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Factors Causing Decreasing Quality of Vaccines: A Systematic Review

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Abstract

Objectives. Vaccines were essential to prevent the spread of disease. The contents would be practical if the storage, distribution, handling, and delivery to the target were carried out correctly and following procedures. Methods. Using guidelines from the PROSPERO platform using the PRISMA flow diagram to select articles. The search keywords are observational studies, experiments, qualitative studies, and grey literature. Studies addressing factors affecting vaccine quality, published between 2009 and 2022 in English, were included. Results. Of the 13 included studies, several factors were identified, all explained due to inaccurate vaccine storage temperature settings. From several studies, it is recommended to carry out consistent SOPs, supervision, training for staff involved in vaccines, innovation of vaccine distribution tools, and policies from local government stakeholders.

Introduction

Vaccines are a very effective health strategy to help prevent disease and extend life expectancy (Pandolfi *et al.*, 2018). Vaccination in European and American countries can prevent outbreaks of diseases such as measles. In addition to the vaccination implementation, its content is crucial because it will affect its effectiveness (Satcher *et al.*, 2022). The success of a vaccine is also determined by the correct selection of the vaccine type, carrier or vector, adjuvant, excipient, dosage form, route of administration, logistics of vaccine production, storage, distribution, and mass vaccination (Wang J, *et al,* 2020). Disease prevention using vaccines has been shown to reduce mortality cost-effectively and increase life expectancy. According to WHO, it can prevent 2 to 3 million deaths annually and is projected to increase by 6 million if vaccinated according to the recommended vaccine schedule. A form of concrete evidence is the Covid 19 Vaccine (Kumraj *et al.,* 2022). The COVID-19 pandemic globally has not ended and is still significantly impacting people worldwide, especially among people in Indonesia. Overcome these vaccination programs are crucial to ending the COVID-19 pandemic as they can reduce morbidity and mortality, achieve herd immunity in communities and build herd immunity against the COVID-19 virus (Tambunan *et al.*, 2022).

Some vaccines are part of a wholly or partially purified protein. Acellular pertussis vaccine has replaced whole cell pertussis vaccine. These licensed acellular vaccines consist of one to five proteins from the pertussis bacillus (Plotkin S., 2014). Stability is an important variable that needs to be considered in any product (Cheng *et al.*, 2023). The stability of biological products, such as vaccines, will be a more significant challenge when compared with other pharmacological molecules. The protein's physical activity, which is the main constituent of the vaccine, originates from the covalent bond structure and the folded conformation of both the secondary and tertiary structures (Kardani, 2021). Vaccines

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not carried out according to standard operating procedures (SOP) will increase morbidity and mortality from preventable diseases (Pandolfi *et al*., 2018). In the manufacture of vaccines, the membrane protein of a disease virus is involved. For example, the S. aureus vaccine contains five antigens containing bacterial toxin molecules, membrane proteins, and proteins that are closely related to the metabolism of bacterial growth and provide enhanced protection by inhibiting or blocking key pathogens(Zeng *et al.,* 2020). In the vaccine protein structure, a conformation causes partial or even complete denaturation of biological activity, which will cause the protein of the vaccine to lose its action, so this needs to be handled carefully (Mohammed *et al*., 2021).

Multiple factors cause the decrease in protein in the vaccine. Related to the vulnerability of the molecules in vaccines, costs, and low-temperature stability must be maintained so that when a vaccine is produced, problems related to *the cold chain* are critical to pay attention to (Gebretnsae *et al*., 2022). The cold chain stores and transports vaccines in their potential state (within the acceptable temperature range) from the producer to the target (Bogale *et al.,* 2019). The cold chain system is vital in maintaining vaccine quality during distribution. This is assumed to pose the most significant risk, especially in tropical countries where the electricity supply is unstable, and facilities for its maintenance need to be better developed (Bogale *et al.,* 2019). Vaccines lose their function and content can also be caused by exposure to heat and sunlight, so a strategy is needed to avoid exposure to heat (Gebretnsae *et al*., 2022).

