 4). Such knowledge deficits and the lack of problem awareness are also reported in other countries (Bell et al., 2001; Gazmararian et al., 2002; Lee et al., 2012; Page et al., 2008).

This project has several limitations. First, we refrained from a randomized, controlled study design for ethical reasons. Thus, only pre-post comparisons were possible. Second, only short-term results reflecting the immediate learning effectiveness were available because of practical reasons during the study conduct. Third, whether the positive results for knowledge translate to quality-ensured long-term cold-chain maintenance is unclear and will be addressed in the future.

This dissertation has several methodological implications for future research. Generally, it adds to the few intervention approaches on vaccine storage worldwide, all of which failed to establish a lasting quality improvement (Gold et al., 1999; Lee et al., 2012; Lewis et al., 2001; Jeremijenko et al., 1996). The low participation rate in the Keep Cool program is particularly noteworthy. First, it points to knowledge behavior gaps and problem awareness deficits. Practices refrained from participation although they received their (insufficient) baseline temperature outputs and were offered a low-threshold, no-cost 'solution'. Second, it suggests that a web-based intervention delivery alone is insufficient to reach the complete target group. Likely, various barriers play a role, e.g., personal preferences, and some practices avoid regular access to the internet as a safety precaution. Also, to our knowledge, this is the first intervention that focuses on both two professional groups in general practices.

7 Conclusion and Perspective

We documented serious but avoidable vaccine storage deficits in German general practices. The following actions are needed to improve the current situation: 1) establish program effectiveness for the primary outcome based on the follow-up data, 2) develop and test additional intervention channels for the delivery of the learning content, 3) take action on a regulatory level, 4) plan a large-scale dissemination to physicians from all medical specialties who provide vaccinations.

8 References

Australian Government. National vaccine storage guidelines. Strive for 5. Canberra: Dept. of Health and Ageing, 2013

Bell KN, Hogue C, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. Pediatrics, 2001; 107: e100

Bishai DM, Bhatt S, Miller LT, Hayden GF. Vaccine storage practices in pediatric offices. Pediatrics, 1992; 89: 193–196

Boros CA, Hanlon M, Gold MS, Roberton DM. Storage at− 3 C for 24 h alters the immunogenicity of pertussis vaccines. Vaccine, 2001; 19: 3537–3542

Centers for Disease Control and Prevention. General Recommendations on Immunization. MMWR Morb Mortal Wkly Rep., 2011; 60: 1–35

Centers for Disease Control and Prevention. Vaccine Storage & Handling Toolkit, 2014

Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Washington, DC: Public Health Foundation, 2015

Chojnacky M, Miller W, Ripple D, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7656), 2009

Chojnacky M, Miller W, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7753), 2010

Gazmararian JA, Oster NV, Green DC, Schuessler L, Howell K, Davis J, Krovisky M, Warburton SW. Vaccine storage practices in primary care physician offices: assessment and intervention. Am. J. Prev. Med., 2002; 23: 246–253

Gemeinsamer Bundesausschuss. Richtlinie des Gemeinsamen Bundesauschusses über Schutzimpfungen nach § 20d Abs. 1 SGB V

Gold MS, Martin L, Nayda CL, Kempe. Electronic temperature monitoring and feedback to correct adverse vaccine storage in general practice. MJA, 1999; 171: 83–84

Grasso M, Ripabelli G, Sammarco ML, Selvaggi TM, Quaranta A. Vaccine storage in the community: a study in central Italy. Bull. World Health Organ., 1999; 77: 352

Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. Vaccine, 2017; 35: 2127–2133

Haworth EA, Booy R, Stirzaker L, Wilkes S, Battersby A. Is the cold chain for vaccines maintained in general practice? BMJ, 1993; 307: 242–244

Health Protection Scotland. Guidance on vaccine storage and handling. Glasgow: Health Protection Scotland, 2013

Jeremijenko A, Kelly H, Sibthorpe B, Attewell R. Improving vaccine storage in general practice refrigerators. BMJ, 1996; 312: 1651–1652

Kassenärztliche Bundesvereinigung, 2013. Statistische Informationen aus dem Bundesarztregister. Verfügbar unter http://www.kbv.de/media/sp/2013_12_31.pdf (Zugriffsdatum: 03.03.2015)

Lee S, Lim H-S, Kim O, Nam J, Kim Y, Woo H, Noh W, Kim K. Vaccine Storage Practices and the Effects of Education in Some Private Medical Institutions. J. Prev. Med. Public Health, 2012; 45: 78–89

Lerman SJ, Gold E. Measles in children previously vaccinated against measles. JAMA, 1971; 216: 1311–1314

Lewis PR, Reimer RF, Dixon AJ. Evaluating the efficacy of vaccine storage in the general practice setting. Aust. N. Z. J. Public Health, 2001; 25: 547–550

Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. Vaccine, 2007; 25: 3980–3986

McColloster P, Vallbona C. Graphic-output temperature data loggers for monitoring vaccine refrigeration: implications for pertussis. Am J Public Health, 2011; 101: 46–47

McIntyre RC, Preblud SR, Polloi A, Korean M. Measles and measles vaccine efficacy in a remote island population. Bull. World Health Organ., 1982; 60: 767

Onoja AL, Adu FD, Tomori O. Evaluation of measles vaccination programme conducted in two separate health centres. Vaccine, 1992; 10: 49–52

Page SL, Earnest A, Birden H, Deaker R, Clark C. Improving vaccination cold chain in the general practice setting. Aust. Fam. Physician, 2008; 37: 892

Paul-Ehrlich-Institut. Ausflückungen in Adsorbatimpfstoffen. Bulletin zur Arzneimittelsicherheit - Informationen aus BfArM und PEI, 2012 12–16

Public Health Agency of Canada. National vaccine storage and handling guidelines. Ottawa: Public Health Agency of Canada, 2015

Robert Koch-Institut. Aktualisierte Mitteilung der Ständigen Impfkommission (STIKO) am RKI: Hinweise für Ärzte zum Aufklärungsbedarf über mögliche unerwünschte Wirkungen bei Schutzimpfungen/Stand: 2007. Epidemiol. Bull., 2007; 25: 219–232

Robert Koch-Institut. Anforderungen an die Hygiene bei Punktionen und Injektionen. Bundesgesundheitsblatt, 2011; 54: 1135–1144

Robert Koch-Institut. Mitteilung der Ständigen Impfkommission am Robert Koch-Institut (RKI). Epidemiologisches Bulletin, 2013; 34: 313–344

Robert Koch-Institut. Mitteilung der Ständigen Impfkommission am Robert Koch-Institut (RKI), 2018/2019 335–382

Salisbury D, Ramsay M, Noakes K. Immunisation against infectious disease. London: TSO, 2006

Thakker Y, Woods S. Storage of vaccines in the community: weak link in the cold chain? BMJ, 1992; 304: 756–758

Thielmann A, Sikora M, Schnell U, Gesenhues S, Weltermann B. Impfkühlschrank-und Impfstoffmanagement in Hausarztpraxen: Eine repräsentative, Web-basierte Umfrage unter Hausärzten (Keep Cool I). Das Gesundheitswesen, 2015a; 38: 1–6

Thielmann A, Viehmann A, Weltermann BM. Effectiveness of a web-based education program to improve vaccine storage conditions in primary care (Keep Cool): study protocol for a randomized controlled trial. Trials, 2015b; 16:

Thielmann A, Weltermann B. Best-practices für die Impfstofflagerung: ein Review von nationalen Empfehlungen und Leitlinien verschiedener Länder (Keep Cool). Der Internist, 2017a 58 (Supplement 1): 39 (PS85)

Thielmann A, Weltermann B. Keep-Cool: Entwicklung einer online-basierten edukativen Intervention zur Optimierung der Impfstofflagerung in Hausarztpraxen. GMS Ger Med Sci, 2017b

Weltermann BM, Markic M, Thielmann A, Gesenhues S, Hermann M. Vaccination Management and Vaccination Errors: A Representative Online-Survey among Primary Care Physicians. PloS one, 2014; 9: e105119

Woodyard E, Woodyard L, Alto WA. Vaccine storage in the physician's office: a community study. The Journal of the American Board of Family Practice, 1995; 8: 91–94

World Health Organization. Temperature sensitivity of vaccines. Department of Immunization, Vaccines and Biologicals, World Health Organization, 2006 1–62

World Health Organization. Aide mémoire for prevention of freeze damage to vaccines. WHO/IVB/07.09. Geneva

Yuan L, Daniels S, Naus M, Brcic B. Vaccine storage and handling. Knowledge and practice in primary care physicians' offices. Can. Fam. Physician, 1995; 41: 1169

9 Publications

9.1 Publication 1

Effectiveness of a web-based education program to improve vaccine storage conditions in primary care (Keep Cool): study protocol of a randomized controlled trial

Anika Thielmann, Anja Viehmann, Birgitta M. Weltermann

Trials
2015
DOI: 10.1186/s13063-015-0824-9
Impact Factor (2015): 1.859

Thielmann et al. Trials (2015) 16:301
DOI 10.1186/s13063-015-0824-9

TRIALS

STUDY PROTOCOL Open Access

Effectiveness of a web-based education program to improve vaccine storage conditions in primary care (Keep Cool): study protocol for a randomized controlled trial

Anika Thielmann, Anja Viehmann and Birgitta M. Weltermann*

Abstract

Background: Immunization programs are among the most effective public health strategies worldwide. Adequate vaccine storage is a prerequisite to assure the vaccines' effectiveness and safety. In a questionnaire survey among a random sample of German primary care physicians, we discovered vaccine storage deficits: 16 % of physicians had experience with cold chain breaches either as an error or near error, 49 % did not keep a temperature log, and 21 % did not use a separate refrigerator for vaccine storage. In a recent feasibility study of 21 practice refrigerators, we showed that these were outside the target range 10.2 % of the total time with some single refrigerators being outside the target range as much as 66.3 % of the time. These cooling-chain deficits are consistent with the international medical literature, yet an effective, easy to disseminate, practice-centered intervention to improve storage conditions is lacking.

Methods/design: This randomized intervention trial will be conducted in a random sample of primary care practices. Based on continuous temperature recordings over 7 days, all practices with readings outside the target range for vaccine storage (+2 °C to +8 °C) will be randomly allocated to a web-based education program or a waiting list control group. The practice physicians and their teams constitute the target population. Participants will be educated about best practices in vaccine storage and will receive a manual including storage checklists and templates for temperature documentation. In all practices, temperatures of the vaccine refrigerators will be monitored continuously using a data logger with a glycol probe as a surrogate for vaccine vial temperature. The effectiveness of the web-based education program will be determined after 6 months in terms of the proportion of refrigerators with vaccine vial temperatures within the target range (+2 °C to +8 °C) during 7-day temperature logging. Secondary outcome parameters include temperature monitoring, no critically low temperatures (≤ -0.5 °C), compliance with storage recommendations, knowledge of good vaccine storage conditions, and assignment of personnel as vaccine storage manager and backup.

Discussion: Keep Cool will develop and evaluate a web-based education program to improve vaccine storage conditions in primary care and thereby ensure immunization safety and effectiveness.

Trial registration: DRKS00006561 (date of registration: 20 February 2015)

Keywords: Vaccine management, Primary care, Vaccine cold chain, Education, E-learning, Quality improvement

* Correspondence: Birgitta.Weltermann@uk-essen.de
Institute for General Medicine, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45147 Essen, Germany

Background

Immunizations are among the most effective and cost-effective public health strategies worldwide [1]. Adequate vaccine storage is a prerequisite to maintain effectiveness and safety of the vaccines. The maintenance of the vaccine cold chain (2 °C to 8 °C) is of utmost importance to assure vaccine potency [2]. Detailed analyses of vaccine temperature sensitivities documented freezing of vaccines as being more critical than heating, at least in our moderate Western European climate. Modern adsorbed hepatitis B vaccines were documented to be the most sensitive vaccines with a freezing point of -0.5 °C [2]. At this temperature, irreversible precipitates of aluminum-containing adsorbents begin to form, which decrease the potency and can induce local irritation upon injection [2, 3].

In a cross-sectional web-based questionnaire survey, we analyzed vaccination management among a 10 % random sample of primary care physicians from one of Germany's largest federal states, North Rhine-Westphalia [4] using international recommendations for vaccine storage [5–9]. The survey (n = 211) revealed that 16 % of the primary care physicians have experience with cold chain breaches either as an error or near error; 8 % do not regularly control their storage with regard to vaccine wrapping, vaccine expiration date, and refrigerator temperature; 49 % do not keep a storage temperature log; and 21 % fail to use a separate refrigerator solely for vaccine storage. In a recent feasibility study, we observed that the correct temperature range of 2 to 8 °C was not consistently maintained in seven of 21 (33.3 %) vaccine refrigerators from teaching practices. Refrigerators were outside the target range 10.2 % of the total time, with single refrigerators outside the target range for as much as 66.3 % of the time. These results are in line with studies worldwide, which discuss the following key problems related to vaccine storage: 1) temperatures outside the target range [10, 11], 2) lack of adequate temperature measurement devices [12–14], 3) lack of continuous temperature documentation [4, 12–14], 4) use of inadequate refrigerators [9, 10, 12], 5) lack of separate refrigerators [13–15], 6) inadequate storage practices [2, 12, 14, 15], 7) lack of designated personnel [14], and 8) insufficient staff training and guidance [12, 14, 16–18].

Prior studies addressing these deficits used the following intervention components either alone or in combination: 1) written educational materials, 2) introduction of thermometers with or without feedback on temperature readings by either graphic display or telephone advice to personnel, and 3) 1:1 onsite education with inspection of refrigerators. In 2002, a prospective intervention study of 721 US primary care practices achieved improved compliance with several storage recommendations of up to 19 % after 3 months following the distribution of a manual, a thermometer and a feedback checklist [12]. Similar results with improvements ranging from 13 to 23 % after 4 weeks were shown in a Korean study of 39 private clinics, which provided onsite 1:1 education including the distribution of a manual. This study also documented improved awareness of various vaccine storage criteria ranging from 3 % to 29 % [16]. With regard to reaching the targeted temperature range, the best result was observed in an Australian study of 50 primary care practices: onsite education and the distribution of min/max-thermometers led to a fourfold increase of practices with refrigerator temperatures in the target range [18]. The two studies available, which provided long-term follow-ups after 6 months, 1 year, and 5 years, documented a tendency for improved temperatures in the populations studied but also reported fluctuations over time in 25 % of the practices with initially optimal temperatures [19, 20]. The repetitive documentation of such fluctuations in intervention as well as control groups underlines the need for structural change as part of educational interventions, including the long-term implementation of practice routines for daily temperature monitoring.

Following recommendations on effectively changing medical practice [21], our study will use a complex approach focusing on the individual as well as the organizational level by encouraging structural changes. The intervention will address both professional groups involved in the management of vaccines, that is, the physician managers in charge, as well as the practice assistants who handle vaccines. Based on didactic approaches such as information tailoring and confidence-based learning, relevant information will be presented in a web-based education program, which tailors information to each users' knowledge. Prospectively, this e-learning approach will allow for widespread dissemination at low cost.

Keep Cool aims to evaluate the effectiveness of a web-based education program to improve vaccine storage conditions in primary care practices. The main outcome used to determine the effectiveness of the intervention is the proportion of refrigerators with vaccine vials within the target range (+2 °C to +8 °C) during 7-day monitoring after 6 months.

Methods/design

Study design

Keep Cool is a prospective, randomized, controlled intervention trial, which will be performed in a random sample of primary care practices (see Fig. 1). After telephone recruitment, all practices will be visited by a study assistant to set up temperature data loggers (t0). Based on continuous temperature recordings over 7 days, all practices with readings outside the target range for

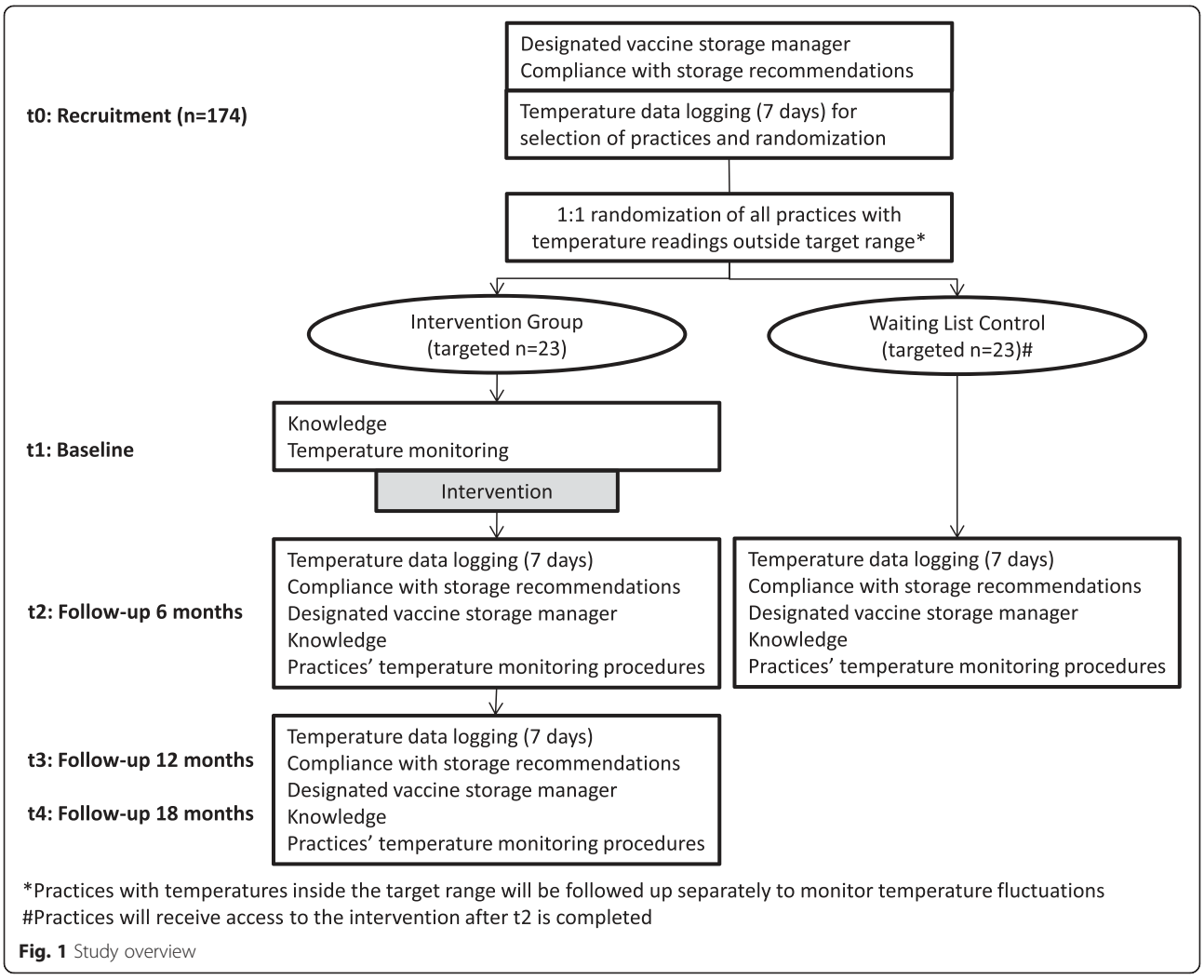

Fig. 1 Study overview

vaccine storage (+2 °C to +8 °C) will be randomly allocated (1:1) to an intervention group or a waiting list control group. Practices with temperatures within the target range will be followed separately to monitor temperature fluctuations. Baseline data on knowledge will be collected at t1 prior to the start of the intervention, whereas the compliance with storage recommendations and the assignment of personnel as vaccine storage manager and backup will have already been documented by the study assistant during recruitment (t0). After baseline measurements at t1, the intervention group will receive access to the e-learning program. Follow-up data will be obtained after 6 months (t2) and, to study the intervention's long-term effectiveness, after 1 year (t3) and 18 months (t4). After the intervention phase is completed, the waiting list control group will receive access to the e-learning program.