In building immunity, each vaccine with different ingredients has different handling. The innate immune system must be activated and recognize antigens as foreign substances to establish an antigen-specific immune response. However, inactivated viruses and recombinant protein antigens are often poorly immunogenic and require adjuvants to enhance their immunogenicity. Viral and bacterial vector-based vaccines do not require adjuvants (Wang *et al.,* 2020). Based on the description above, researchers want to examine several things related to what factors cause vaccines to lose or lack the protein content in them, which in this case is called vaccine quality.

Methods

We preferred Reporting Item Systematic Review and Meta-Analysis Guidelines (PRISMA) Guidelines. The search strategy aims to retrieve studies that discuss the factors that cause protein in vaccines to decrease. We also reviewed *the gray literature* and the bibliography of relevant and included studies to minimize the risk of missing eligible studies. The keywords used are "storage area" AND vaccine AND protein OR "vaccine raw materials" AND "cold chain management".

Researchers included observational and experimental studies using RCT, quasi-experimental, *case-control, cohort*, and *cross-sectional study designs*, qualitative studies, and articles published from 2009-2022. In addition, the researchers (DL and MF) conducted a critical appraisal of the reports analyzed using the JBI essential appraisal guidelines. Five researchers (N, HR, DL, MF, and WS) independently reviewed three databases: PubMed, ScienceDirect, and Google Scholar. The search strategy is described in Figure 1. The search was conducted between April 2022 to June 2022. The feasibility of the article is assessed from the process of evaluating the abstract and the title of each article for inclusion and exclusion. The inclusion criteria are articles that use English, discussing the protein content in vaccines, while the exclusion criteria are articles before 2000. After extraction, identical pieces are removed and extracted into Microsoft Excel. Two researchers (N and HR) applied the eligibility criteria, and the results were validated by a third researcher (WS) to consolidate the final study selection. This difference was resolved by conducting discussions between the three researchers.