Ethical approval was obtained from the Ethic Commission of the Medical Faculty of the University Hospital Essen, University of Duisburg-Essen (reference number: 14-6118-BO, date of approval: 04/02/2015). Keep Cool follows the Ethical Principles of the World Medical Association Declaration of Helsinki (WMA 1964).

Study population

The target population of this randomized controlled trial is primary care physicians and their practice personnel. The majority of these personnel completed a 3-year vocational training with a degree (practice assistants). A few practices also employ secretaries, nurses or personnel without a degree, but with on-the-job training. The intervention will address all staff members handling vaccines regardless of their prior training. Practices are eligible if they administer vaccinations and are situated within a 50-km radius of Essen, Germany. All participating physicians and practice personnel will sign an informed consent form.

Intervention: web-based education program

Physicians and practice personnel will participate in a web-based education program on the storage of vaccines according to international best practices (for example, WHO and CDC). To ensure the target populations' acceptance of the program, we will ask primary care physicians and practice assistants of academic teaching practices of our research network to join recurrent focus group sessions. This group will facilitate the development, adaptation, implementation, and evaluation phase of the intervention.

The e-learning program will be developed using a teaching software that allows the tailoring of information to each user group (that is, physicians and medical assistants) and each individual's previous response behavior. Following confidence-based learning, the e-learning program will require participants to a) answer concrete vaccine storage-related questions and b) indicate the degree to which they feel confident in the correctness of each answer. Depending on the respondents' answers, that is, correctness and confidence of answers, each participant will receive learning input with subsequent learning-success-adjusted repetitions of questions to achieve optimal memorizing effects. All participants will receive tailored feedback during the course of answering questions on an item level and for all items after completion of the program.

Five educational topics will be addressed by the web-based education program:

1. Requirements for technical equipment including refrigerator criteria; types of thermometers; equipment maintenance.
2. Vaccine temperature sensitivity, target temperature, and daily reviewing and recording of temperatures: freezing thresholds of freeze-sensitive vaccines; refrigerator target range (2-8 °C = 35.6-46.4 °F); necessity of daily recording; recording criteria; need for long-term temperature logs; and use of data logs (paper-based or electronically).
3. Principles of vaccine storage inside a refrigerator including the preparation of refrigerators for vaccine storage, background knowledge about the use of domestic refrigerators for vaccine storage (incl. refrigerator cycles, temperature zones), necessity of a separate refrigerator for the sole purpose of vaccine storage, standards for vaccine storage within refrigerators, and use of storage aids.
4. Vaccine cold chain-related processes including vaccine arrival procedures, periodic manual storage control, and procedures for dealing with cold chain breaches and equipment failure.
5. Responsibilities of practice personnel including the assignment of personnel as vaccine storage manager and backup.

To facilitate long-term changes at the organizational level, all practices will be advised to assure the following two structural components: 1) the assignment of personnel as vaccine storage manager and at least one backup and 2) the set-up of a comprehensive temperature monitoring system. This includes reviewing temperatures using a standard thermometer, recording temperatures in a temperature log, taking immediate action if needed, and retaining temperature logs. In addition to a storage manual summarizing the program content, the following material will be made available as a web download: a "temperature log template," guides for "preparing a refrigerator for vaccine storage," "storing vaccines in the refrigerator," "refrigerator maintenance," plans for "routine vaccine management," and "emergency response," as well as a summarizing overview of the "tasks of the vaccine coordinator."

Outcomes

Primary outcome: The proportion of refrigerators with vaccine vials within the target range (+2 °C to +8 °C) during a 7-day monitoring at 5-minute intervals after 6 months. Temperature inside the target range is chosen as the primary outcome, because it is of utmost importance that nonfreezing vaccines are stored in this temperature range. When absorbed mono- and combination vaccines reach their individual freezing thresholds, their chemical structures irreversibly change. This can lead to increased local reactions and reduced effectiveness. The most sensitive vaccines are hepatitis B vaccines with a freezing threshold of -0.5 °C [2]. A thermal analysis of frequently used types of refrigerators by the US Department of Commerce [22, 23] showed that vaccine vial temperatures vary depending on the refrigerator type, loading density and location of vaccines inside the refrigerator. Typical refrigerators used in German primary care are the types "freezerless" (single refrigerator compartment without a freezer) and "dual zone" (separate compartments for refrigerator and freezer, both with individual doors), both so-called domestic refrigerators. Based on different scenarios, that is, door openings and loading density, temperatures can vary by +/-2.3 °C in the type "freezerless" and by +/-4.5 °C in the type "dual zone" [22, 23]. The maintenance of the temperature range of +2 to +8 °C, as recommended by vaccine manufacturers and public health authorities worldwide, is hence justified and therefore serves as a primary outcome measure.

Temperatures will be measured via a data logger that is approved by the US Center for Disease Control

(CDC), and the same type will be distributed to each practice in order to ensure consistency of temperature readings across locations. Continuous measurements over 7 days are planned for baseline (t0) and continuously thereafter, with follow-ups after 6 months (t2), 1 year (t3) and 18 months (t4). Continuous measurements are preferable to single-point measurements because many practices use nonpurpose built refrigerators (so-called domestic refrigerators). Such refrigerators are known to have temperature cycles that result from their on-/off-construction: using the physical principle of the Carnot cycle, they cool down to a specific temperature, after which the cooling department is shut off until a higher temperature is reached [22, 23]. To analyze such temperature fluctuations, we chose a logging interval of one reading every 5 minutes. Similar logging rates were used in prior studies [12, 14, 17, 19, 20]. The logging period of 7 days ensures that at least one regular working week and one weekend are included. This takes differences in patient flow and refrigerator door openings into account (for example, typically more patients on Mondays).

Secondary outcomes follow international best practices and guidelines:

1. Temperature monitoring - Improvement in temperature monitoring with optimal monitoring defined as electronic or paper-based recording with a minimum of two readings per day for the previous 5.5 months (5 % missing entries allowed). Prior studies indicated that temperature fluctuations without adequate adjustments over time are a main barrier to intervention success. To overcome this barrier, this intervention program will emphasize temperature monitoring, including temperature reviewing, recording, taking immediate action if needed and retention of temperature logs.
2. Refrigerators not freezing - The proportion of practices with vaccine vials not reaching critically low temperatures (-0.5 °C or lower) will be determined.
3. Compliance with storage recommendations - Improvement in actual refrigerator-related storage quality will be assessed at practice level according to the following examples:

a. Refrigerator is used exclusively for vaccine storage.
b. Standard thermometer is located in refrigerator.
c. No vaccines are stored in refrigerator door.
d. Vaccines are stored in their original wrapping.
e. e Vaccines are stored in the center of the refrigerator.
f. Use of a stock management system (for example, "earliest expiry first out (EEFO)" principle) and regular manual stock control.

4. Knowledge about vaccine storage - Improvement in knowledge of good vaccine storage conditions in physicians and practice personnel will be studied using a standardized questionnaire.
5. Assignment of personnel - During the initial practice visit the study assistant will ask if practices currently have assigned personnel as vaccine storage manager and backup. This is considered an important structural characteristic to maintain long-term changes at practice level.

Measurement instruments

Temperature data logging

An important distinguishing factor from previous studies, but in line with international best practices [5–7], is the use of a data logger with one high-accuracy thermistor probe immersed in glycol. In contrast to a standard air probe, the slow-reacting glycol probe resembles the temperature changes of the vaccine vials, whereas the fast-reacting air probe only shows the ambient air temperatures inside the refrigerator and the effects of door openings on refrigerator temperatures.

Specifications and set-up of the chosen data logger are described below:

1. Type - EL-GFX-DTP.
2. Manufacturer - Lascar Electronics Ltd, UK.
3. Probe - High-accuracy thermistor probe immersed in glycol.
4. Accuracy for probe within the operating range -5 °C to +10 °C - +/− 0.1 °C.
5. Logging rate - 1 reading per 5 minutes.

According to standards, this data logger will be placed in the center of the refrigerator for continuous recording. In practices using more than one refrigerator for vaccine storage, the refrigerator most frequently used and closest to the reception desk will be selected.

Self-administered questionnaire (knowledge and temperature monitoring)

The questionnaire will consist of a knowledge part (part 1) and a part addressing current structures and procedures used for monitoring of temperatures (part 2). The knowledge part will be developed drawing on the international body of recognized best practices and guidelines (for example, WHO), official checklists used in other countries (UK, US, and AUS) and

previous studies (for example, [12, 14, 16, 17, 20]). Items will correspond to the five educational topics detailed above. In addition, sociodemographic characteristics of physician and practice personnel (sex, age, years in practice/job, part-/full-time, and job content) and practice characteristics (single/group, number of physicians/medical assistants in practice, number of patients quarterly, average number of vaccinations daily, age structure of patients, and urban/rural) will be included. In part two, the current structures and procedures used for the monitoring of temperatures will be obtained. Participants will complete part 1 and 2 of the questionnaire after accessing the web-based program, but before starting with the educational program itself (t1). Follow-up measurements will use a paper-based version of part 1 of the questionnaire, handed out and collected when downloading follow-up data logger readings (t2 and t4). Inspections of temperature logbooks at t2 and t4 will serve as the follow-up measurement for part 2.

Storage checklist

Changes in the compliance with storage recommendations will be assessed using a checklist completed by the study assistant. This checklist will be a modification of a tool used in the previously mentioned intervention study by Lee et al. (2012) [16] and draws on the same sources listed above. This checklist is completed when the data loggers are set up (t0) and again when the temperature readings are downloaded (t2, t3, t4).

Waiting list control group The control group will consist of practices that have temperature readings outside the target range during baseline data collection. The control group will be monitored via a temperature data logger but will receive access to the e-learning program only after t2. By including a control group, an intervention bias due to the set-up of data loggers is taken into account. The control group is closest to regular everyday care and serves as a baseline to better determine the effectiveness of the intervention.

Safety issues

All practices will be informed in detail about their vaccine refrigerator temperature. The tailored education and the download material will address the issue of how to deal with temperature breaches. Practices with temperature readings outside the target range will receive additional information after t2. The following safety regulations will be followed:

1. Practices with any temperature beyond the target range will receive detailed information on the date and duration of the incident.
2. They will also receive detailed information recommending that the manufacturer's hotline(s) be contacted for information on how to deal with vaccines exposed to inadequate temperatures, and if additional vaccinations of patients are required to assure patient immunity.
3. In addition, practices will receive the contact data of the Paul Ehrlich Institute, the Federal German agency responsible for vaccines and appropriate management thereof.

Data collection procedure

Practice recruitment

The study will be performed in a random sample of primary care practices in North Rhine-Westphalia, Germany. The sample will be restricted to practices within a 50-km radius of the University Hospital Essen. To support a systematic recruitment process and ensure detailed documentation of all contact attempts and communications with the practices, we will use a response-tracking database. To achieve a high response rate, we will follow a multi-level approach, consisting of up to three invitation letters and up to five phone calls on different days and at different times. The first phone call with each physician is to ensure the eligibility of practice, that is, vaccines are administered, provide additional study information, schedule an appointment for the first practice visit by the study assistant. In order to allow for a nonparticipant analysis, practices refusing participation will be asked to complete a short questionnaire on their practice characteristics (solo/group practice, number of patients quarterly, number of physicians in practice, number of refrigerators used, and availability of a refrigerator thermometer).

Randomization

Based on results of the temperature baseline data collection, practices with temperatures outside the target range will be randomized equally to the two study arms (1:1). The randomization procedure is computer-based through www.random.org. No participant will be informed about the study hypotheses in detail.

Sample size estimation

The intervention study will be performed in a sample of 46 primary care practices (23 practices per arm) with suboptimal temperature readings at baseline during a 7-day monitoring period (t0). A sample size of 23 practices per group provides an 80 % power to detect anticipated differences between the groups at a significance level of 0.05 %. We assume that 70 % of the practices in the intervention group will reach the temperature target range at follow-up. This assumption is based on two intervention studies of comparable intensity that observed

optimal storage conditions in 83 % and 77 % of previously suboptimal practices, using continuous temperature readings as the outcome [18, 19]. Regarding the control group, we expect that 30 % of practices will reach the temperature target range at follow-up due to a study participation effect because of being exposed to temperature monitoring via data logger. This assumption is based on an intervention study that observed optimal temperature readings in 33 % of the control group at follow-up [18].

Owing to the lack of intervention studies available, the power calculation is based on more conservative assumptions.

As the intervention will only be conducted in practices with suboptimal temperatures, a total of 174 practices will have to be recruited for t0. This is based on the assumption that 33.3 % of refrigerators will be outside the target range (n = 58). This percentage is derived from the abovementioned prospective feasibility study in 17 primary care practices with 21 vaccine refrigerators and similar results reported by Bell et al. (2001), Jeremijenko et al. (1996) and Lewis et al. (2001) [14, 18, 20]. Our calculation takes into account a dropout rate of 20 %. This dropout rate is based on our experience and corresponds to reports from other cluster-randomized trials [24]. Using an adaptive design, baseline temperature measurements for t0 will be stopped as soon as the anticipated total sample of n = 58 is reached.

Statistical analysis

Descriptive statistics will be used to describe baseline characteristics for both study arms with regard to practice characteristics (single/group, number of physicians/medical assistants in practice, number of patients quarterly, average number of vaccinations daily/per week, age structure of patients), participating physician and practice personnel characteristics (sex, age, years in practice/job, part-time/full-time, job content). The effectiveness will be assessed by comparing the intervention and control group and by intragroup comparison (baseline versus follow-up). We will evaluate the effectiveness based on temperature as the main outcome (within range yes/no) by comparing both groups using the chi-square test. For intergroup analyses, all dichotomous secondary outcomes will be evaluated using chi-square tests for each item. In addition, compliance with storage recommendations will be analyzed on the basis of a sum score calculated across all items by using a t-test. For in-group comparisons, McNemar tests will be calculated for dichotomous outcomes and t-tests for dependent samples for sum scores. Temperature monitoring will be measured on an ordinal level to allow for application of the Mann-Whitney U Test (intergroup comparison) and the Wilcoxon signed rank sum test (intragroup comparison). A P value <0.05 will be considered significant. All statistical analyses will be performed using IBM SPSS 22® on Windows.

Discussion

To our knowledge, this will be the first randomized controlled trial evaluating a web-based approach in comparison to a control group addressing the issue of vaccine storage. The topic is important to ensure vaccine effectiveness and safety but currently plays a minor role, at least in German primary care practices. Some of this lack of recognition is due to the fact that this topic is only marginally addressed, if addressed at all, in the medical education of physicians and practice personnel.

Effectively changing medical practice requires a "complex approach focused on different levels, tailored to specific settings and target groups" [21]. To address the issue of vaccine storage, we chose a web-based education that combines a number of benefits. First, while being as effective and satisfactory as traditional educational approaches [25, 26], it addresses both target populations, that is, physicians and practice team members. The tailored presentation of relevant learning content is discussed to increase the appropriateness of the information on a personal level, thereby implying that contents are better remembered and more frequently discussed (for example, [27]). Although computer tailoring has not been studied in healthcare providers, it was proven to be effective in patients' health education and promotion [28, 29]. Second, an e-learning intervention tool can easily be used for recurrent training, for example, to train new personnel in case of fluctuation or to retrain staff in the form of continuous medical education. Third, in contrast to 1:1 education our web-based learning format can be disseminated on a larger scale at low cost.

Methodologically, the study exhibits a number of strengths. First, in contrast to prior studies, continuous vial temperature using a glycol probe as opposed to single-point measurements of ambient air temperature is used as a primary outcome parameter. Second, to take into account the frequently reported fluctuations in performances, several strategies to intensify the intervention are combined: the intervention is directed at both the individual physician and practice personnel as well as the organizational level. Participants will receive tailored information and a manual for later reference, whereas the practice as an organizational unit will receive managerial support in the form of templates, plans and guides for various aspects of vaccine management, for example, for temperature recording and emergency plans in the event of equipment failure. A manual on vaccine storage management is a novelty to German practices as currently no agreed-upon reference is available, and the official German recommendations for vaccines contain only little information on storage issues. Third, in contrast to

some prior interventions lacking in-depth descriptions of intervention contents and implementation processes, we will describe the content of the web-based education intervention in detail to allow for replication and/or building on research findings. Fourth, our web-based intervention is designed for future widespread use in small and larger healthcare institutions at low cost.

Trial status

Practice recruitment is planned to start in January 2016.

Abbreviations

AUS: Australia; C: Celsius; CDC: Centers for Disease Control; F: Fahrenheit; UK: United Kingdom; US: United States of America; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BW and AT developed the study idea and concept. BW, AT and AV developed the intervention. BW secured its funding. BW and AT drafted the first version of the manuscript. BW, AT and AV drafted the analysis plan. All authors critically reviewed the first draft and provided feedback on it. All authors read and approved the final manuscript.

Acknowledgements

Funding for the thermometers used in the study was received from the Stiftung Universitätsmedizin Essen. Funding for the educational software and its adjustments was granted from the Kulturstiftung Essen, Essen, Germany. The sources of funding do not influence the study design, analyses, interpretation of results or the decision on publication.