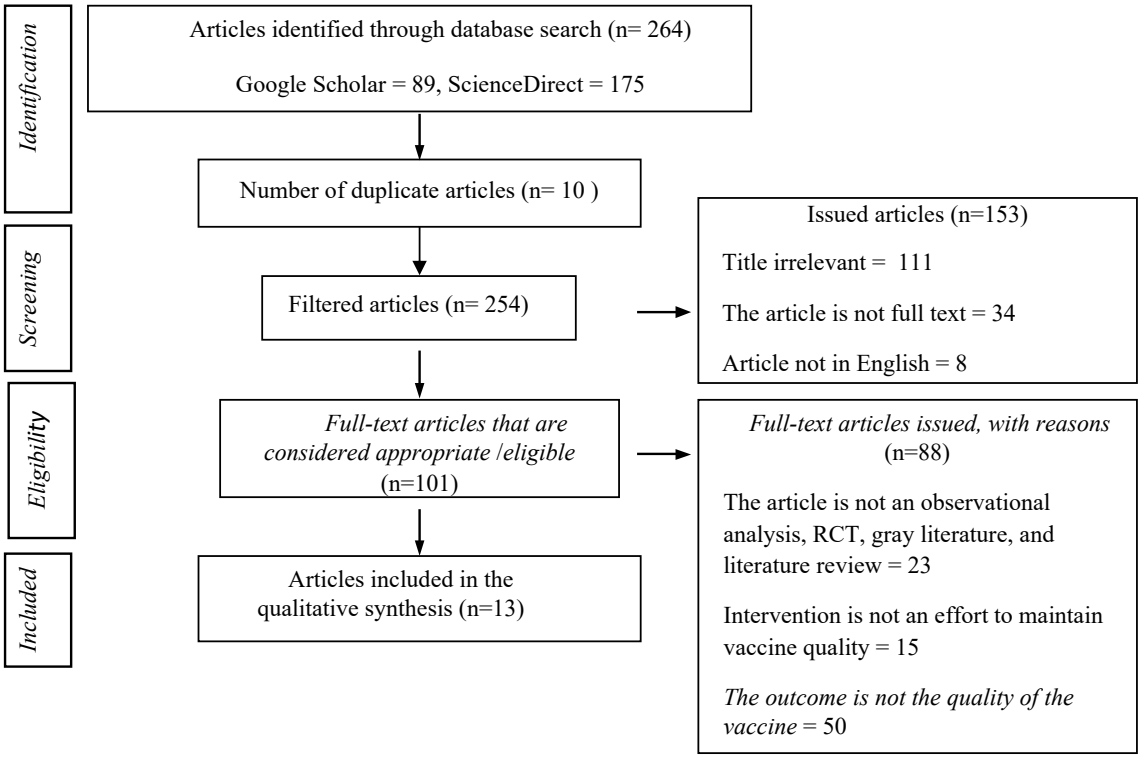
Results and Discussion

In April 2022, researchers found 264 articles using *the keywords* they sought. Among the articles that have been obtained, researchers choose relevant articles. Many factors cause the quality of vaccines to decline. This is very important to study because it affects the quality of vaccines that will be given to prevent certain

diseases. The search for the initial identification of articles was 264, with ten duplicates, so they were excluded, and 254 articles went to the next stage. There were 111 irrelevant titles, 34 non-full text articles, and eight non-English articles, so 153 were issued. Ninety-eight full-text articles were screened, but 88 were excluded for reasons, not observational analysis, 23 experimental articles were included, 15 were not the intended intervention, and 50 were not outcomes to maintain vaccine quality. So, the remaining thirteen articles were analyzed (Fig. 1).

The articles found for analysis came from high-income countries (HICs) such as the United States of America and Australia and low- or middle-income countries (LMIC) such as Ethiopia, Vietnam, Ghana, Africa, and India, with the year of article publication being between 2009-2021. Shows that the findings in this article are still relevant and in a good year of publication. The implementation of research conducted by David (2016) in Nigeria is a cross-sectional study regarding the bonding of protein content and how to stabilize it related to this content, in contrast to Manoja (2020), who conducted research in 213 health facilities in vaccine rooms at the level of three states in India. Meanwhile, another study by Bogale (2019) made an observational study that recommended an urgent need to improve cold chain management knowledge and practices through enhanced monitoring. Other articles conducted a cross-sectional study and quasi-experiment to observe the causes of decreased vaccine quality.

The study results cover high-income countries (HICs) (United States of America and Australia) and low- or middle-income countries (LMIC) (Ethiopia, Vietnam, Ghana, Africa, and India). Various vaccines are examined in this article, such as measles, polio, influenza, and hepatitis B vaccines which are included in the VFC. The same problem is found in the distribution of vaccines, both in high and low-income countries. The existence of temperature regulation in the distribution of vaccines makes this one of the most influential factors in reducing the quality of the vaccine. In addition, the knowledge of vaccine workers and the lack of training for officers is also a factor that influences vaccine quality.



Source: Prepared by authors based on the PRISMA flow diagram.
Figure 1. Prisma Flow Diagram Systematic Review

Table 1. Summary of Research on the Factors that Affect the Decline in Vaccine Quality

Title/Author Name (Year)	Country	Types of Vaccines and Proteins	Method	Research result	Outcomes
Factors affecting vaccine handling and storage practices among immunization service providers in Ibadan, Oyo State, Nigeria., David et al. 2016, Dairo & Osizimete, 2016 (Mojtabavi et al., 2019)	Nigeria	Vaccines in LGA's	Cross-sectional	73% knew vaccine handling and storage guidelines, and 68.4% had read such guidelines. Only 15.3% of the study said they had read the guidelines one month before. Approximately 65.0% had received immunization administration training. Reported mishandling included storing the injection with the vaccine (13.7%) and maintaining the temperature of the vaccine with an ice block (7.6%). Approximately 43.0% had good knowledge of immunization management, but 66.1% had good immunization management practices.	Regular training is recommended to enhance vaccine handling and storage practices.
Evaluation of Cold Chain Management Performance for Temperature-Sensitive Pharmaceuticals at Public Health Facilities Supplied by the Jimma Pharmaceuticals Supply Agency Hub, Southwest Ethiopia: Pharmaceuticals Logistic Management Perspective Using a Multicentered, Mixed-Method Approach, Diriba, Feyisa et al., 2021 (Chen & Kristensen, 2009)	Ethiopia	All types of vaccines and temperature-sensitive medicines	Cross-sectional	According to the survey, the average inventory rate of major cold chain products was 72.1±14.8%, and the average non-stock rate was 26.2±8.6%. The mean length of stay across all public health facilities visited was 23 ± 21 days. We found 263 (43.06 ± 15.3%) of the inventory records from public health facilities to be correct, with a rejection rate of 9.2 ± 7.8% across all health facilities visited. Thirty public health facilities (63.8 ± 36.2%) had acceptable storage conditions.	Facility management by providing proper training and supervision of cold chain pharmaceutical staff

Title/Author Name (Year)	Country	Types of Vaccines and Proteins	Method	Research result	Outcomes
Temperature integrity and exposure of vaccines to suboptimal temperatures in cold chain devices at different levels in three states of India, Manoja Kumar et al., 2020 (Das et al., 2020)	India	All types of vaccines	Cross-sectional	Vaccine stability and efficacy are generally temperature-dependent. The effects of exposure to vaccines at elevated temperatures are usually cumulative, altering protein structure and chemical stability and potentially rendering vaccines ineffective.	Vaccine stabilization method
Assessment of Factors Affecting Vaccine Cold Chain Management Practice in Bahir Dar City Health Institutions, Mulatu et al. (Mulatu et al., 2020; Sykes, 2018)	Ethiopia	All types of vaccines	Cross-sectional	The fitted model showed that well-informed respondents were 2.6 times more likely to practice good cold chain management than uninformed respondents. HCWs with 2+ years of professional experience are 95% 5.2 (1.4-19.14) and 95% 1.97 (0.77-5.03) in cold chain management, nearly five times more likely than their peers to perform well. It was very reasonable.	Ongoing efforts to maintain a safe and effective cold chain Required for both education and training to improve the knowledge of medical professionals and improve both infrastructure capacity and suitable equipment
Cold chain temperature monitoring in Vietnam, Robertson, 2010 (Hanson et al., 2017)	Vietnam	HPV vaccine	Observational study	There is a documented risk of exposure to ambient temperatures, seasonal and geographical effects during storage and transportation, and temperatures below recommended storage temperatures.	Recommendations for temperature regulation, transport, and storage of the HPV vaccine.
Vaccine instability in the cold chain: Mechanisms, analysis and formulation strategies, Kumru, 2014 (Kumru et al., 2014)	United States of America	Vaccination against measles, polio, influenza, and hepatitis B	Observational study	Vaccine instability is due to a lack of stabilization in the vaccine cold chain.	Modifying and innovating vaccine development, production, and distribution capabilities.
Effective Vaccine Management: The Case of a Rural District in Ghana, Osei, 2019 (Osei et al., 2019)	Ghana	All types of vaccines	Qualitative study	Vaccine management and supply are inadequate and need improvement. Health workers need training in distributing and procuring vaccines to bridge the knowledge gap regarding vaccine storage and distribution.	EVM assessment recommendations are carried out for vaccine distribution.