Received: 4 March 2015 Accepted: 26 June 2015
Published online: 14 July 2015

References

1. World Health Organization, Unicef. Global Immunization Data [http://www.who.int/immunization_monitoring/Global_Immunization_Data_v2.pdf].
2. World Health Organization. Temperature sensitivity of vaccines. Department of Immunization, Vaccines and Biologicals, World Health Organization. 2006:1–62.
3. Bundesinstitut für Arzneimittel und Medizinprodukte & Paul-Ehrlich-Institut. Ausflückungen in Adsorbatimpfstoffen. Bulletin zur Arzneimittelsicherheit - Informationen aus BfArM und PEI. BfArM & PEI. 2012;12–16.
4. Weltermann BM, Markic M, Thielmann A, Gesenhues S, Hermann M. Vaccination management and vaccination errors: a representative online-survey among primary care physicians. PLoS ONE. 2014;9:e105119.
5. Centers for Disease Control and Prevention. General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2011;60:1–35.
6. Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 12th ed. Washington, DC: Public Health Foundation; 2012.
7. Salisbury D, Ramsay M, Noakes K. Immunisation against infectious disease. 3rd ed. London: TSO; 2006.
8. Australian Government: National vaccine storage guidelines. Strive for 5 [http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/IMM77-cnt]
9. Australian Government: The Australian Immunisation Handbook [http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home]
10. Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. Vaccine. 2007;25:3980–6.
11. Yakum MN, Ateudjieu J, Walter EA, Watcho P. Vaccine storage and cold chain monitoring in the North West region of Cameroon: a cross sectional study. BMC Res Notes. 2015;8:145.
12. Gazmararian JA, Oster NV, Green DC, Schuessler L, Howell K, Davis J, et al. Vaccine storage practices in primary care physician offices: assessment and intervention. Am J Prev Med. 2002;23:246–53.
13. Bailey HD, Kurinczuk JJ, Kusel MM, Plant AJ. Barriers to immunisation in general practice. Aust Nz J Publ Heal. 1999;23:6–10.
14. Bell KN, Hogue CJ, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. Pediatrics. 2001;107:e100.
15. Yuan L, Daniels S, Naus M, Brcic B. Vaccine storage and handling. Knowledge and practice in primary care physicians' offices. Can Fam Physician. 1995;41:1169.
16. Lee S, Lim H, Kim O, Nam J, Kim Y, Woo H, et al. Vaccine Storage Practices and the Effects of Education in Some Private Medical Institutions. J Prev Med Public Health. 2012;45:78–89.
17. Page SL, Earnest A, Birden H, Deaker R, Clark C. Improving vaccination cold chain in the general practice setting. Aust Fam Physician. 2008;37:892.
18. Jeremijenko A, Kelly H, Sibthorpe B, Attewell R. Improving vaccine storage in general practice refrigerators. BMJ. 1996;312:1651–2.
19. Gold MS, Martin L, Nayda CL, Kempe AE. Electronic temperature monitoring and feedback to correct adverse vaccine storage in general practice. MJA. 1999;171:83–4.
20. Lewis PR, Reimer RF, Dixon AJ. Evaluating the efficacy of vaccine storage in the general practice setting. Aust NZ J Publ H. 2001;25:547–50.
21. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362:1225–30.
22. Chojnacky M, Miller W, Ripple D, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7656). NIST. 2009;1-41.
23. Chojnacky M, Miller W, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7753): Report on Pharmaceutical Grade Refrigerator and Household Refrigerator/Freezer. NIST. 2010;1-59.
24. Gensichen J, von Korff M, Peitz M, Muth C, Beyer M, Güthlin C, et al. Case management for depression by health care assistants in small primary care practices: a cluster randomized trial. Ann Intern Med. 2009;151:369–78.
25. Wutoh R, Boren SA, Balas EA. eLearning: a review of Internet-based continuing medical education. J Contin Educ Health Prof. 2004;24:20–30.
26. Cobb SC. Internet continuing education for health care professionals: an integrative review. J Contin Educ Health Prof. 2004;24:171–80.
27. Kreuter MW, Wray RJ. Tailored and targeted health communication: strategies for enhancing information relevance. Am J Health Behav. 2003;27:227–32.
28. Oenema A, Brug J, Dijkstra A, de Weerdt I, de Vries H. Efficacy and use of an internet-delivered computer-tailored lifestyle intervention, targeting saturated fat intake, physical activity and smoking cessation: a randomized controlled trial. Ann Behav Med. 2008;35:125–35.
29. Krebs P, Prochaska JO, Rossi JS. A meta-analysis of computer-tailored interventions for health behavior change. Prev Med. 2010;51:214–21.

9.2 Publication 2

Vaccine cold chain in general practices:

A prospective study in 75 refrigerators (Keep Cool study)

Anika Thielmann, Marie-Therese Puth, Christine Kersting, Johannes Porz, Birgitta Weltermann

PLoS ONE

2019

DOI: 10.1371/journal.pone.0224972

Impact Factor (2018): 2.776

PLOS ONE

RESEARCH ARTICLE

Vaccine cold chain in general practices: A prospective study in 75 refrigerators (Keep Cool study)

Anika Thielmann[1,2]*, Marie-Therese Puth[2,3], Christine Kersting[1], Johannes Porz[2], Birgitta Weltermann[1,2]

1 Institute for General Practice, University of Duisburg-Essen, University Hospital Essen, Essen, Germany, **2** Institute of General Practice and Family Medicine, University of Bonn, Bonn, Germany, **3** Department of Medical Biometry, Informatics and Epidemiology, Faculty of Medicine, University of Bonn, Bonn, Germany

* Anika.Thielmann@ukbonn.de

OPEN ACCESS

Citation: Thielmann A, Puth M-T, Kersting C, Porz J, Weltermann B (2019) Vaccine cold chain in general practices: A prospective study in 75 refrigerators (Keep Cool study). PLoS ONE 14(11): e0224972. https://doi.org/10.1371/journal.pone.0224972

Editor: Sanjai Kumar, Food and Drug Administration, UNITED STATES

Received: January 23, 2019

Accepted: October 8, 2019

Published: November 19, 2019

Data Availability Statement: The manuscript's data cannot be shared publicly because of ethical restrictions as our data set includes potentially identifying information. Data are available from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (ethikkommission@uk-essen.de), Germany, for researchers who meet the criteria for access to confidential data.

Funding: The study received grants from Stiftung Universitätsmedizin Essen

Abstract

Introduction

Protecting vaccines from freeze damage is considered one of the most poorly addressed problems in vaccine management. Freezing may impair the potency especially of adsorbed vaccines. The Keep Cool study aims at ensuring optimal vaccine storage conditions in general practices. This publication analyses the baseline data using standardised temperature recordings.

Methods

This prospective study in German general practices analysed 7-day temperature recordings of refrigerators used for vaccine storage. Temperatures were recorded continuously using a standardised data logger with an accuracy of ±0.4 ˚C. The prevalence rates of refrigerators within the target range (2 to 8 ˚C) and of those reaching critically low temperatures (≤0 ˚C) were calculated. In addition, the cumulative time and the duration of single episodes beyond the target range were computed. To assess for structural deficits, the prevalence of refrigerators with a cycling of >5 ˚C was determined. Generalised linear mixed models were applied to analyse correlating factors between the dependent variables 'within temperature range' and 'reaching critically low temperatures' with practice characteristics.

Results

The study included 64 of 168 practices (38.1% response rate) with 75 refrigerators. The prevalence of refrigerators with temperatures within the target range was 32.0% (n = 24), and 14.7% (n = 11) reached critically low temperatures <0 ˚C. 44.0% of refrigerators (n = 33) showed temperatures >8 ˚C and 28.0% (n = 21) <2 ˚C. Of the 168 hours recorded per refrigerator, the average cumulative time >8 ˚C was 49 hours, <2 ˚C 75 hours and ≤0 ˚C 74 hours. The longest consecutive period of critically low temperatures was 168 hours (mean: 39±53). The prevalence of refrigerators with a cycling range of >5 ˚C was 29.3%.

(http://www.universitaetsmedizin.de/) to buy thermometers. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

Given the importance of immunisation, the results of our study call for action, as two-thirds of the refrigerators exhibited cold chain breaches and 15% reached critically low temperatures threatening vaccine potency.

Introduction

Immunisations are among the most effective and cost-effective public health strategies worldwide [1]. However, their effectiveness depends on adequate vaccine storage conditions. Maintaining the cold chain, i.e. a temperature range of 2 ˚C to 8 ˚C, is crucial to ensure vaccine potency [2] and tolerability [3]. In the past, cold chain breaches were suspected of causing disease outbreaks, but confirming this suspicion is difficult [4–8]. Preventing freezing is especially important to maintain the potency of adsorbed vaccines (e. g. hepatitis A, hepatitis B, tetanus, diphtheria, pertussis, pneumococcal disease) [2]. Adsorbed hepatitis B vaccines are considered the most sensitive vaccines, with a freezing threshold of -0.5 ˚C [2]. At this temperature, irreversible precipitates of aluminium-containing adsorbents begin to form which decrease the potency of the vaccines. Also, these may induce local irritation upon injection [2,3]. Furthermore, all vaccines are at risk of contamination when exposed to freezing temperatures, as hairline cracks in the pre-filled syringe can develop which are not necessarily noticeable to the human eye [9]. The World Health Organization (WHO) considers protecting vaccines from freeze damage "one of the most poorly addressed problems in vaccine management" that requires attention in order not to jeopardise disease-prevention goals. [10].

Research of the American National Institute of Standards and Technology showed that refrigerators' suitability to maintain the cold chain varies drastically depending on the type of refrigerator [11,12]. Relevant parameters are 'temperature control stability, air circulation patterns, defrost cycles, and long-term drift of the temperature set point' [11]. A crucial aspect is the technical design of the cooling compressor and its regulation based on on-off mechanisms. Purpose-built refrigerators for the storage of medical products, so-called pharmaceutical refrigerators, have several advantages compared to household models: enhanced temperature set point control, a better ventilation system, and a narrower temperature range [12]. Many household models are designed to allow different temperature zones required in food storage [13] and allow for freezing temperatures, e. g. -5 ˚C [11].

According to a systematic literature review, freezing temperature exposure occurred in approximately 33.3% of refrigerators used for vaccine storage in ten wealthier countries [14]. In our prior cross-sectional questionnaire study, 16% of German general practices self-reported experiencing cold chain breaches either as an error or near-error, and 49% lacked adequate monitoring and documentation [15,16]. The Keep Cool study aims at ensuring optimal vaccine storage conditions: after visual inspections of refrigerators used to store vaccines and a baseline temperature survey of seven days, general practices with temperature violations are offered access to a tailored online learning program [17,18].

This publication presents the baseline data of the Keep Cool study: standardised, continuous 7-day temperature data are analysed for cold chain breaches in general practices. First, we aimed to identify the prevalence of refrigerators with temperatures within the target range (2–8 ˚C). Second, we determined the prevalence of critically low temperatures ($\leq$0 ˚C) and analysed the temperature cycling ranges of refrigerators in order to assess their capacity to

maintain the cold chain. Third, associations between practice characteristics and temperature were analysed.

Methods

Study design

Details on this prospective intervention study with two temperature measurement periods have been reported elsewhere [17]. Briefly, this publication describes the baseline of the Keep Cool study, which was developed by two researchers (A.T., B.W.), formerly Institute for General Medicine, University of Duisburg-Essen, now: Institute for Family Medicine and General Practice, University of Bonn, Germany. We report about the quality of the vaccine cold chain in general practices with temperature readings over a 7-day monitoring period. Details on the quality of vaccine refrigerator management (e.g. temperature monitoring frequency, presence of a thermometer, placement of temperature probe) based on visual inspections of the refrigerators studied have been reported elsewhere [18].

Ethical approval was obtained from the Ethic Commission of the Medical Faculty of the University of Duisburg-Essen (14-6118-BO). Participants provided written informed consent.

Study population and recruitment procedure

The study was conducted in general practices affiliated with the University of Duisburg-Essen (N = 185) as teaching practices. Practices (n = 17) involved in study pre-tests were excluded. Recruitment followed a structured approach: Practices were contacted by phone and fax up to three times or until they responded. To estimate participation bias, non-participants received a short questionnaire by fax asking them to provide details on: 1) their reason for non-participation, 2) the number of refrigerators in practices including those in the recreation room, 3) the use of a thermometer, and 4) whether the temperature is monitored twice daily.

Temperature monitoring

Temperatures were measured with a data logger (testo 175T), which has an accuracy of ±0.4 ˚C within the operating range -5 ˚C to +10 ˚C (calibrated under a DIN EN ISO 9001:2008 certified quality assurance system). The device was equipped with a standard probe which measures the ambient air temperatures inside the refrigerator and the effects of door openings on refrigerator temperatures. We used continuous measurements over seven days with a logging interval of one reading per minute. Similar logging rates were used in prior studies [19–23].

In preparation for this study, we developed a protocol for the set-up of the data logger which had been piloted in a sample of 17 general practices with 21 refrigerators. In line with standards [11–13,24], the data logger was positioned in the centre of the refrigerator and placed in a plastic bin (see Fig 1). During the recording, the display of the data logger was turned off and access to its memory was locked.

Practice and physician characteristics

The following practice characteristics were obtained by questionnaire: type of practice (solo/group), number of practice team members by professional groups, patients per quarter (caseload), number of treatment rooms, thermometer in each vaccine refrigerator, vaccine spectrum offered, and selected services offered (tropical medicine and/or yellow fever, travel medicine, adolescent preventive services, paediatric preventive services and/or adolescent medicine), percentage of patients with statutory health insurance, and certified quality management. Data on the type of refrigerator used for vaccine storage were collected while setting

Fig 1. Set-up of data logger in plastic bin.

https://doi.org/10.1371/journal.pone.0224972.g001

up the data logger (pharmaceutical-grade/household refrigerator; location and insulation of ice compartment, if any).

Statistical analysis

Descriptive statistics were used to describe participating and non-participating practices for practice and physician characteristics. For the non-participant analysis, the χ^2 test was used for categorical data, and Student's t-test was used for continuous data.

The temperature readings of the 7-day monitoring period (10,080 minutes) were analysed. The first 120 minutes after each data logger set-up were excluded from analyses to allow the probe to acclimatise to the temperature of the refrigerator.

The primary outcome was the prevalence of refrigerators with temperatures within the target range (2 ˚C to 8 ˚C) for seven days. Secondary outcomes included reaching different cut-offs based on data on temperature sensitivity of the WHO [2], personal manufacturer information (GlaxoSmithKline) and systematic reviews [14,25]: <2 ˚C and >8 ˚C, >8 ˚C, <2 ˚C, ≤1 ˚C, ≤0 ˚C. In order to provide a better indication of unacceptable temperature exposure, we calculated the cumulative and consecutive time (in hours) outside the target range and beyond different cut-offs. Analyses were performed for each individual refrigerator and for the total sample using mean, standard deviation (SD) and range.

A further secondary outcome addressed the refrigerators' capacity to keep temperatures within the target range. A temperature cycling range >5.0 ˚C was considered unacceptable. Temperature ranges were analysed for each refrigerator, for the total sample and stratified by household and pharmaceutical-grade refrigerators as well as by refrigerators considered acceptable and unacceptable for vaccine storage. Acceptable refrigerators included pharmaceutical-grade, freezerless refrigerators and full-size dual-zone refrigerators/freezers with separate exterior doors, while unacceptable refrigerators included any mini refrigerators and refrigerators with an internal ice compartment [11–13].

To estimate the relationship between practice characteristics and the two dependent variables 'within temperature range (2–8 ˚C) versus outside target range' and 'reaching critically low temperatures (0 ˚C) versus within target range', we used hierarchical generalised linear mixed models (GLMM) for binomial responses with random practice-specific intercepts (to account for practices with more than one refrigerator). Independent characteristics were: type of practice (solo/group), number of patients in practice (≤1,750/ >1,750), percentage of patients with statutory health insurance, yellow fever licence (yes/no), physician trainee in practice (yes/no), certified quality management (yes/no), and the provision of paediatric preventive services and/or adolescent medicine (yes/no).

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (Armonk, NY: IBM Corp.) and R, version 3.5.1. Percentages and mean values are reported for valid cases.

The trial is registered with the German Clinical Trials Register (DRKS00006561).

Results

Practice characteristics

Of the 168 practices contacted, 64 agreed to participate (response rate: 38.1%). The mean practice size was 2.1 general practitioners (±1.2) and 5.3 medical assistants (±3.3); 59.4% (n = 38) were group practices. 51.9% (n = 27) of the practices provided medical care to up to 1,750 patients per quarter (caseload). In total, 75 refrigerators were included in this study. 14.1% (n = 9) had more than one refrigerator for the storage of vaccines. See Table 1 for details.

73 of the 104 non-participating practices provided a reason for non-participation. The most frequent reasons were (multiple responses): no time (37.0%, n = 27), no interest in topic/study participation (35.6%, n = 26), no need (11.0%, n = 8), other (Σ7, 23.3%, n = 17). The non-participant analysis showed no differences regarding key practice characteristics, except that participating practices were more likely to provide care to ≤1,750 patients per quarter (48.1% versus 68.1%, p = 0.029). See S1 Table for details.

Refrigerators and temperature recordings

Of the 75 refrigerators included, 88.0% (n = 66) were household refrigerators and 12.0% (n = 9) were pharmaceutical-grade models (see Table 1 for details). In 24 of 75 included refrigerators (32.0%), temperatures were within the target range of 2 ˚C to 8 ˚C (see Fig 2). This corresponds to 74.8% of the total measurement time. The mean temperature was 5.3 ˚C (±2.9), with readings ranging between -6.7 and +12.2 ˚C.

Based on their ability to maintain the target temperature range, refrigerators were categorised into six exclusive groups (Table 2). Refrigerators that were within the target range but had at least one temperature breach >8 ˚C (n = 28) had a mean temperature of 7.3 ˚C (±0.7) and were outside the target range 25.3% of the time. Refrigerators within the target range that had at least one temperature breach <2 ˚C (n = 17) had a mean temperature of 1.8 ˚C (±1.5) and were outside the target range 45.5% of the time. Separate data on individual refrigerators is presented in S2 Table.

Critically low temperatures ≤0 ˚C were recorded at least once in 14.7% (n = 11) of all refrigerators. This corresponds to 5.8% of the temperature recording time, i.e. the total time based on all refrigerators (mean cumulative time: 74.1 hours ±56.1). The longest consecutive time ≤0 ˚C was 39.1 hours on average (±52.9: 0.6–168.0): one refrigerator was below zero at all times (168 hours), for the other refrigerators the average cumulative time was 64.7 hours). Temperatures <2 ˚C were recorded in 28.0% (n = 21) of refrigerators, corresponding to 12.4% of the complete temperature recording time. These refrigerators had a mean of 31.6 episodes

Table 1. Characteristics of participating practices (N = 64).

	n	%*
Practice type		
Solo	26	40.6
Group	38	59.4
Staff		
Mean no. of physicians in practice ± SD [10]	2.1±1.2	
Mean no. of medical assistants ± SD [11]	5.3±3.3	
Number of treatment rooms [10]		
≤ 3	31	57.4
> 3	23	42.6
Patients per practice per quarter (caseload) [12]		
≤ 1,750	27	51.9
> 1,750	25	48.1
Percentage of patients with statutory health insurance [8]		
≤ 85%	19	33.9
> 85%	37	66.1
Certified quality management [15]	14	28.6
Physician qualifications		
Travel medicine [10]	12	22.2
Tropical medicine and/or yellow fever license [10]	7	13.0
Services offered [10]		
Paediatric preventive services and/or adolescent medicine	22	40.7
Adolescent preventive services	44	81.5
Practice vaccine spectrum [10]		
Mean no. of vaccines ±SD	17.9±1.8	
Tetanus	54	100.0
Diphtheria	54	100.0
Pertussis	54	100.0
Influenza	54	100.0
Pneumococcal disease	54	100.0
Hepatitis A	54	100.0
Measles	54	100.0
Poliomyelitis	53	98.1
Hepatitis B	53	98.1
Tick-borne encephalitis	53	98.1
Rubella	53	98.1
Mumps	53	98.1
Meningococcal disease	52	96.3
Typhus	50	92.6
Varicella	50	92.6
Rabies	46	85.2
Human papilloma	44	81.5
Haemophilus influenzae b	41	75.9
Cholera	26	48.1
Rotavirus	14	25.9
Refrigerator type (n = 75)		
Pharmaceutical grade	9	12.0
Household model	66	88.0
Freezerless refrigerator	30	47.0

(*Continued*)

Table 1. (Continued)

	n	%*
Refrigerator with internal ice compartment (one exterior door)	31	45.5
Refrigerator with internal non-insulated ice compartment (one exterior door)	2	3.0
Full-size dual-zone refrigerator/freezer (separate exterior doors)	2	3.0
Unclear	1	1.5

*valid percentages

[missing values]

https://doi.org/10.1371/journal.pone.0224972.t001

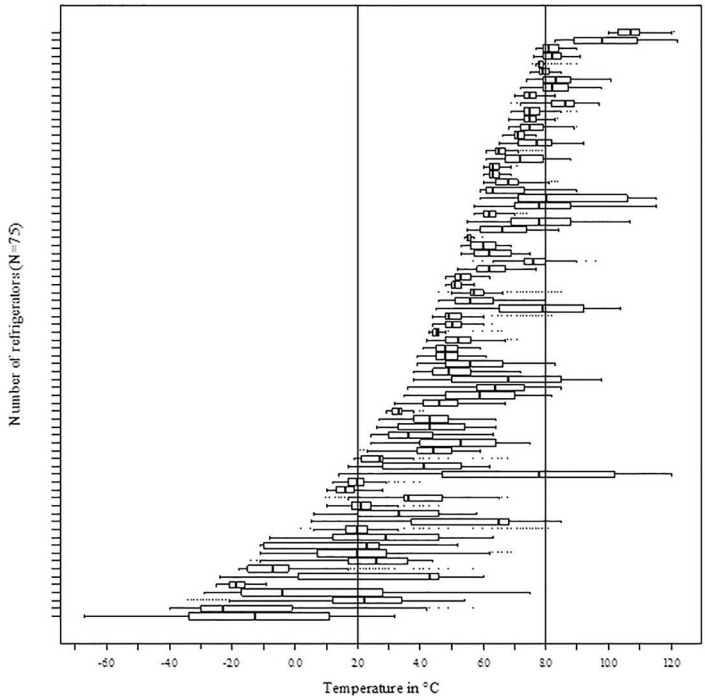

Fig 2. Temperature ranges per refrigerator (N = 75).

https://doi.org/10.1371/journal.pone.0224972.g002

Table 2. Refrigerators categorised according to their ability to maintain the target temperature range, i.e. 2 to 8 ˚C (N = 75).

	No. of refrigerators (n = 75)		Target range		Temperature			
	n	%	% inside	% outside	mean±SD on average	min-max of all means	mean of all ranges	min-max of all ranges
Within target range but at least once >8 ˚C	28	37.3	74.7	25.3	7.3±0.7	5.1–8.8	3.5	1.3–6.0
Always within target range	24	32.0	100.0	0.0	5.2±0.5	3.3–6.6	2.4	0.7–5.1
Within target range but at least once <2 ˚C	17	22.7	54.5	45.5	1.8±1.5	-1.2–4.0	6.5	1.8–10.4
Always >8 ˚C	2	2.7	0.0	100.0	10.3±0.8	9.9–10.7	3.0	2.1–3.9
<2 ˚, in target range, >8 ˚C	3	4.0	64.4	35.6	5.0±2.0	2.0–7.5	8.8	7.9–10.6
Always <2 ˚C	1	1.3	0.0	100.0	-1.8±0.4	n/a	2.6	n/a

Mean and SD refer to row n

https://doi.org/10.1371/journal.pone.0224972.t002

(±36.3: 1–142) below <2 ˚C with an average duration of 18.7 hours (±41.0: 12 min to 168 hours). Further temperature cut-offs are presented in Table 3. On average, the target temperature range (8 ˚C) was exceeded for 48.6 hours (±51.4). This accounts for 12.7% of the total study. See Table 3 for details.

Structural characteristics: Cycling range of refrigerators

In 29.3% (n = 22) of refrigerators, temperature cycling was >5 ˚C. Cycling ranges ≤3.0 ˚C were recorded in 45.3% (n = 34), >3.0 to ≤4.0 ˚C in 17.3% (n = 13), >4 ˚C in 37.3% (n = 28) and >6 ˚C in 17.3% (n = 13). Of the 22 refrigerators with cycling ranges >5 ˚C, only one refrigerator maintained the cold chain. In comparison, in refrigerators with cycling ranges ≤5 ˚C, 43.4% (n = 23) maintained the cold chain and 56.6% (n = 30) had cold chain breaches. Refrigerators varied with regard to the range of temperature cycling during the day and over the course of the 7-day monitoring period. Fig 3 shows typical temperature curves encountered. The overall mean temperature range was 4.0 ˚C (±2.5), with readings ranging between 0.7 to 10.6 ˚C.

The mean temperature in pharmaceutical refrigerators (n = 9) was 5.3 ˚C (±1.1: 4.3 to 7.9 ˚C) with a mean temperature range of 3.1 (±1.5: 0.7 to 5.9 ˚C). In comparison, the mean temperature in household refrigerators (n = 66) was 5.3 ˚C (±2.8: -1.8 to 10.7 ˚C) with a mean temperature range of 4.1 (±2.6: 1.0 to 10.6 ˚C).

Associations between temperature outcomes and practice characteristics

Analysis using the GLMM showed no significant associations between both dependent variables (within temperature range, critically low temperature) and the independent variables considered.

Discussion

Of the 75 refrigerators analysed, only 32% maintained the vaccine cold chain. However, 68% were beyond the target range and 15% reached a critically low temperature of 0 ˚C. We found that continuous freezing temperature exposure lasted longer than one day on average (39 hours) with a longest episode of seven days recorded. These data suggest that freeze damage likely occurred.

In line with the systematic review of freezing temperatures by Hanson [14] to assess whether freezing remains an ongoing issue, we cannot answer the question regarding the number of vaccines that were actually damaged or had reduced immunogenicity. Nevertheless, there is a link between disease outbreak and temperature excursions below the freezing threshold for hepatitis B [26] and pertussis [4]. In our practice sample, more than 98% store hepatitis B vaccines. Thus, until thermostable vaccines are available or freeze-free technologies are used across all practices, freeze prevention requires close attention.

To ensure the cold chain, two components need to be fulfilled: 1) structural component with a cycling range below 5 ˚C and 2) continuous refrigerator management targeting for a mean temperature of +5 ˚C. In 29% of refrigerators, cycling ranges exceeded the cut-off of 5 ˚C and thus constituted a major barrier for successful cold-chain maintenance. Interestingly, even in refrigerators with narrower temperature ranges, about 60% failed to maintain the cold chain, indicating procedural deficits.

In line with prior studies, our observations in the practices during the study conduct shed an interesting light on key influencing factors. Practices did not have adequate temperature monitoring rigor (i. e., a suitable thermometer, monitoring at least twice daily), which is a significant predictor of noticing critical temperatures [18,25]. Overall, knowledge and problem

Table 3. Overview of temperature recordings based on different cut-offs (N = 75).

Cut-offs	No. of refrigerators (n = 75)[+]		Cumulative time (in hours)			No. of episodes		Duration of episodes (in hours)		Longest consecutive time (in hours)	
	n	%	mean±SD on average	study total[*]	% of study total[#]	mean±SD on average	min-max of all means	mean±SD on average	min-max of all means	mean±SD on average	min-max of all means
Above target range											
>8 ˚C	33	44.0	48.6±51.4	1,605.4	12.7	39.5± 42.3	1–145	11.3±40.4	0.1–168.0	17.7±41.9	0.1–168.0
Below target range											
<2 ˚C	21	28.0	74.5±52.3	1,565.5	12.4	31.6±36.3	1–142	18.7±41.0	0.2–168.0	34.1±50.9	0.3–168.0
≤1 ˚C	17	22.7	57.7±58.8	981.7	7.8	16.6±17.9	1–55	19.5±42.9	0.1–168.0	27.2±46.7	0.1–168.0
≤0 ˚C	11	14.7	74.1±56.1	815.1	6.5	14.7±15.8	1–45	28.8±51.4	0.4–168.0	39.1±52.9	0.6–168.0
≤-0.5 ˚C	11	14.7	74.1±55.4	729.8	5.8	12.2±13.2	1–45	27.8±50.8	0.2–166.1	36.4±52.9	0.3–166.1
≤-3.0 ˚C	3	4.0	33.5±28.6	100.4	0.8	20.7±21.4	2–44	1.5±1.4	0.3–3.0	4.8±5.6	0.5–11.1

All values refer to row n

[+]Of the 51 refrigerators with temperatures beyond the target range, n = 3 had temperatures below and above the target range. For this reason, numbers do not add up to 100%.

[#]Refers to the percentage of the study total time based on 75*168h.

https://doi.org/10.1371/journal.pone.0224972.t003

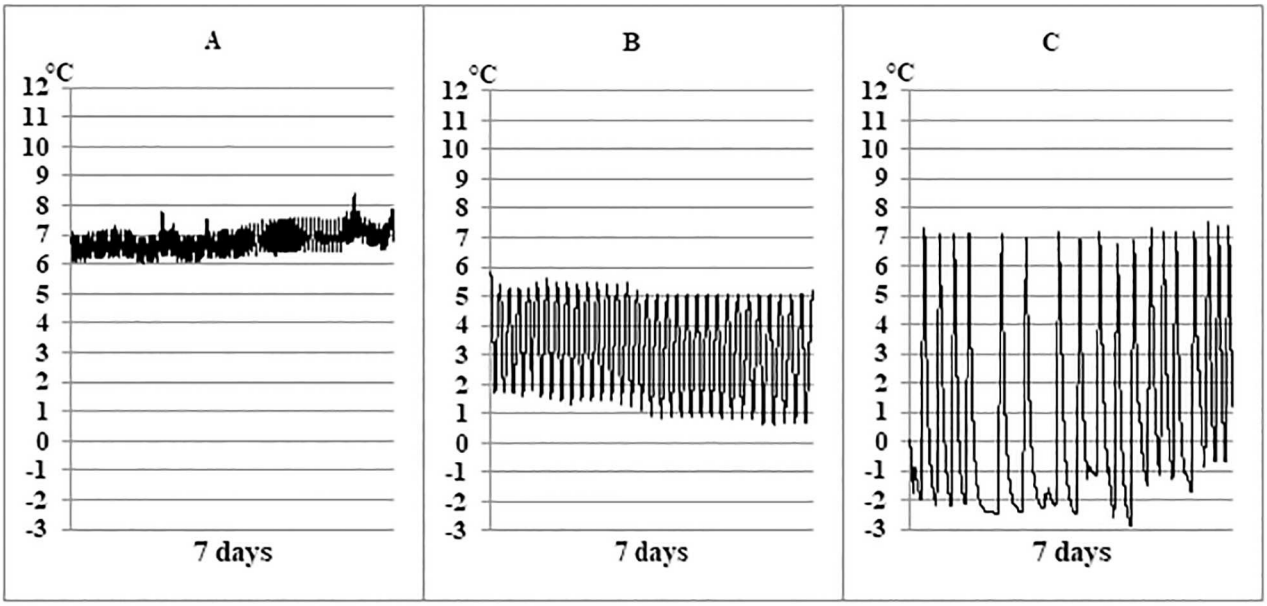

Fig 3. Examples of temperature recordings in three different refrigerators. All data were recorded at 1-minute intervals over 7 days. The graphs illustrate common problems regarding temperature cycling range and mean temperature: A: an adequate cycling range of 3˚C with a too-high mean temperature at approx. 7˚C; B: a cycling range of 5.5˚C with a too-low mean temperature at approx. 3.5˚C; C: a too-high cycling range of 10˚C and a too-low mean temperature at approx. 2˚C.

https://doi.org/10.1371/journal.pone.0224972.g003

awareness deficits prevailed, which is known from other countries [19–21,27]. For instance, physicians and medical assistants expressed astonishment with regard to the encountered temperature ranges when shown the temperature curves of their refrigerators. With the exception of door opening times, most participants expected rather stable temperatures, as they were unaware of the construction-based cycling of refrigerators. In practices affected by freezing temperature exposure, we even encountered disbelief ('your thermometer is broken'). There was a general belief that freezing temperatures would be noticed in the form of frozen vaccines. Frequently, constant fluctuations between freezing and thawing were never considered before. Misshapen cardboard packaging due to thawing ice (two practices) and thick ice walls (one practice) went unnoticed (for details see Thielmann et al.) [18].

Limitation

All participating practices are members of a teaching practice network. A potential selection bias can be excluded as we showed in a prior study that the practice sample is representative for general practices in Germany [28]. In order to assess participation bias, we conducted a thorough non-responder analysis. For financial reasons, we used a standard air probe to measure temperature. In contrast to that, a slow-reacting glycol probe resembles the temperature changes of the vaccine vials. Given the accuracy, all measured temperature values are within ±0.4 ˚C of the true value.

Conclusion

The prevalence of refrigerators with cold chain breaches and critically low temperatures is high, which emphasises the need for an intervention aimed at adequate vaccine storage. Risk communication should address the dangers associated with too cold temperatures and

refrigerators' temperature cycling issues. Furthermore, greater attention needs to be paid to structural and procedural best practices in vaccine storage that are used as a safeguard against temperature excursions.

Supporting information

S1 Table. Characteristics of participating practices (N = 64).
(DOCX)

S2 Table. Temperature recordings per refrigerator (N = 75).
(DOCX)

Acknowledgments

We would like to thank all general practices of the University of Duisburg-Essen who participated in the study. We also wish to thank Kim Steiner who conducted practice visits and helped with the data entry.

Author Contributions

Conceptualization: Anika Thielmann, Birgitta Weltermann.

Data curation: Anika Thielmann.

Formal analysis: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

Funding acquisition: Anika Thielmann, Birgitta Weltermann.

Investigation: Anika Thielmann, Christine Kersting, Johannes Porz.

Methodology: Anika Thielmann, Christine Kersting, Birgitta Weltermann.

Project administration: Anika Thielmann, Johannes Porz.

Resources: Anika Thielmann, Birgitta Weltermann.

Software: Anika Thielmann, Marie-Therese Puth.

Supervision: Birgitta Weltermann.

Validation: Anika Thielmann, Marie-Therese Puth.

Visualization: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

Writing – original draft: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

Writing – review & editing: Anika Thielmann, Birgitta Weltermann.

References

1. World Health Organization, Unicef. Global Immunization Data; 2013. http://www.who.int/immunization_monitoring/Global_Immunization_Data_v2.pdf. Accessed 17 January 2014.
2. World Health Organization. Temperature sensitivity of vaccines. Department of Immunization, Vaccines and Biologicals, World Health Organization. 2006: 1–62.
3. Paul-Ehrlich-Institut. Ausflückungen in Adsorbatimpfstoffen. Bulletin zur Arzneimittelsicherheit—Informationen aus BfArM und PEI; 2012: 12–16.
4. McColloster P, Vallbona C. Graphic-output temperature data loggers for monitoring vaccine refrigeration: implications for pertussis. Am J Public Health. 2011; 101: 46–47. https://doi.org/10.2105/AJPH.2009.179853 PMID: 21088272
5. Lerman SJ, Gold E. Measles in children previously vaccinated against measles. JAMA. 1971; 216: 1311–1314. PMID: 4102807

6. Onoja AL, Adu FD, Tomori O. Evaluation of measles vaccination programme conducted in two separate health centres. Vaccine. 1992; 10: 49–52. https://doi.org/10.1016/0264-410x(92)90419-k PMID: 1539460
7. Boros CA, Hanlon M, Gold MS, Roberton DM. Storage at− 3 C for 24 h alters the immunogenicity of pertussis vaccines. Vaccine. 2001; 19: 3537–3542. https://doi.org/10.1016/s0264-410x(01)00063-9 PMID: 11348721
8. McIntyre RC, Preblud SR, Polloi A, Korean M. Measles and measles vaccine efficacy in a remote island population. Bull World Health Organ. 1982; 60: 767. PMID: 6983927
9. Salisbury D, Ramsay M, Noakes K. Immunisation against infectious disease. 3rd ed. London: TSO; 2006.
10. World Health Organization. Aide mémoire for prevention of freeze damage to vaccines. WHO/IVB/07.09. Geneva; 2007.
11. Chojnacky M, Miller W, Ripple D, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7656); 2009.
12. Chojnacky M, Miller W, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7753). Report on Pharmaceutical Grade Refrigerator and Household Refrigerator/Freezer; 2010.
13. Center for Disease Control. National Center for Immunization and Respiratory Diseases. Vaccine Storage & Handling Toolkit: Centers for Disease Control and Prevention; 2018.
14. Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. Vaccine. 2017; 35: 2127–2133. https://doi.org/10.1016/j.vaccine.2016.09.070 PMID: 28364920
15. Thielmann A, Sikora M, Schnell U, Gesenhues S, Weltermann B. Impfkühlschrank-und Impfstoffmanagement in Hausarztpraxen: Eine repräsentative, Web-basierte Umfrage unter Hausärzten (Keep Cool I). Das Gesundheitswesen. 2015; 38: 1–6.
16. Weltermann BM, Markic M, Thielmann A, Gesenhues S, Hermann M. Vaccination Management and Vaccination Errors: A Representative Online-Survey among Primary Care Physicians. PloS one. 2014; 9: e105119. https://doi.org/10.1371/journal.pone.0105119 PMID: 25118779
17. Thielmann A, Viehmann A, Weltermann BM. Effectiveness of a web-based education program to improve vaccine storage conditions in primary care (Keep Cool): study protocol for a randomized controlled trial. Trials. 2015; 16. https://doi.org/10.1186/s13063-015-0824-9 PMID: 26169675
18. Thielmann A, Puth M-T, Weltermann B. Visual inspection of vaccine storage conditions in general practices:. A cross-sectional study of 75 vaccine refrigerators (Keep Cool study). PloS one: in Revision.
19. Gazmararian JA, Oster NV, Green DC, Schuessler L, Howell K, Davis J, et al. Vaccine storage practices in primary care physician offices: assessment and intervention. Am J Prev Med. 2002; 23: 246–253. https://doi.org/10.1016/s0749-3797(02)00512-3 PMID: 12406478
20. Bell KN, Hogue C, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. Pediatrics. 2001; 107: e100. https://doi.org/10.1542/peds.107.6.e100 PMID: 11389298
21. Page SL, Earnest A, Birden H, Deaker R, Clark C. Improving vaccination cold chain in the general practice setting. Aust Fam Physician. 2008; 37: 892. PMID: 19002316
22. Gold MS, Martin L, Nayda CL, Kempe. Electronic temperature monitoring and feedback to correct adverse vaccine storage in general practice. MJA. 1999; 171: 83–84. PMID: 10474583
23. Lewis PR, Reimer RF, Dixon AJ. Evaluating the efficacy of vaccine storage in the general practice setting. Aust N Z J Public Health. 2001; 25: 547–550. https://doi.org/10.1111/j.1467-842x.2001.tb00322.x PMID: 11824993
24. Australian Government. National vaccine storage guidelines. Strive for 5. 2nd ed. Canberra: Dept. of Health and Ageing; 2013.
25. Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. Vaccine. 2007; 25: 3980–3986. https://doi.org/10.1016/j.vaccine.2007.02.052 PMID: 17382434
26. Davaalkham D, Ojima T, Wiersma S, Lkhagvasuren T, Nymadawa P, Uehara R, et al. Administration of hepatitis B vaccine in winter as a significant predictor of the poor effectiveness of vaccination in rural Mongolia: evidence from a nationwide survey. J Epidemiol Community Health. 2007; 61: 578–584. https://doi.org/10.1136/jech.2006.051375 PMID: 17568048
27. Lee S, Lim H-S, Kim O, Nam J, Kim Y, Woo H, et al. Vaccine Storage Practices and the Effects of Education in Some Private Medical Institutions. J Prev Med Public Health. 2012; 45: 78–89. https://doi.org/10.3961/jpmph.2012.45.2.78 PMID: 22509448

28. Viehmann A, Thielmann A, Gesenhues S, Weltermann BM. Repräsentieren akademische Hausarztpraxen die hausärztliche Regelversorgung. Eine methodische Annäherung. Do Academic Family Practices Reflect Routine Primary Care? A Methodological Approach. Z Allg Med. 2014; 90: 354–359.