Title/Author Name (Year)	Country	Types of Vaccines and Proteins	Method	Research result	Outcomes
Calling for the next WHO Global Health Initiative: The use of disruptive innovation to meet the healthcare needs of displaced populations, Staruch, 2018 (Staruch et al., 2018)	United States of America	All types of vaccines	Observational study	There is a need for proprietary formulations for biologics and vaccines due to stability in the risk of an unstable environment.	Vaccine stabilization innovation
Factors that affect vaccine availability in public health facilities in Nairobi City County: a cross-sectional study, Kanja et al., 2021 (Kanja et al., 2021; Tan et al., 2014)	Africa	Vaccines for Children (VFC)	Cross-sectional	Most facilities had shortages of vaccines and deliveries during the survey and in the last 12 months. The most affected vaccines were tetanus (88%), measles-rubella (81%), and oral polio (79%). Inventory shortages were caused by rationing (82%), inventory levels (93%), transport shortages (55%), and forecast shortages (50%). The majority of facilities (91%) used public transportation, and only 1% used reliable government commercial vehicles for vaccine delivery and other logistics.	Cross-sectoral collaboration of all stakeholders in support of vaccination to harmonize roles between national and local governments and improve vaccine availability in public health settings.
Practice nurses best protect the cold vaccine chain in general practice, Carr (2009)	Australia	All types of vaccines	Quasi experiment	A key finding of this study was the positive impact of general practice nurses on achieving the integrity of the vaccine cold chain as defined by WHO. His 98% (98%) of general practices employing GPs maintained the integrity of the vaccine cold chain, whereas in general practices not employing GPs, he was only 42% (95% CI: 10, 58) obtained similar results.	The primary outcome criteria were adherence to acceptable cold-chain management practices for vaccines according to the National Health and Medical Research Council guidelines and keeping vaccines refrigerated within the World Health Organization (WHO) recommended range of 2 °C to 8 °C to maintain the temperature.

Title/Author Name (Year)	Country	Types of Vaccines and Proteins	Method	Research result	Outcomes
Evaluation of cold chain and logistics management practice in Durg district of Chhattisgarh: pointer from Central India, Sinha et al. (Sinha et al., 2017)	India	Vaccines for Children (VFC)	Cross-sectional	Correct placement of ice packs in the freezer was only observed with one CCP. T-series vaccine vials were placed correctly in the ILR at 85 µP. When it came to knowledge about freeze-sensitive vaccines and shake tests, 74% of cold chain workers had correct knowledge compared to 53% of them. Also, cold chain and logistics management components did not meet the requirements of the study area.	We recommend continued training and the supportive monitoring of cold chain handlers to take into account the surprising findings of this study. Regular on-site monitoring by local physicians/vaccinators responsible for proper cold chain practices will help ensure the quality of immunization services in the study area.
Assessment of factors affecting cold vaccine chain management practice in public health institutions in the east Gojam zone of Amhara region, Bogale et al. (Bogale et al., 2019)	Ethiopia	All types of vaccines	Cross-sectional	Thirty-five (58.3%) had adequate cold chain management of vaccines, and the remaining 25 (41.7%) had inadequate practices. Logistic regression showed that knowledge gaps and occupations were significantly associated with P< cold vaccine chain management practices $p < 0.05$.	Recommendations for there is an urgent need to improve knowledge and practice on cold chain management through improved supervision.
Knowledge of vaccine handlers and status of cold chain and vaccine management in primary health care facilities of Tigray region, Northern Ethiopia: Institutional based cross-sectional study, Gebretnsae et al. (2022)	Ethiopia	All types of vaccines	Cross-sectional	In this study, fifty Primary Health Care Facilities (PHCFs) were included with a response rate of 94.4%. The overall level of good knowledge of vaccine handlers and good status of cold chain and vaccine management was 48% (95% CI; 30.7%-62%) and 46% (95%CI; 26.1%-61.3%) respectively. Receiving training on cold chain and vaccine management (AOR = 5.18; 95%CI: 1.48–18.18) was significantly associated with knowledge of vaccine handlers. Furthermore, receiving supportive supervision (AOR = 4.58; 95%CI: 1.04–20.17) and good knowledge of vaccine handlers (AOR = 10.97; 95%CI: 2.67–45.07) were significantly associated with cold chain and vaccine management.	The cold chain and vaccine management status was poor. Program-based supportive supervision is needed to improve cold chain and vaccine management.