9.3 Publication 3

Visual inspection of vaccine storage conditions in general practices:

A study of 75 vaccine refrigerators

Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann

PLoS ONE

2019

DOI: 10.1371/journal.pone.0225764

Impact Factor (2018): 2.776

PLOS ONE

RESEARCH ARTICLE

Visual inspection of vaccine storage conditions in general practices: A study of 75 vaccine refrigerators

Anika Thielmann[1,2]*, **Marie-Therese Puth**[2,3], **Birgitta Weltermann**[1,2]

1 Institute for General Practice, University of Duisburg-Essen, University Hospital Essen, Essen, Germany, **2** Institute of General Practice and Family Medicine, University of Bonn, Bonn, Germany, **3** Department of Medical Biometry, Informatics and Epidemiology, Faculty of Medicine, University of Bonn, Bonn, Germany

* Anika.Thielmann@ukbonn.de

OPEN ACCESS

Citation: Thielmann A, Puth M-T, Weltermann B (2019) Visual inspection of vaccine storage conditions in general practices: A study of 75 vaccine refrigerators. PLoS ONE 14(12): e0225764. https://doi.org/10.1371/journal.pone.0225764

Editor: Abhijit P. Pakhare, All India Institute of Medical Sciences Bhopal, INDIA

Received: May 10, 2019

Accepted: November 12, 2019

Published: December 3, 2019

Data Availability Statement: The manuscript's data cannot be shared publicly because of ethical restrictions as our data set includes potentially identifying information. Data are available from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (ethikkommission@uk-essen.de), Germany, for researchers who meet the criteria for access to confidential data.

Funding: The study received funding from Stiftung Universitätsmedizin Essen (http://www.

Abstract

Introduction

Adequate vaccine storage is a prerequisite to assure vaccine effectiveness and tolerability. In this context, maintaining the cold chain (2˚C to 8˚C) is the paramount objective. To establish quality-ensured cold chain maintenance, compliance with several structural and procedural aspects is necessary.

Main objective

The aim of this publication is to assess the quality of vaccine refrigerator management in general practices.

Methods

This study describes baseline results of an intervention study. To evaluate the quality of vaccine refrigerator management, visual inspections were conducted of refrigerators used to store vaccines in general practices of a German teaching practice network. The study instrument was a checklist with ten quality criteria based on international best practices for vaccine storage. A data logger recorded refrigerator temperatures for 7 days. We analyzed associations between reaching more than half (6+) of the ten quality criteria and temperature data.

Results

The study included 64 of 168 practices (38.1% response rate) with 75 refrigerators. No practice fulfilled all 10 quality criteria. On average, 4.7 (standard deviation = 1.9) criteria were met. The most frequent deficits were: no drawers/bins/baskets for vaccines (81.3%), no temperature logbook near refrigerator (75.0%), no temperature recording device in the center of the refrigerator (54.0%), vaccines boxes with contact to outer walls (46.3%), and refrigerator unsuitable for vaccine storage (44.6%). Refrigerators with better management (≥6

universitaetsmedizin.de). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

quality criteria) were more likely to have temperatures in the target range (62.5% vs. 27.5%, p = 0.008).

Conclusion

We identified a large number of avoidable vaccine storage errors. Effective strategies, e.g. web-based programs, to improve vaccine storage conditions in general practices are needed.

Introduction

Adequate vaccine storage is a prerequisite to assure the effectiveness and tolerability of vaccines [1,2]. Maintaining a continuous cold chain between +2 and +8˚C is of utmost importance as the thermostability of vaccines varies considerably [1]. Freeze exposure is especially dangerous to adsorbed vaccines (e.g. hepatitis A, hepatitis B, tetanus, diphtheria, pertussis, pneumococcal disease), as the aluminum-containing adsorbents form irreversible precipitates which decrease vaccine potency and may induce local irritation upon injection [1,2]. Adsorbed hepatitis B vaccines are considered the most sensitive vaccines, with a freezing threshold of -0.5˚C [1]. Also, heat exposure has a negative cumulative effect on vaccine potency [1]. For instance, pertussis vaccine is stable for 2 weeks at 20–25˚C, for one week at 37˚C, and loses 10% or more per day at >45˚C [1]. Overall, the World Health Organization (WHO) considers protecting vaccines from freeze damage "one of the most poorly addressed problems in vaccine management" that requires attention in order to not jeopardize disease-prevention goals [3].

A recent systematic review focusing on freezing temperatures showed that vaccine exposure to freezing temperatures is an ongoing issue even in wealthier countries [4] where detailed recommendations and guidelines exist [5–10]. Best practices to store vaccines at recommended temperatures require compliance with a number of structural and procedural aspects, ranging from refrigerator and thermometer equipment, temperature monitoring, storage procedures to the assignment of responsibilities [5,6,8–10]. In Germany, refrigerator management for laboratories and pharmacies is subject to quality management regulations [11], yet this is not the case for the primary care sector, where the majority of patients are vaccinated. Primary care is provided in privately owned general and pediatric practices who serve patients insured by statutory and private health insurance funds.

Many studies assessing vaccine storage practices rely on checklists, which are used as a self-administered tool or by third-party visual inspections combined with interviews [7,12–21]. These checklists are less prone to bias and are now considered standard procedures in quality management. The most frequently reported deficits from these studies were a lack of any type of thermometer (6.9% to 91.9%) [7,13–17,19], lack of a temperature logbook (26% to 94%) [13,15,19], lack of at least daily monitoring and recording (7.9% to 90.5%) [13,18], lack of regular thermometer checks (80%) [13,14], storing vaccines in door shelves (20.3% to 72.7%) [7,14,19], and storing items other than vaccines (3.6% to 96.3%) [7,12–15]. In 2014, an online-based survey among a random sample of German primary care physicians identified several vaccine storage deficits [22]. In response to the deficits, the Keep Cool study was initiated with the aim of ensuring good vaccine storage conditions. The Keep Cool intervention study consisted of three parts: after a baseline temperature survey of seven days (part one), general practices with temperature deficits were offered access to an online learning program (part two)

[23] and were followed up seven weeks later [24]. This publication describes the baseline data of the Keep Cool study focusing on the quality of vaccine refrigerator management assessed in checklist-based direct observations of refrigerators.

Material and methods

Study design

The Keep Cool study is a prospective intervention study with two temperature measurement periods addressing vaccine cold chain management in primary care practices in Germany. The study protocol has been previously published [24]. The main objective is to improve vaccine storage conditions in German primary care practices. The primary outcome is the number of refrigerators with temperatures within the target range (2˚C to 8˚C) for seven days [23]. This manuscript presents the results for one of the secondary outcomes, namely the quality of vaccine refrigerator management as assessed by direct visual observations using a checklist. The primary outcome was the quality of vaccine refrigerator management based on reaching ten defined quality criteria. Ethical approval was obtained from the Ethic Commission of the Medical Faculty of the University of Duisburg-Essen (14-6118-BO). Participants provided written informed consent.

Study population and recruitment procedure

The study invited all general practices of the teaching practice network associated with the University of Duisburg-Essen, Germany (N = 185). Practices (n = 17) involved in the study pre-tests (see 2.3.) were excluded, yielding a study population of 168 practices. Practices were recruited via email, fax and telephone. Practices not interested in participation received a short questionnaire via fax to allow for a non-participant analysis. Recruitment took place between January 2018 and August 2018.

Development of the study instrument

As detailed guidelines or recommendations on vaccine storage are lacking in Germany, we reviewed recommendations and guidelines of comparable Western nations (United Kingdom, Australia, the United States Scotland, and Canada) to derive best practices for our setting [5,6,8–10]. Various structural and procedural aspects were identified and categorized into five core issues: 1) refrigerator, 2) temperature, 3) storage, 4) monitoring, and 5) responsibilities. For each core issue, quality criteria were derived from the literature. Individual aspects within these core issues that were included in several guidelines or relevant for the German setting were considered best practice. The criteria were subsequently used to develop a 10-item checklist which was compared and refined using checklists from eleven previous studies [7,12–19]. Items which were considered irrelevant for the German setting, e.g. storage in cool boxes, were not included. Because the checklists were embedded in the Keep Cool intervention study, items (e.g., designated responsibilities, frequency of resetting minimum-maximum thermometers, age of refrigerator) requiring enquiry beyond a visual inspection of the refrigerator were omitted to prevent an intervention bias. The instrument was finalized after a critical review by two general practice academics as regarded their relevance for the German primary care setting. In a pre-test with 21 refrigerators from 17 general practices of the network, we evaluated the feasibility of the study instrument and the practice visits. Data were collected by one of the research team members. Pre-testing lasted until data saturation occurred, i.e. no new aspects with regard to vaccine storage appeared. Answer keys were refined on the basis of the results of each pre-test. The final checklist consisted of 10 items and allowed for the recording of

further observations (see Tables 1 and S1 for the original German version and S2 Table for the English translation). Based on scoring on the checklist items, a sum score was computed. We defined "good refrigerator management" as scoring positive on all 10 of 10 items.

Data collection

Practice visits for data collection were conducted by the same researcher who had been involved in the pre-tests. The checklist was completed by means of a visual inspection while setting up data loggers to monitor the temperature for seven consecutive days. The checklist was completed immediately after each practice visit to prevent recall and intervention bias.

Temperatures were measured with a data logger (testo 175T, accuracy of ±0.4˚C). We used continuous measurements over seven days at a logging interval of one reading every minute. According to standards [6,8,25,26], the data logger was positioned in the center of the refrigerator and placed in a plastic bin. The display was turned off and access to its memory was locked.

Data from the university teaching practice database were used to analyze associations between vaccine storage criteria and practice characteristics: type of practice (solo/group), number of practice team members differentiated by professional groups, practice size/caseload (patients per quarter), certified quality management, number of treatment rooms, thermometer in each vaccine refrigerator, vaccine spectrum offered, selected services offered (tropical medicine and/or yellow fever, travel medicine, adolescent preventive services, pediatric preventive services and/or adolescent medicine), and percentage of patients with statutory health insurance.

Statistical analysis

To compare practices that participated in the study with those that did not (non-participants) for practice and physician characteristics, the χ^2 test for categorical data and Student's t-test for continuous data were used. Descriptive statistics were performed on an item level for all checklist items, including the quality criteria, and for the sum of quality criteria met. The latter was described for a) the total sample, b) refrigerators that continuously maintained the cold chain (2˚C to 8˚C), and c) refrigerators that reached critically low temperatures (≤0˚C). For temperature data, readings of the 7-day monitoring period (10,080 minutes) were analyzed. The first 120 minutes after setting up each data logger were excluded from the analyses to allow the probe to acclimatize to the temperature of the refrigerator.

To analyze the association between practice characteristics and vaccine storage conditions, we used hierarchical generalized linear mixed models (GLMM) for binomial responses with random, practice-specific intercepts (to account for practices with more than one refrigerator). The sum score was dichotomized based on reaching more than half (6+) of the quality criteria. Independent characteristics were: type of practice (solo/group), number of patients in practice (≤1,750/ >1,750), percentage of patients with statutory health insurance, yellow fever license (yes/no), certified quality management (yes/no), and the provision of pediatric preventive services and/or adolescent medicine (yes/no).

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (Armonk, NY: IBM Corp.) and R, version 3.5.2. Percentages and mean values are reported for valid cases. Statistical significance was assigned at a level of $p<0.05$.

The trial is registered with the German Clinical Trials Register (DRKS00006561).

Table 1. Quality indicator 'good refrigerator management' (10 items).

Item	Description	Governmental source
Refrigerator	1. Type of refrigerator suitable for vaccine storage	[6,8,10,25,26]
Temperature	2. Thermometer allows for digital minimum-maximum recording	[5,6,9,10]
	3. Temperature probe/thermometer in center of refrigerator	[6,8–10]
Monitoring	4. Temperature logbook visible near refrigerator	[5,6,8–10]
Storage	5. No vaccines stored on door shelves	[6,8–10]
	6. No food and no biomaterial stored	[5,6,8–10]
	7. All vaccines kept in original cardboard wrapping	[5,6,8–10]
	8. All vaccine boxes without contact to outer walls	[5,6,8–10]
	9. All vaccines in bins/baskets/separated shelves	[6,8,10]
	10. No overstocking (i.e., enough space between boxes)	[5,6,8–10]

https://doi.org/10.1371/journal.pone.0225764.t001

Results

Practice characteristics

Of the 168 practices invited, 64 agreed to participate (response rate: 38.1%). The non-participant analysis did not show differences regarding key characteristics, except that participants less frequently provided care to >1,750 patients per quarter (48.1% versus 68.1%, p = 0.029). See S3 Table for details.

Table 2 lists characteristics of participating practices. In total, 75 refrigerators were included in this study. 14.1% (n = 9) of the practices had more than one refrigerator for storing vaccines (eight practices had two refrigerators, one practice four refrigerators).

Description of refrigerator management

No practice had 'good refrigerator management', defined as meeting all ten quality criteria (see Fig 1). On average, refrigerators met 4.7 (SD = 1.9) criteria. See Fig 2 and Table 3 for an overview of the individual criteria. Refrigerators that continuously maintained the cold chain (n = 24) met 5.6 (SD = 2.3) items on average, and refrigerators with temperatures ≤0˚C (n = 11) met 4.2 (SD = 1.4) items. Of all refrigerators that continuously maintained the cold chain, 62.5% (n = 15) met at least six of the quality criteria, compared to 27.5% (n = 14) of refrigerators with temperatures outside the cold chain (p = 0.008). At least six criteria were reached by 11.1% (n = 2) of refrigerators with temperatures <2˚C and 18.2% (n = 2) of refrigerators that reached temperatures ≤0˚C, respectively.

Type of refrigerator used

Nine practices had purpose-built refrigerators for pharmaceuticals (12%), while the remaining used household refrigerators (n = 66; 88.0%) (Table 3). Of the household refrigerators, 50.8% (n = 33, n = 1 missing) were unsuitable for vaccine storage: 93.9% (n = 31) had an internal ice compartment with a less insulated separate door beyond the main exterior door, and two refrigerators had a non-insulated ice compartment without an extra door (6.1%).

Type of thermometer used

Any type of functioning thermometer was absent in 26.7% (n = 20) of the refrigerators (see Table 3 for an overview of the thermometers used). Three thermometers were defective according to physicians or practice assistants, and one was placed next to the refrigerator. A thermometer that allowed for digital minimum-maximum recording or better was lacking in

Table 2. Characteristics of participating practices (N = 64).

	n	%*
Practice type, group	38	59.4
Mean no. of physicians in practice ± SD (10)	2.1±1.2	
Mean no. of medical assistants ± SD (11)	5.3±3.3	
Number of treatment rooms, ≤ 3 (10)	31	57.4
Patients per practice per quarter (caseload), ≤ 1,750 (12)	27	51.9
Percentage of patients with statutory health insurance, > 85% (8)	37	66.1
Certified quality management (15)	14	28.6
Physician qualifications (at least 1 physician in practice):		
Travel medicine (10)	12	22.2
Tropical medicine and/or yellow fever license (10)	7	13.0
Services offered (10)		
Pediatric preventive services and/or adolescent medicine	22	40.7
Adolescent preventive services	44	81.5
Practice vaccine spectrum (10)		
Mean no. of vaccines ±SD	17.9±1.8	
Tetanus	54	100.0
Diphtheria	54	100.0
Pertussis	54	100.0
Influenza	54	100.0
Pneumococcal disease	54	100.0
Hepatitis A	54	100.0
Measles	54	100.0
Poliomyelitis	53	98.1
Hepatitis B	53	98.1
Tick-borne encephalitis	53	98.1
Rubella	53	98.1
Mumps	53	98.1
Meningococcal disease	52	96.3
Typhus	50	92.6
Varicella	50	92.6
Rabies	46	85.2
Human papilloma	44	81.5
Haemophilus influenzae B	41	75.9
Cholera	26	48.1
Rotavirus	14	25.9

*valid percentages

(missing values)

SD = standard deviation

https://doi.org/10.1371/journal.pone.0225764.t002

36.5% (n = 19) of refrigerators. Two refrigerators were equipped with two thermometers each. Three thermometers allowed remote control and one was a data logger.

Storage of food and biomaterial

Food or biomaterial was stored in 20.3% (n = 14) of the refrigerators alongside vaccines (Table 3). Of these, food was stored in 71.4% (n = 10), most frequently water, soft drinks, milk and bread spreads (meat and cheese). We also found sparkling wine, fresh cherries and

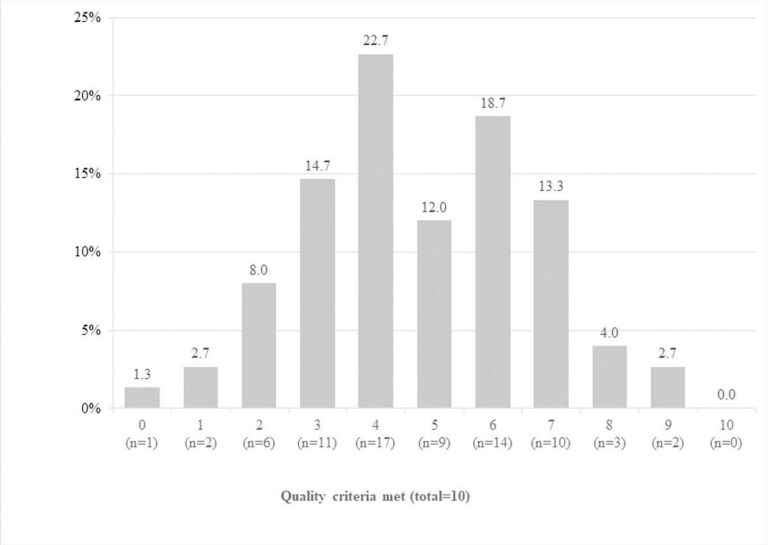

Fig 1. Frequencies for meeting the 10 quality criteria for 'good refrigerator management' (N = 75).

https://doi.org/10.1371/journal.pone.0225764.g001

yoghurt. One practice used half of the refrigerator's volume for the storage of foodstuffs (inside plastic tubs without lids). Drinks were usually stored in the door.

Placement of temperature probe/thermometer

In 54.0% (n = 27, 25 missings) of refrigerators a temperature probe/thermometer was not integrated or not placed in the center: 40.4% (n = 21) of the probes/thermometers had contact with external walls, 52.4% (n = 11) of these with the back wall. In six pharmaceutical-grade refrigerators, the probe was permanently installed. In one refrigerator, the thermometer was in the door shelf below the plastic container for eggs.

Storage in original cardboard wrapping

In 31.1% (n = 23) of the refrigerators, not all vaccines were stored in their original cardboard wrapping (Table 3). Vaccines were systematically unpacked in ten refrigerators; most of the time this concerned the same types of vaccines (e.g. influenza). In six practices, vaccines were removed from their cardboard wrapping and stored in their plastic container.

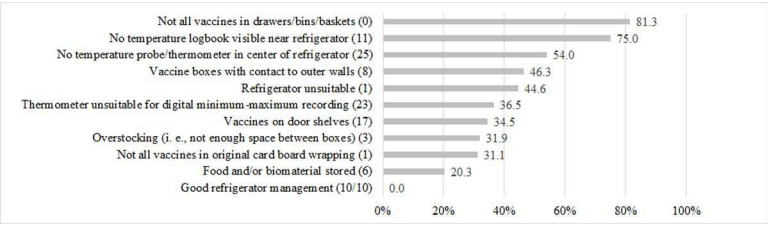

Fig 2. Frequencies for the 10 quality criteria for 'good refrigerator management' (N = 75). (missing values).

https://doi.org/10.1371/journal.pone.0225764.g002

Table 3. Visual inspection of refrigerators used for vaccine storage based on (N = 75).

	n	%
Type of refrigerator		
Pharmaceutical grade*	9	12.0
Household refrigerator	66	88.0
Freezerless refrigerator*	30	45.5
Full-size dual-zone refrigerator/ freezer (separate exterior doors)*	2	3.0
Refrigerator with internal ice compartment	31	47.0
Refrigerator with internal non-insulated ice compartment	2	3.0
Household refrigerator, details unclear	1	1.5
Functioning thermometer		
None	20	26.7
1 functioning thermometer	53	70.7
2 functioning thermometers	2	2.7
Type of functioning thermometer (n = 57)		
Digital: Minimum-maximum+	23	40.4
Digital: Minimum-maximum remote+	3	5.3
Digital: Data logger cloud-based+	1	1.8
Digital: Integrated because pharmaceutical grade+	6	10.5
Digital: Digital thermometer, details unclear	4	7.0
Non-digital: Minimum-maximum	5	8.8
Non-digital: Plain thermometer without minimum-maximum function	15	26.3
Placement of temperature probe/thermometer (n = 57) (5)		
Close to outer walls	21	40.4
Center of refrigerator	17	32.7
In door shelves	8	15.4
Integrated (purpose-built refrigerator)	6	11.5
Vaccines are stored in refrigerator door shelves (17)	20	34.5
Vaccine boxes are with contact to outer walls (8)	31	46.3
Vaccines NOT kept in original cardboard wrapping (1)	23	31.1
Systematically unpacked	10	43.5
Sporadically unpacked	13	56.5
Bins/baskets/separated shelves NOT used for all vaccines	61	81.3
Food and/or biomaterial stored (8)	14	20.3
Food stored (1)	10	71.4
Biomaterial stored (8)	4	28.6
Temperature logbook NOT visible in vicinity of refrigerator (11)	48	75.0
No. of entries in logbook (62)		
Not daily	7	53.8
1x/day	6	46.2
2x/day	0	0.0

(missing values)

*suitable for vaccine storage according to NIST [25,26] and CDC [8].

+suitable for vaccine storage according to [5,6,9,10].

https://doi.org/10.1371/journal.pone.0225764.t003

Temperature logbook near refrigerator

In 75.0% (n = 48) of cases, no temperature logbook was found near the refrigerator. No practice recorded the temperature twice daily; see Table 3 for details. Temperature logbooks varied in quality, with most of them indicating only the current temperature.

Stocking of vaccines (overstocking, storage in door shelves, use of bins/baskets/separate shelves, contact of vaccine boxes with outer walls)

In 31.9% (n = 23) of cases, refrigerators were overstocked, i.e., not enough space was left between boxes or vaccines were removed from their cardboard wrapping to save space. In 34.5% (n = 20) of refrigerators, vaccines were stored in door shelves, in one practice even below the plastic container for eggs. One practice kept all vaccines in the door shelves, 'reserving the main body for other things'. In 81.3% (n = 61) of refrigerators, bins/baskets or separate shelves were not used for all vaccines. Of these, 4.9% (n = 3) used containers only for some types of vaccines, and 11.5% (n = 7) only for all unwrapped vaccines. In 46.3% (n = 31) of refrigerators, vaccine cardboard boxes had contact with outer walls.

Associations between quality criteria and practice characteristics

An analysis using GLMM showed no significant associations between scoring positive on at least half (6 out of 10) of the quality criteria and the independent variables considered (S4 Table).

Discussion

Of the 75 refrigerators analyzed, none met all ten quality criteria for 'good refrigerator management'. The items with the highest potential for improvement in at least 45% to 81% of refrigerators were using bins, baskets or other means to organize all vaccines, keeping a temperature logbook visible near the refrigerator, measuring temperatures in the center of the refrigerator, preventing contact of vaccine boxes with outer walls, and using refrigerator types suitable for vaccine storage.

Overall, the amount of avoidable vaccine management errors is remarkable. The types of errors are rather diverse ranging from structural aspects concerning equipment to procedural aspects such as unwrapping and overstocking vaccines. When the sum of additional observations (see S5 Table) is further taken into account, refrigerator management can be described as markedly heterogeneous between practices with an enormous need for improvement. A positive association between reaching more than six quality criteria and temperatures in the target range was identified. However, we did not identify associations between reaching more than six quality criteria and any practice characteristics. Interestingly, also physicians' qualification for tropical medicine and/or yellow fever (special license required) was not associated with better quality.

When interpreting the results it must be noted that previous studies indicate that quality in vaccine storage is not constant but subject to fluctuations [13,27]. For instance, some of the deficits, e.g. unwrapping of vaccines or contact with outer wall, might be greater during the influenza season when practices store larger quantities of vaccines. The influenza season was not a factor in our study, which was conducted in spring and summer.

Comparing our data with other studies is difficult due to the heterogeneity of quality indicators and setting-specific characteristics (e.g., storage of frozen vaccines, which are used in our setting). We collected data on the use of tools to organize vaccines, the most frequently encountered deficit. Other studies focused more on organizational methods such as organizing

by type of vaccines [15] and expiration dates [7,12,13,16], and less on tools that facilitate these methods. The identified absence of a temperature logbook is within the range of previous studies (26% to 94%; our study: 75.0%) [13,15,19]. However, actual numbers might be higher considering that our observations focused only on visible logbooks. Regarding the location of temperature-monitoring devices, a study in the US reported that 86.0% positioned their temperature-monitoring device not in the center but rather at the front of the refrigerator (51.2%) [28]. Actual contact of vaccine boxes with outer walls was not mentioned elsewhere. Regarding the type of refrigerator, 'full-size dual-zone refrigerator/freezers (separate exterior doors)' were used by 3% in our sample, compared to at least 44.4% of US physicians [16,28]. Pharmaceutical-grade refrigerators were used by 3.9% to 13.3% of Australian and US general practices, compared to 12.0% in our sample [28,29]. Smaller refrigerator/freezer units were used by 15.6% to 51.2% of US and Australian practices (53% in our study) [16,28,29], 36% of which lacked a separately sealed freezer compartment (5.7% in our study) [16]. In Italy, of 39 vaccination offices in 1999, 24% did not have any refrigerator and relied on neighboring facilities; three of seven practices selected for the monitoring used pharmaceutical-grade refrigerators [17]. The absence of any type of thermometer was reported in 6.9% to 91.9% of refrigerators [7,13–16,18,19,21]. In a study among US physicians, 37.8% also had a backup thermometer (2.7% in our study) [28]. Whether the thermometer was suitable for recording the digital minimum-maximum was considered in only one study (0% compared to 36.5% in our study) [14]. We know from other studies with self-administered questionnaires that unspecified minimum-maximum thermometers are lacking in 18.2% to 100% of refrigerators [17,20]. Storage of vaccines in door shelves was reported in 20.3% to 52.6% as compared to 34.5% in our study [7,13,19].

Overstocking as a cause of most vaccine storage errors

Many of the vaccine storage errors identified in our study trace back to a mismatch between the storage capacity available in each practice refrigerator and the volume occupied by each vaccine (and diluent), including its cardboard wrapping. Practices that overstock engage in unacceptable procedures. Examples include 1) systematically storing vaccines without their insulating cardboard wrapping to save space, 2) using door shelves for storage, 3) allowing contact with external walls, 4) not using baskets/bins for the sake of organization (also regarding the opportunity to organize vaccines by their expiration date), 5) placing vaccines in refrigerators intended for the food of the practice team, and 6) failing to permanently install the probe/thermometer in the center of the refrigerator. The aspect of overstocking and its many consequences are discussed in guidelines, but have not been studied elsewhere. Practical advice includes a) improving the planning by reconciling the number of vaccinations administered, e.g. in a month, with according vaccine orders, b) reducing the number of vaccines stored at any given time by making use of pharmacy deliveries more frequently, c) investing in a larger refrigerator, d) refraining from food storage, and e) installing regular monitoring as well as f) supervisory checks.

Strengths and limitations

The strength of this study lies in having obtained data by standardized, objective observations as opposed to self-reported methods. There are also several limitations. We designed the checklist as a measurement tool for an intervention study. To prevent bias, items that required direct questioning or closer inspection were excluded (e.g., responsibilities, frequency/procedure of resetting minimum-maximum thermometers, temperature logbooks not immediately visible). Collecting data by observation could have induced a measurement bias. First, the

amount of items and the chaotic storage in the refrigerators and, based on that, the time needed to set up the monitoring device were the defining factors for the time that doors were left open. Most notes to complete the checklist had to be made within 3 to 20 seconds. Therefore, we allowed for the completion of missing items during the second practice visit after seven days when refrigerators were accessed again to download the data from the temperature loggers. Second, observations might be different at other times of the year [13,27]. Regarding the dependent variable, we selected meeting more than half of the ten quality criteria as the primary outcome, even though we consider meeting all criteria as important and assign an equal significance to the individual criteria. However, no practice met all ten criteria and the total number of refrigerators that met seven criteria or more was low. Participating practices are part of a teaching practice network. A potential selection bias can be excluded as we showed in a prior study that the practice sample in Essen is representative for general practices in Germany [30]. In order to assess participation bias, we conducted thorough non-responder analyses.

Conclusion

Our results show that current storage conditions are a threat to the effectiveness of immunizations, our most effective public health strategy against contagious diseases. Efforts to guarantee quality-ensured cold chain management on a regulatory, educational and practice level are urgently needed. On a regulatory level, more detailed recommendations/guidelines/quality management regulations for primary care practices are needed, addressing e.g. acceptable types of refrigerators and thermometers. On an educational level, physicians and medical assistants need to be made aware of the relevance and procedures of adequate vaccine storage during their training. To assure widespread implementation of recommendations, an online-based learning program is currently being tested.

Supporting information

S1 Table. Checklist for the visual inspection of refrigerators (German version).
(DOCX)

S2 Table. Checklist for the visual inspection of refrigerators (English translation).
(DOCX)

S3 Table. Non-participant analysis (n = 168).
(DOCX)

S4 Table. Hierarchical generalized linear mixed models (GLMM) for associations between practice characteristics and reaching more than half (6+) of the ten quality criteria.
(DOCX)

S5 Table. Additional observations.
(DOCX)

Acknowledgments

We sincerely thank Professor Dr. med. Stefan Gesenhues, Director of the Institute for General Practice of the University Duisburg-Essen, for his continuous support. We also thank the physicians and staff members of the participating teaching practices of the University of Duisburg-Essen for their assistance in conducting the study. We are grateful for the financial support given by 'Stiftung Universitätsmedizin Essen'.

Author Contributions

Conceptualization: Anika Thielmann, Birgitta Weltermann.

Data curation: Anika Thielmann, Marie-Therese Puth.

Formal analysis: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

Funding acquisition: Anika Thielmann, Birgitta Weltermann.

Investigation: Anika Thielmann.

Methodology: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

Project administration: Anika Thielmann, Birgitta Weltermann.

Resources: Anika Thielmann, Birgitta Weltermann.

Software: Anika Thielmann, Marie-Therese Puth.

Supervision: Anika Thielmann, Birgitta Weltermann.

Validation: Anika Thielmann, Birgitta Weltermann.

Visualization: Anika Thielmann, Birgitta Weltermann.

Writing – original draft: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

Writing – review & editing: Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann.

References

1. World Health Organization. Temperature sensitivity of vaccines. Department of Immunization, Vaccines and Biologicals, World Health Organization. 2006: 1–62.
2. Paul-Ehrlich-Institut. Ausflückungen in Adsorbatimpfstoffen. Bulletin zur Arzneimittelsicherheit—Informationen aus BfArM und PEI; 2012: 12–16.
3. World Health Organization. Aide mémoire for prevention of freeze damage to vaccines. WHO/IVB/07.09. Geneva; 2007.
4. Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. Vaccine. 2017; 35: 2127–2133. https://doi.org/10.1016/j.vaccine.2016.09.070 PMID: 28364920
5. Salisbury D, Ramsay M, Noakes K. Immunisation against infectious disease. 3rd ed. London: TSO; 2006.
6. Australian Government. National vaccine storage guidelines. Strive for 5. 2nd ed. Canberra: Dept. of Health and Ageing; 2013.
7. Yuan L, Daniels S, Naus M, Brcic B. Vaccine storage and handling. Knowledge and practice in primary care physicians' offices. Can Fam Physician. 1995; 41: 1169. PMID: 7647622
8. Centers for Disease Control and Prevention. Vaccine Storage & Handling Toolkit; 2014.
9. Health Protection Scotland. Guidance on vaccine storage and handling.: Health Protection Scotland; 2013.
10. Public Health Agency of Canada. National vaccine storage and handling guidelines. For immunization providers 2015: Public Health Agency of Canada; 2015.
11. Verordnung über den Betrieb von Apotheken. ApBetrO; 12.06.2012.
12. Woodyard E, Woodyard L, Alto WA. Vaccine storage in the physician's office: a community study. The Journal of the American Board of Family Practice. 1995; 8: 91–94. PMID: 7778494
13. Gazmararian JA, Oster NV, Green DC, Schuessler L, Howell K, Davis J, et al. Vaccine storage practices in primary care physician offices: assessment and intervention. Am J Prev Med. 2002; 23: 246–253. https://doi.org/10.1016/s0749-3797(02)00512-3 PMID: 12406478
14. Lewis PR, Reimer RF, Dixon AJ. Evaluating the efficacy of vaccine storage in the general practice setting. Aust N Z J Public Health. 2001; 25: 547–550. https://doi.org/10.1111/j.1467-842x.2001.tb00322.x PMID: 11824993

15. Lee S, Lim H-S, Kim O, Nam J, Kim Y, Woo H, et al. Vaccine Storage Practices and the Effects of Education in Some Private Medical Institutions. J Prev Med Public Health. 2012; 45: 78–89. https://doi.org/10.3961/jpmph.2012.45.2.78 PMID: 22509448

16. Bell KN, Hogue C, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. Pediatrics. 2001; 107: e100. https://doi.org/10.1542/peds.107.6.e100 PMID: 11389298

17. Grasso M, Ripabelli G, Sammarco ML, Selvaggi TM, Quaranta A. Vaccine storage in the community: a study in central Italy. Bull World Health Organ. 1999; 77: 352. PMID: 10327715

18. Haworth EA, Booy R, Stirzaker L, Wilkes S, Battersby A. Is the cold chain for vaccines maintained in general practice. BMJ. 1993; 307: 242–244. https://doi.org/10.1136/bmj.307.6898.242 PMID: 8369691

19. Bishai DM, Bhatt S, Miller LT, Hayden GF. Vaccine storage practices in pediatric offices. Pediatrics. 1992; 89: 193–196. PMID: 1734382

20. Bailey HD, Kurinczuk JJ, Kusel MM, Plant AJ. Barriers to immunisation in general practice. Aust N Z J Public Health. 1999; 23: 6–10. https://doi.org/10.1111/j.1467-842x.1999.tb01198.x PMID: 10083683

21. Thakker Y, Woods S. Storage of vaccines in the community: weak link in the cold chain. BMJ. 1992; 304: 756–758. https://doi.org/10.1136/bmj.304.6829.756 PMID: 1571683

22. Weltermann BM, Markic M, Thielmann A, Gesenhues S, Hermann M. Vaccination Management and Vaccination Errors: A Representative Online-Survey among Primary Care Physicians. PloS one. 2014; 9: e105119. https://doi.org/10.1371/journal.pone.0105119 PMID: 25118779

23. Thielmann A, Puth M-T, Kersting C, Porz J, Weltermann B. Vaccine cold chain in general practices. A prospective study in 75 refrigerators (Keep Cool study). PloS one: under Revision.