Title/Author Name (Year)	Country	Types of Vaccines and Proteins	Method	Research result	Outcomes
Vaccine Cold Chain Management and Associated Factors in Public Health Facilities and District Health Offices of Wolaita Zone, Ethiopia, Erassa et al.(2022)	Ethiopia	All types of vaccines	Cross-sectional	The study indicates that 83 (61%) public health facilities had good cold chain management practices at 95% CI (52.2–68.4). Experience greater than 2 years (AOR=2.8, 95% CI=1.13–6.74), good knowledge on cold chain management (AOR=3.02, 95% CI=1.2–7.4), training on cold chain management (AOR=1.86, 95% CI=1.36–9.84), and supportive supervision on cold chain management (AOR=2.71, 95% CI=1.1–7.14) were statistically significantly associated with good cold chain management practice.	Strengthening the knowledge of healthcare workers and supportive supervision on cold chain management by giving training and monitoring their practice toward cold chain management may help to improve the cold chain management practice.
Assessment of cold chain equipment and their management in government health facilities in a District of Delhi: A cross-sectional descriptive study, Kumar et al. (2020)	India	All types of vaccines	Cross-sectional	Out of 56 electrical CCEs, 8.9% were nonfunctional, 48.2% were noncompliant with WHO standards, 5.4% were not chlorofluorocarbon free, 4.7% did not have a temperature monitoring device, and 18.8% did not have a stabilizer. Eighty-six percent of passive containers were compliant with the WHO standards. The storage capacity of electrical vaccine storage equipment was insufficient in 3.4%, passive container capacity in 65.5%, and ice pack preparation and storage capacity in 24.1% of HFs.	Many CCEs used in the ISC of assessed sites were noncompliant with the WHO standards. There was no PPM of CCEs and no guidelines for emergency event management.
The Analysis of Cold Chain Management of Basic Immunization Vaccine in Health Service Centers, 2018, Fauza et al. (2018)	Indonesia	All types of vaccines	Qualitative study.	The availability of human resources, funds, facilities infrastructure, and work procedures are sufficient, although there is still one untrained health service center staff, a lack of vaccine flasks in two health service centers, and a lack of voltage stabilizers in seven health service centers. Almost all health service centers have applied vaccine boxes 20C-80C in the vaccine transportation system. Based on the evaluation, only one health service center needs to improve, especially in temperature evaluation procedure by thermometer. The vaccine storage procedure has been applied by the health service center. However, the observation noticed three health service centers have problems with the time delay in the melting process	it is necessary to provide a thermometer in a vaccine flask that is brought from the puskesmas to the posyandu and improvement of daily and weekly refrigerator maintenance so that frost does not form > 0.50cm

Source: prepared author from studied retrieved

Protein consists of amino acids, and a high-pressure environment, low pH, and high temperature can cause unstable protein content (Wang *et al.,* 2020). Giving osmolytes gives the impression of stability in various existing proteins. However, apart from that, the change in protein is also influenced by pH, temperature, and pressure. The vaccine is a product that has a high sensitivity to temperature (Yakum *et al.,* 2015). Vaccine storage needs at different temperatures, oral polio vaccine (2-8 °C), DPT vaccine (< 0 °C), and HPV vaccine (-20 °C) are also different, and the vaccine protein will be damaged if the vaccine is exposed to heat at temperatures of more than 8 °C. In addition, other studies have shown that some drugs and vaccines will react to exposure to moisture, light, vibration, and shock (Yakum *et al.,* 2015). Air that is too cold or too hot, as well as the sun's intensity that continuously hits a product, will negatively impact the product's effectiveness.

Vaccine packaging will be the key to maintaining the quality of the vaccine itself. The protein contained will also be safe if distributed in the right conditions. Packaging using temperature or thermal controllers can monitor the temperature in a particular room. In its development, materials from PCM (Phase Change Materials) will provide the ideal or desired temperature and are relatively consistent (Das & Arora, 2020). Besides materials and distribution methods, vaccine shelf life also needs to be considered.

Another laboratory study, at Vexes Technologies, at the Harvard Life Lab in Boston, Massachusetts, used silkworms to help change the behavior of the molecules in vaccines. It can overcome degradation when the vaccine is at room temperature or higher. The interaction between the vaccine and this charge causes the molecules to stick together and denature the vaccine antigen, thereby changing its molecular structure. This access starts with a solid but flexible fiber that the silkworm makes from a protein solution that it secretes through the glands, and this can protect the vaccine molecules so that the contents in the vaccine cannot move and stick to each other (Yang *et al*., 2021; Sykes C., 2018).