24. Thielmann A, Viehmann A, Weltermann BM. Effectiveness of a web-based education program to improve vaccine storage conditions in primary care (Keep Cool): study protocol for a randomized controlled trial. Trials. 2015; 16. https://doi.org/10.1186/s13063-014-0536-6

25. Chojnacky M, Miller W, Ripple D, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7656); 2009.

26. Chojnacky M, Miller W, Strouse G. Thermal Analysis of Refrigeration Systems Used for Vaccine Storage (NISTIR 7753). Report on Pharmaceutical Grade Refrigerator and Household Refrigerator/Freezer; 2010.

27. Gold MS, Martin L, Nayda CL, Kempe. Electronic temperature monitoring and feedback to correct adverse vaccine storage in general practice. MJA. 1999; 171: 83–84. PMID: 10474583

28. Angoff R, Wood J, Chernock MC, Tipping D. Visual Indicators on Vaccine Boxes as Early Warning Tools to Identify Potential Freeze Damage. Infect Dis Clin Pract (Baltim Md). 2015; 23: 184–189. https://doi.org/10.1097/IPC.0000000000000253 PMID: 27330265

29. Carr C, Byles J, Durrheim D. Practice nurses best protect the vaccine cold chain in general practice. Austr J Adv Nurs. 2009; 27: 35–39.

30. Viehmann A, Thielmann A, Gesenhues S, Weltermann BM. Repräsentieren akademische Hausarztpraxen die hausärztliche Regelversorgung. Eine methodische Annäherung. Do Academic Family Practices Reflect Routine Primary Care? A Methodological Approach. Z Allg Med. 2014; 90: 354–359. https://doi.org/10.3238/zfa.2014.0354–0359

9.4 Publication 4

Improving Knowledge on Vaccine Storage Management in General Practices: Learning Effectiveness of an Online-Based Program

Anika Thielmann, Marie-Therese Puth, Birgitta Weltermann

Vaccine

2020

Under review

Vaccine 38 (2020) 7551–7557

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Improving knowledge on vaccine storage management in general practices: Learning effectiveness of an online-based program

Anika Thielmann [a,b,*], Marie-Therese Puth [b,c], Birgitta Weltermann [a,b]

[a] Institute for General Practice, University of Duisburg-Essen, University Hospital Essen, Hufelandstraße 55, 45147 Essen, Germany
[b] Institute of General Practice and Family Medicine, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany
[c] Department of Medical Biometry, Informatics and Epidemiology, Faculty of Medicine, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

ARTICLE INFO

Article history:
Received 25 February 2020
Received in revised form 11 September 2020
Accepted 14 September 2020
Available online 9 October 2020

Keywords:
Vaccine
Cold-chain
Storage
Knowledge
Quality
General practice

ABSTRACT

Background: Adequate vaccine storage is a prerequisite for assuring effective vaccinations yet storage conditions in practices are frequently inadequate. The online learning program Keep Cool aims at improving knowledge on international best practices. This study evaluates the program's learning effectiveness focusing on key indicators for knowledge on vaccine storage, such as temperature target range (2 to 8 °C) and documentation requirements.

Methods: Participants were recruited from within a university teaching practice network. Knowledge was measured with an online-based questionnaire (11 correct items = optimal vaccine storage knowledge) which was completed before and after the online program.

Results: 60 physicians and practice assistants from 25 practices participated. The mean knowledge score was 5.6 correct answers (standard deviation [SD] 1.9), which increased to 9.8 (SD 1.2) after program participation ($p < 0.001$). The item with the highest net change addressed the need for twice-daily documentation of temperatures (+76.7%). Knowledge of the lower and upper temperature targets improved from 58% respectively 63% to 100% each. Optimal vaccine storage knowledge after participation (38% of participants) was associated neither with age, gender, occupational group nor practice type.

Conclusion: The new online education program showed a high learning effectiveness regarding key indicators for the quality of vaccine storage management.

Clinical Trial Registry Number: DRKS00006561.

1. Background

Immunizations are among the most effective and cost-effective public health strategies worldwide [1]. However, their effectiveness and tolerability depend on adequate vaccine storage: maintaining the vaccines' cold chain within recommended temperature ranges (in Germany 2–8 °C) is the paramount objective [2,3]. Cold-chain breaches are an ongoing issue [4], and the World Health Organization considers protecting vaccines from freeze damage as 'one of the most poorly addressed problems in vaccine management' [5]. In the past, disease outbreaks were likely linked to inadequate storage conditions [6–10].

In our previous physician questionnaire survey, indicators showed deficits in vaccine management in German primary care practices. This also included vaccine storage deficits. For instance, only 51% reported monitoring and documenting temperatures twice daily, and 16% described cold-chain breaches as an error or near error [11,12]. Aiming to improve vaccine storage, several studies have addressed knowledge deficits [13–22]. Regarding the most important aspect, i.e. knowledge of the correct temperature range (2–8 °C), correct responses ranged from 10% to 73% among practice personnel [15,16,18–20,22]. Also, knowledge deficits on vaccines' thermo-sensitivity were identified [15,16,19,20].

In a study of 75 refrigerators in German primary care practices, we showed that 68% (n = 51) had cold-chain breaches [23]. As data on vaccine storage knowledge among German practice personnel is missing and guidance related to vaccine storage is scarce, we developed the web-based education program 'Keep Cool' for personnel working in primary care practices based on recommendations and guidelines from other Western nations [24–29].

The Keep Cool study aims at assuring optimal vaccine storage conditions through tailored learning. After a 7-day baseline vaccine refrigerator temperature recording, physicians and practice assistants were offered access to the education program. This publica-

* Corresponding author at: Institute of General Practice and Family Medicine, University of Bonn, Venusberg-Campus 1, 53127 Bonn, Germany.
E-mail address: Anika.Thielmann@ukbonn.de (A. Thielmann).

https://doi.org/10.1016/j.vaccine.2020.09.049
0264-410X/

tion evaluates the program's learning effectiveness focusing on key indicators of knowledge on vaccine storage.

2. Methods

The study was registered in the German Trial Register (DRKS00006561) and approved by the Ethic Commission of the Medical Faculty of the University Hospital Essen, University of Duisburg-Essen (14-6118-BO). Participants provided written informed consent.

2.1. Study design

Details on the Keep Cool study design have been reported [30]. Briefly, this is an intervention study with 23 general practices which were monitored using continuous temperature recordings with a data logger at 1-minute intervals over 7 days [30]. Practices received their temperature records uncommented before program participation.

This publication evaluates the program's effectiveness in improving knowledge using an online-based questionnaire, which participants completed immediately before and after the program (pre-post design).

2.2. Keep Cool program

The Keep Cool program is an online-based education program designed to increase knowledge on good vaccine storage conditions as a prerequisite to improve vaccine storage conditions. The average program duration is 45 min. Technical requirements are internet access with the browser Mozilla Firefox or Google Chrome, the activation of JavaScript and cookies, and an email address.

Upon registering and commencing the learning program, participants complete a questionnaire to assess their baseline knowledge. The presentation of the learning content follows a didactic approach consisting of three key features: a) content is tailored to an individual's baseline knowledge by providing feedback, b) content is targeted to the two occupational groups that work and handle vaccines in German general practices (physicians or trained practice assistants, who undergo a three-year vocational training), and c) the program addresses each participant by using their name which they provide upon registration.

The learning content is based on national [3] and international recommendations, guidelines [24–29], and scientific literature [2,31,32]. The learning content is presented in five tutorials: temperature (9 subtopics), refrigerator (3 subtopics), storage (4 subtopics), responsibilities (5 subtopics), and monitoring (8 subtopics). Participants receive immediate access to basic information and practical tips. They are offered expert knowledge for in-depth understanding including access to relevant scientific literature [2,3,31,32]. See Fig. 1 for an example of the presentation of the learning content.

The following templates are offered (printout or download): temperature logbook, checklist for vaccine storage, emergency numbers, criteria for recommended data loggers and vaccine refrigerators, list of adsorbed vaccines, checklists for expiration dates and keeping an inventory.

After completing the program, participants test their learning success. If <8 of 11 (73%) knowledge questions were answered correctly, participants were allowed to repeat the learning program and final test once after revisiting the learning content. After successful completion participants receive a certificate; physicians additionally receive one continuous medical education point (CME).

The development of the program prototype was supported by internal and external tests. The internal tests were carried out with four healthcare researchers, four laypersons, and four primary care physicians. The external tests were conducted in the target population using the think-aloud method [33]: four practice assistants and two primary care physicians from three practices participated. The experimenter observed and noted the participants' behavior and understanding of the programs' functionality, layout, and overall usability.

2.3. Development of the web-based knowledge questionnaire

The knowledge questionnaire was developed based on previous studies [14,21], international recommendations and guidelines [24–29], as well as scientific data on vaccines' temperature sensitivity and the performance of different refrigerator types [2,31,32]. The final questionnaire comprised 11 items (see Supplemental Tables 1 and 2). The items allocate to the tutorials as follows: temperature: 1, 4, 5; refrigerator: 10; storage: 2, 9, 11; responsibilities: 8; and monitoring: 3, 6, 7. The questionnaire is embedded at the start and end of the program to provide feedback on learning success. To obtain official approval for CME points, the questionnaire at follow-up had to be modified slightly to match the requested one of five formats, while content remained identical. The questionnaire was initially pre-tested on paper with five researchers, later in its electronic version as part of the internal and external tests.

2.4. Study population, recruitment and study materials

Participation in the study was offered to 168 general practices affiliated with the University of Duisburg-Essen (N = 185) as teaching practices; however, practices (n = 17) involved in pre-tests were excluded. All non-participants received a short questionnaire by fax to allow for a non-responder analysis. Recruitment took place between January 2018 and August 2018.

In participating practices, a temperature data logger was placed in the middle shelf of the refrigerator(s). After 7 days, readings were downloaded. The visualization of the temperature recording was presented to the practices immediately. For ethical reasons, all practices were offered access to the learning program, refraining from a randomized controlled design. Data on practice characteristics were obtained from the university's teaching practices database.

2.5. Statistical analysis

Descriptive statistics were used to compare participating and non-participating practices as well as physicians and practice assistants. For their comparison, the χ^2 test and the Wilcoxon rank-sum test were used. The frequency of all knowledge items and the learning effectiveness was calculated for all participants and separately by professional group as well as per practice (at least one person with 8/11 or 11/11 correct). The outcome 'good vaccine storage knowledge' was defined as answering at least 8 of the 11 questions correctly. For participants with available data at both times, the degree of improvement after program participation within the groups was compared using McNemar's test or the Wilcoxon signed-rank test. To assess the relationship between practice characteristics and 'optimal vaccine storage knowledge' (<11/11 correct answers), hierarchical generalized linear mixed models (GLMM) for binomial responses with random practice-specific intercepts (to account for variations within and between practices) were used. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (Armonk, NY: IBM

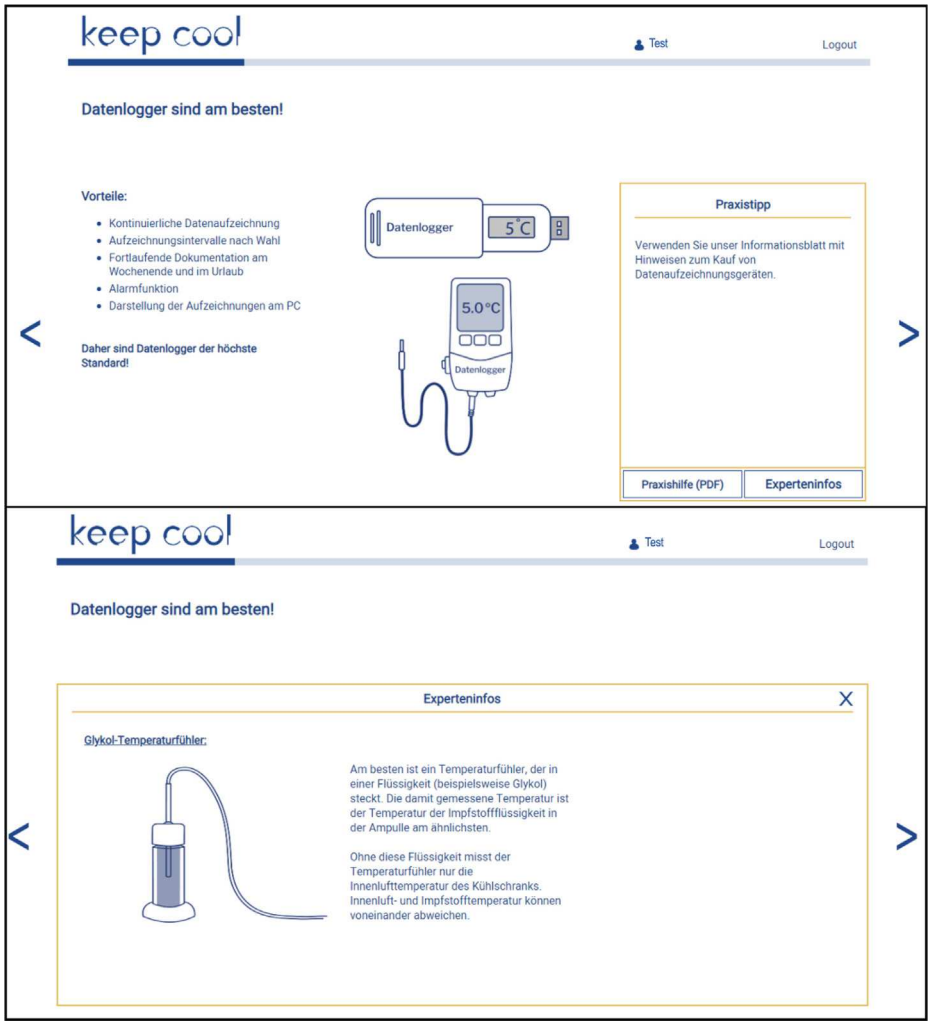

Fig. 1. Example for the presentation of the learning content: basic knowledge and practical tip (top), expert information (bottom).

Corp.) and R, version 3.5.2. Percentages and mean values are reported for valid cases.

3. Results

3.1. Characteristics of participating practices and practice personnel

Of the 64 practices that took part in the two-week temperature monitoring period and were offered study participation, 25 participated (response rate: 39.1%). Participating practices did not differ significantly from non-participants, except that 92% of these practices (vs. 61.5%, respectively) had at least one refrigerator with temperatures outside the target range. For details see Supplemental Table 3.

A total of 60 participants completed the learning program: 16 physicians (including 1 physician in training) and 44 practice assistants (including 4 trainees). On average, 2.4 (±0.8) persons participated per practice: in 64.0% (n = 16) one physician and at least two practice assistants, in 36.0% (n = 9) only practice assistants. 52.0% of the practices were group practices. For details see Table 1.

3.2. Learning effectiveness

At baseline, the mean knowledge score for the complete sample was 5.6 (±1.9) out of 11 correct answers: 5.9 (±2.3) in physicians, 5.5 (±1.7) in practice assistants. No participant had 'optimal vaccine storage knowledge' (11 of 11 items correct) at baseline. Of the participants, 13.3% (n = 8) had 'good vaccine storage knowledge' (at least 8 of 11 questions correct): 25.0% of the physicians and 9.1% of the practice assistants. At follow-up, there was a significant improvement in knowledge, both in physicians and practice assistants: the mean knowledge score was 9.8 ± 1.2, corresponding to an increase of 4.2 points ($p < 0.001$). In physicians, knowledge increased by 75.0 percentage points (n = 12) and in practice assistants by 90.9 percentage points (n = 38). The mean knowledge score at follow-up increased by 4.6 points in physicians ($p < 0.001$) and by 4.0 points in practice assistants ($p < 0.001$). At follow-up 100.0% had 'good vaccine storage knowledge' (at least 8 of 11 items correct) and thus passed the test at first attempt. This corresponding to an increase of 86.7 percentage points compared to baseline. The item with the highest net change (+76.7%) addressed the best-practice of recording temperatures twice-daily. Knowledge of the lower and upper temperature targets improved from 58% respectively 63% to 100% each. See Table 2 and Fig. 2 for details.

3.3. Factors associated with 'optimal vaccine storage knowledge' at follow-up

Analysis using the GLMM showed no significant associations between 'optimal vaccine storage knowledge' (<11/11 correct answers) and the independent variables considered.

Table 1
Characteristics of participating practices (n = 25) and practice personnel (n = 60).

	n	%
Participants:		
Physicians	16	26.7
Mean years since medical license ± SD [1]	25.1 ± 7.7	
Gender, female	5	31.3
Frequency of administering ≥ 1 vaccination		
About daily	12	75.0
Weekly	4	25.0
Monthly	0	0.0
Rarely/never	0	0.0
Medical assistants	44	73.3
Mean years since vocational training ± SD [7*]	16.4 ± 11.7	
Gender, female	44	100.0
Frequency of administering ≥ 1 vaccination [2]		
About daily	30	71.4
Weekly	10	23.8
Monthly	0	0.0
Rarely/never	2	4.8
Practice characteristics:		
Practice type, group	13	52.0
Mean no. of physicians ± SD [10]	2.0 ± 1.4	
Mean no. of medical assistants ± SD [11]	4.4 ± 3.1	
Patients per practice per quarter (caseload) > 1,750 [12]	10	50.0
Mean percentage of patients with statutory health insurance ± SD [8]	90.1 ± 7.5	
Certified quality management [15]	2	10.5
Physician qualifications, travel medicine [10]	4	20.0
Physician qualifications, tropical medicine and/or yellow fever license [10]	1	5.0
Services offered, pediatric and/or adolescent medicine [10]	8	40.0
Services offered, adolescent preventive services [10]	18	90.0
Practice vaccine spectrum, mean no. of vaccines ± SD [10]	17.7 ± 2.0	
Total number of refrigerators+	33	
Temperature of refrigerators		
Always within target range (2–8 °C)	7	21.2
Within target range but at least once > 8 °C	10	30.3
Within target range but at least once < 2 °C	12	36.4
Always > 8 °C	1	3.0
<2°, in target range, >8°C	2	6.1
Always < 2 °C	1	3.0
Type of refrigerator used, household	32	97.0

* Of these n=4 still in vocational training SD = standard deviation.
+ Of the 25 practices, 19 practices had one refrigerator, 5 two refrigerators, 1 practice with 4 sites had one refrigerator per site.