Each vaccine has its characteristics, but the available vaccines generally survive at temperatures of 70 to 8 °C (WHO, 2021). Controlling temperature, light intensity, vibration, and cold storage is critical because this vaccine is a substance that contains a protein that changes its properties and properties quickly when stored at an inappropriate temperature (Hanson *et al*., 2017). Temperatures above average should be, pose a risk of ineffective vaccine administration. Therefore, it is also necessary to innovate tools for storing vaccines at cold temperatures using appropriate methods, such as cold storage (Bogale *et al*., 2019; Hatchett, 2017).

The selection of the proper cold storage is essential because of the nature of the vaccine, which is sensitive to changes in temperature. The vaccine will be stable by providing an effective cold chain, from manufacture, distribution, and storage, to administration (Kumru *et al*., 2014). Several things make vaccine storage refrigerators according to standards, such as the type of refrigerator that is suitable for cold storage of vaccines, the presence of a thermometer that can record the maximum and minimum temperature, in the vaccine cabinet, there is no food stored together with the vaccine (Yakum *et al*., 2015; Thielmann *et al*., 2019). Research shows that cold storage is generally reserved at room temperature between 20 and 25 degrees Celsius, with a humidity recommended by WHO of around 55% and a humidity level of about 45% to 75% (Kumru *et al*., 2014; CDC, 2021; Osei *et al*., 2019; WHO, 2020).

Many studies mention and highlight knowledge gaps in relevant health professionals in vaccines about the damage caused by vaccine freezing and improper temperature regulation, and it is vital to educate and train vaccine manufacturers and workers who manage cold chain temperature monitoring to improve temperature maintenance and chain management that facilitates targeted vaccine distribution (Hanson *et al*., 2017; Alonso-García *et al*., 2019). The process of storing, handling, preparing, and administering vaccines is complicated, and this requires efforts to simplify and improve overall education and training for staff involved in vaccines (Tan *et al*., 2014). That way, officers can have good knowledge about vaccine cold chain management and help

maintain vaccine quality to the target (Mulatu *et al*., 2020; Tan *et al*., 2014; Pambudi *et al*., 2022).

Cold chain management is very important for vaccine distribution, damage to vaccines, both the content and packaging, occurs because there is no good management in the cold chain management, good knowledge of cold chain management will help distribute vaccines properly to ensure good quality vaccine content (Fauza *et al*., 2019). In addition to temperature regulation, cold storage innovation, lack of staff knowledge, and lack of consistent standards, another critical thing that regulates all of this is the presence of government policies that also contribute. Several organizations such as Disease Control and Prevention (CDC), VFC Programs, Public Health Immunization Programs, the World Health Organization (WHO), and other health departments need to collaborate to recommend the best so that it becomes a guideline for the government to implement policies to comply with the best vaccine distribution implementation standards (Alvarez *et al*., 2022; Tan *et al*., 2014).

Effective maintenance of cold chain standards is also influenced by the knowledge and practice of the health worker or staff on duty. The results of the study revealed that only 38.3% of respondents had sufficient knowledge about vaccine cold chain management. Related potential factors were possibly responsible for this low level of cold chain management practices including inadequate knowledge or training, and inadequate support. So, in this case, the knowledge of officers regarding cold chain management is something that needs to be improved because it is important in maintaining vaccine quality (Bogale *et al*., 2019).

Conclusions

The protein content in vaccines varies depending on the function of the vaccine itself. Factors that reduce the quality of vaccines are humidity, temperature, the intensity of sunlight, vibration, and the pattern of vaccine distribution until it reaches consumers or patients. It is necessary to pay attention to the packaging and distribution methods to maintain the quality of the vaccine content and protein, as well as the knowledge of health workers regarding cold chain management so that all of them can create stable and quality vaccines.

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