4. Discussion

This study evaluated the learning effectiveness of the web-based education program Keep Cool on vaccine storage knowledge in general practice personnel. The didactic strategy used a combination of information tailoring based on prior knowledge of key aspects and personal address. The reported learning effectiveness immediately after program participation was very good: while around half of the questions were answered correctly at baseline, this increased to all questions but one afterwards, on average. In more than half of all practices at least one person answered all questions correctly after program participation.

Interestingly, although vaccinations are an important primary care service and adequate knowledge on vaccine storage is paramount, only few studies on knowledge are available that allow for a comparison. With the exception of one study, they are either cross-sectional without an intervention or do not provide pre-post comparisons [14–16,18–22,34]. Focusing on the most important aspect, i.e. knowledge of the correct temperature range of 2 °C to 8 °C, results in prior studies range from 10% in staff members of Australian general practices [22], 16% of storage coordinators in US pediatric offices [19], 40% in GB general practices and child health clinics [18], 48% of coordinators in US family practices and pediatric offices [16], 63% of vaccine coordinators in Canadian primary care practices [15], to 73% in US private provider offices [20]. This compares to 48% in our study at baseline, 63% for the upper limit, and 58% for the lower.

Prior studies also addressed the appraisal of vaccines' thermosensitivity. Considering heat exposure, 18% of US coordinators in pediatric offices were aware of 'harms to some vaccines' [19], 84% of Canadian coordinators of 'harms to all' vaccines [15], and 100% of US coordinators in family practices and pediatric offices of 'harms to potency' [16]. 'Harm/damage to some/certain vaccines' due to freeze exposure was stated by 28.1% of Canadian coordinators [15], by 36% [19] and 81.5% [16] of US coordinators, and 4% of Australian GP staff 'knew which vaccines were damaged by freezing' [22]. Interestingly, according to Bell et al. [20], some US physician practices believed that colder temperatures were safer and managed their refrigerator accordingly, which is consistent with unsystematic observations in our study. In Germany, there is teaching material available which encourages practice assistants to look out for too warm, but not cold temperatures [35].

Only one intervention study reports pre-post results for knowledge, thus allowing for a comparison with our follow-up data. This South Korean study in private practice institutions in 2012 provided one-to-one education in practices combined with a manual on vaccine storage [14]. In the study, 83.9% were aware at baseline that temperatures should be recorded, compared to 90.3% at follow-up. Our study inquired about the frequency of recording temperatures, which was answered correctly by 23.3% at baseline and 100.0% at follow-up. In the South Korean study, measuring temperatures on the middle shelf was correctly reported by 61.3% at baseline and 90.3% at follow-up, compared to 88.3% and 94.8% in our study [14].

Table 2
Learning effectiveness regarding key knowledge items: total study population and stratified by physicians (n = 16) and practice assistants (n = 44/42) before and after the program.

	Before program (N = 60)[+]		After program (N = 58[#])[+]		p-value[~]	Net change (%)
	n	%[*]	n	%[*]		
Tutorial: Temperature						
1. The active agent of vaccines is affected by high and low temperatures.	58	96.7	56	96.6	n.s.	−0.1[$]
Physicians	16	100.0	16	100.0		0.0
Practice assistants	42	95.5	40	95.2		−0.3[$]
4. The lower temperature limit for vaccines is 2 °C	35	58.3	58	100.0	<0.001	+41.7
Physicians	10	62.5	16	100.0		+37.5
Practice assistants	25	56.8	42	100.0		+43.2
5. The upper temperature limit for vaccines is 8 °C.	38	63.3	58	100.0	<0.001	+36.7
Physicians	10	62.5	16	100.0		+37.5
Practice assistants	28	63.6	42	100.0		+36.4
Tutorial: Refrigerator						
10. Appropriate refrigerators for vaccine storage are [...]	1	1.7	30	51.7	<0.001	+50.0
Physicians	1	6.3	11	68.8		+62.5
Practice assistants	0	0.0	19	45.2		+45.2
Tutorial: Storage						
2. Vaccines should be stored according to expiration date, in boxes/drawers, according to name, in original packaging.	9	15.0	49	84.5	<0.001	+69.5
Physicians	5	31.3	15	93.8		+62.5
Practice assistants	4	9.1	34	81.0		+71.9
9. In refrigerators, vaccines may be stored together with medications, not with food.	52	86.7	57	98.3	<0.05	+11.6
Physicians	14	87.5	16	100.0		+12.5
Practice assistants	38	86.4	41	97.6		+11.2
11. Inside refrigerators, vaccines should NOT have contact with the back wall or side walls and must NOT be stored on the lowest shelf or in door shelves	19	31.7	53	91.4	<0.001	+59.7
Physicians	6	37.5	15	93.8		+56.3
Practice assistants	13	29.5	38	90.5		+61.0
Tutorial: Responsibilities						
8. Two practice assistants per practice should be designated as responsible for vaccine storage.	39	65.0	53	91.4	<0.001	+26.4
Physicians	9	56.3	16	100.0		+43.7
Practice assistants	30	68.2	37	88.1		+19.9
Tutorial: Monitoring						
3. The temperature in refrigerators should be documented twice daily.	14	23.3	58	100.0	<0.001	+76.7
Physicians	4	25.0	16	100.0		+75.0
Practice assistants	10	22.7	42	100.0		+77.3
6. Inside the refrigerator the temperature should be measured on the middle shelf.	53	88.3	55	94.8	n.s.	+6.5
Physicians	13	81.3	16	100.0		+18.7
Practice assistants	40	90.9	39	92.9		+2.0
7. Appropriate thermometers for monitoring the temperature in vaccine refrigerators are [...]	17	28.3	40	69.0	<0.001	+40.7
Physicians	7	43.8	15	93.8		+50.0
Practice assistants	10	22.7	25	59.5		+36.8

[+] Comparisons of physicians and practice assistants before/after the program using Fisher's exact test were not significant except for items 2 (before program: p = 0.048) and 7 (after program: p = 0.012).
[*] Valid percentages.
[#] Drop-out of n = 2 practice assistants with an average score of 5 and 6 at baseline.
[$] Drop-out of n = 2 practice assistants with correct answers at baseline.
[~] McNemar's test comparing differences between before and after the program.

After completing the program, physicians had significantly more correct answers than practice personnel (on average one answer more). A significant difference in learning success between professions was found only for one item: 94% of physicians compared to 60% of practice assistants correctly identified thermometers allowed for temperature monitoring.

4.1. Limitations

A potential selection bias by involving only primary care teaching practices is unlikely as we showed in a prior study that results on vaccine management were similar between a teaching practice sample and a random practice sample [36]. We cannot exclude that an intervention bias applies for two reasons: First, the time between recruitment, data logger setup and program participation allowed practices to inform themselves about the topic. Second, at least some of the participants saw the visualization of their temperature readings. In case of an intervention bias, the real knowledge quality would be worse.

4.2. Conclusion

This web-based education program was shown to be very effective in improving knowledge on vaccine storage in primary care practices. The results can be extrapolated to other physicians, practices as well as other institutions who handle vaccinations. In Germany, all share a lack of storage-related recommendations/guidelines.

Due to the severe knowledge deficits identified, large-scale implementation of Keep Cool will not result in a ceiling effect but will have a strong impact on vaccine storage quality. Keep Cool is cost-effective and can be easily disseminated in the target population. Further studies will assess its long-term effectiveness and explore on-site education as an alternative delivery mode to increase the program's reach.

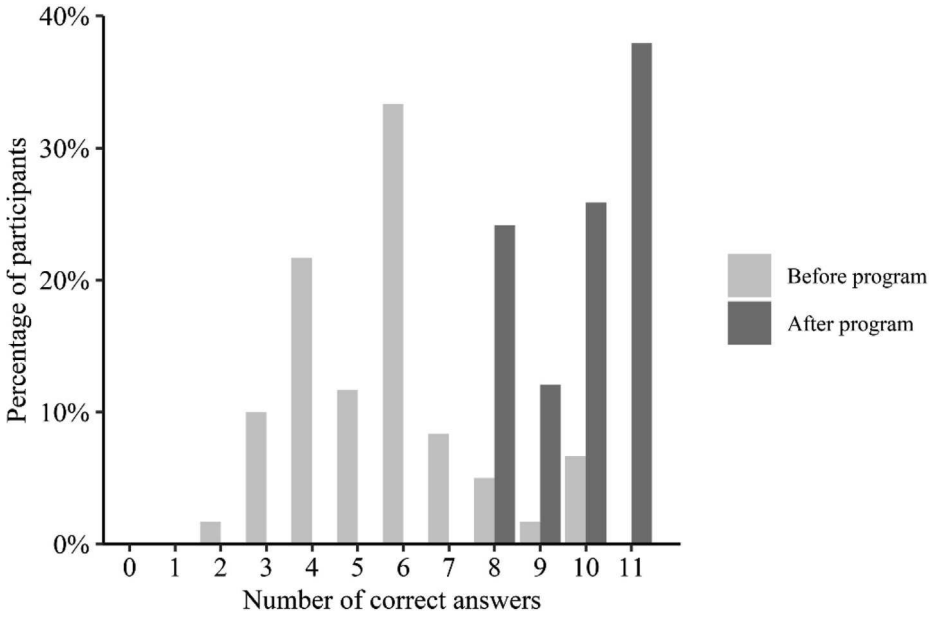

Fig. 2. Knowledge on vaccine storage. Number of correct answers per participant (maximum 11 items) before and after program participation (before program N = 60/after program N = 58).

CRediT authorship contribution statement

Anika Thielmann: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Marie-Therese Puth:** Software, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Birgitta Weltermann:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The study received grants from Stiftung Universitätsmedizin Essen to buy thermometers and from 'Kulturstiftung Essen' for the development of the online program. The funders of the study had no influence on the study design, data collection, data analysis, data interpretation, or writing of the report.

Acknowledgements

We would like to thank Professor Dr. med. Stefan Gesenhues, Director of the Institute for General Practice in Essen, for his continuous support as well as all the institute's teaching practices that participated in the study. We also wish to thank 'Stiftung Universitätsmedizin Essen' and 'Kulturstiftung Essen' for their funding. We also thank Christine Kersting who supported data analysis and Anna Herwig who reviewed all program materials.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.09.049.

References

[1] World Health Organization, Unicef. Global Immunization Data; 2013. Available: http://www.who.int/immunization_monitoring/Global_Immunization_Data_v2.pdf. Accessed 17 January 2014.
[2] World Health Organization. Temperature sensitivity of vaccines. Department of Immunization, Vaccines and Biologicals, World Health Organization. 2006: 1–62.
[3] Paul-Ehrlich-Institut. Ausflückungen in Adsorbatimpfstoffen. Bulletin zur Arzneimittelsicherheit - Informationen aus BfArM und PEI; 2012: 12–16.
[4] Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. Vaccine 2017;35:2127–33.
[5] World Health Organization. Aide mémoire for prevention of freeze damage to vaccines. WHO/IVB/07.09. Geneva; 2007.
[6] McColloster P, Vallbona C. Graphic-output temperature data loggers for monitoring vaccine refrigeration: implications for pertussis. Am J Public Health 2011;101:46–7.
[7] Lerman SJ, Gold E. Measles in children previously vaccinated against measles. JAMA 1971;216:1311–4.
[8] Onoja AL, Adu FD, Tomori O. Evaluation of measles vaccination programme conducted in two separate health centres. Vaccine 1992;10:49–52.
[9] Boros CA, Hanlon M, Gold MS, Roberton DM. Storage at− 3 C for 24 h alters the immunogenicity of pertussis vaccines. Vaccine 2001;19:3537–42.
[10] McIntyre RC, Preblud SR, Polloi A, Korean M. Measles and measles vaccine efficacy in a remote island population. Bull World Health Organ 1982;60:767.
[11] Thielmann A, Sikora M, Schnell U, Gesenhues S, Weltermann B. Impfkühlschrank-und Impfstoffmanagement in Hausarztpraxen: Eine repräsentative, Web-basierte Umfrage unter Hausärzten (Keep Cool I). Das Gesundheitswesen 2015;38:1–6.
[12] Weltermann BM, Markic M, Thielmann A, Gesenhues S, Hermann M. Vaccination management and vaccination errors: A representative online-survey among primary care physicians. PLoS One 2014;9:e105119.
[13] Yakum MN, Ateudjieu J, Walter EA, Watcho P. Vaccine storage and cold chain monitoring in the North West region of Cameroon: a cross sectional study. BMC Res Notes 2015;8:145. https://doi.org/10.1186/s13104-015-1109-9.
[14] Lee S, Lim H-S, Kim O, Nam J, Kim Y, Woo H, et al. Vaccine storage practices and the effects of education in some private medical institutions. J Prev Med Public Health 2012;45:78–89. https://doi.org/10.3961/jpmph.2012.45.2.78.
[15] Yuan L, Daniels S, Naus M, Brcic B. Vaccine storage and handling. Knowledge and practice in primary care physicians' offices. Can Fam Phys 1995;41:1169.
[16] Woodyard E, Woodyard L, Alto WA. Vaccine storage in the physician's office: a community study. J Am Board Family Practice 1995;8:91–4.
[17] Haworth EA, Booy R, Stirzaker L, Wilkes S, Battersby A. Is the cold chain for vaccines maintained in general practice. BMJ 1993;307:242–4.
[18] Thakker Y, Woods S. Storage of vaccines in the community: weak link in the cold chain. BMJ 1992;304:756–8.
[19] Bishai DM, Bhatt S, Miller LT, Hayden GF. Vaccine storage practices in pediatric offices. Pediatrics 1992;89:193–6.
[20] Bell KN, Hogue C, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. Pediatrics 2001;107:e100. https://doi.org/10.1542/peds.107.6.e100.

[21] Page SL, Earnest A, Birden H, Deaker R, Clark C. Improving vaccination cold chain in the general practice setting. Aust Fam Physician 2008;37:892.
[22] Jeremijenko A, Kelly H, Sibthorpe B, Attewell R. Improving vaccine storage in general practice refrigerators. BMJ 1996;312:1651–2.
[23] Thielmann A, Puth M-T, Kersting C, Birgitta Weltermann. Vaccine cold chain in general practices: A prospective study in 75 refrigerators (Keep Cool study). PloS One. 2019. doi:10.1371/journal.pone.0224972.
[24] Centers for Disease Control and Prevention. Vaccine Storage & Handling Toolkit; 2014.
[25] Australian Government. National vaccine storage guidelines. Strive for 5. 2nd ed. Canberra: Dept. of Health and Ageing; 2013.
[26] Public Health Agency of Canada. National vaccine storage and handling guidelines. For immunization providers 2015: Public Health Agency of Canada; 2015.
[27] Salisbury D, Ramsay M, Noakes K. Immunisation against infectious disease. 3rd ed. London: TSO; 2006.
[28] Health Protection Scotland. Guidance on vaccine storage and handling.: Health Protection Scotland; 2013.
[29] Centers for Disease Control and Prevention. General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2011; 60: 1–35.
[30] Thielmann A, Viehmann A, Weltermann BM. Effectiveness of a web-based education program to improve vaccine storage conditions in primary care (Keep Cool): study protocol for a randomized controlled trial. Trials 2015;16. https://doi.org/10.1186/s13063-015-0824-9.
[31] Chojnacky M, Miller W, Ripple D, Strouse G. Thermal analysis of refrigeration systems used for vaccine storage (NISTIR 7656); 2009.
[32] Chojnacky M, Miller W, Strouse G. Thermal analysis of refrigeration systems used for vaccine storage (NISTIR 7753). Report on Pharmaceutical Grade Refrigerator and Household Refrigerator/Freezer; 2010.
[33] van Someren MW, Barnard YF, Sandberg JAC. The think aloud method. A practical approach to modelling cognitive processes. London: Academic Press; 1994.
[34] Lewis PR, Reimer RF, Dixon AJ. Evaluating the efficacy of vaccine storage in the general practice setting. Aust N Z J Public Health 2001;25:547–50.
[35] Ley-Köllstadt S, Arndt U, Grüber A, Quast U. Schwierige Impffragen - kompetent beantwortet. 3rd ed. Marburg: DGK - Beratung und Vertrieb GmbH; 2013.
[36] Viehmann A, Thielmann A, Gesenhues S, Weltermann BM. Repräsentieren akademische Hausarztpraxen die hausärztliche Regelversorgung. Eine methodische Annäherung. Do Academic Family Practices Reflect Routine Primary Care? A Methodological Approach. Z Allg Med 2014;90:354–9. https://doi.org/10.3238/zfa.2014.0354-0359.

9.5 Published Contributions to Congresses

German College of General Practitioners and Family Physicians; Erlangen, Germany; September 2019

Thielmann A, Puth, M, Kersting K, Porz J, Weltermann B. *Optimierungsbedürftige Impfstoffkühlkette in Hausarztpraxen: Eine Querschnittsstudie in 75 Kühlschränken (die Keep Cool-Studie* [The vaccine cold-chain in German primary care requires optimization: a cross-sectional study in 75 refrigerators (the Keep Cool Study)]. German Medical Science GMS Publishing House, 2019. DocV13-04. DOI: 10.3205/19degam015.

Thielmann A, Klidis K, Weltermann B. *Von MFA für MFA: Präsenzfortbildung zur Optimierung der Impfstofflagerung in Hausarztpraxen* [By medical assistants to medical assistants: face-to-face educational training to optimize vaccine storage in general practices]. German Medical Science GMS Publishing House, 2019. DocV13-06. DOI: 10.3205/19degam017.

German Society of Internal Medicine; Mannheim, Germany; April 2017

Thielmann A, Weltermann B. *Best-practices für die Impfstofflagerung: ein Review von nationalen Empfehlungen und Leitlinien verschiedener Länder (Keep Cool)* [Best-practices for vaccine storage: a review of national recommendations and guidelines of different countries (Keep Cool)]. Der Internist 2017, 58 (Supplement 1): 39 (PS85). (Poster Prize)

German College of General Practitioners and Family Physicians; Düsseldorf, Germany; September 2017

Thielmann A, Weltermann B. *Keep-Cool: Entwicklung einer online-basierten edukativen Intervention zur Optimierung der Impfstofflagerung in Hausarztpraxen* [Keep-Cool: developing an online-based educational intervention to improve vaccine storage in general practices]. German Medical Science GMS Publishing House, 2017, Doc17degam154, DOI: 10.3205/17degam154.

German Society of Internal Medicine; Mannheim, Germany; April 2015

Thielmann A, Gesenhues S, Weltermann B. *Impfstofflagerung in Hausarztpraxen: Eine Pilotstudie zur Qualität der Impfstoffkühlung* [Vaccine storage in general practices: a pilot study on the quality of the vaccine cold-chain]. Der Internist 2015, 56 (Supplement 1): 66 (Z114).