

Cold Chain: A Lynchpin of National Immunization Program

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Abstract Cold chain management (CCM), a lynchpin of National Immunization Program (NIP) is to deliver the vaccines or other immunological products/ vaccines to right people, at right place, and in right time ineffective manner under the controlled conditions to ensure its potency. To comply it, CCM is required with standardized equipment's and standard procedures to transport the immunological products to ensure the availability of high-quality vaccines and immunization-related materials to all levels of the program. It is vital to ensure accurate implementation of pertinent strategies focusing on vaccine storage; transportation, immunization, safety, management & monitoring. If the CCM is managed properly, the program costs can be reduced markedly without sacrificing the potency of product. Apart from that, high and unwanted vaccine wastage rates are due to poorly managed planning resulting into significant variation in operation program cost, improper management of waste with the negative impact on public health.

The review enlightens on how vaccines are stored, transported and monitored to sustain immunological products/vaccines integrity throughout the way of their transportation emphasizing on the various equipment's and logistic needs to cover the entire cold chain management rigorously till the reach of target population child/mother at the primary healthcare centers(PHCs).

Keywords: Vaccine, National Immunization Program (NIP), Freeze Sensitivity, Heat Sensitivity, Primary healthcare centers (PHCs), eVIN (Electronic Vaccine Intelligent Network)

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1. INTRODUCTION

Immunization plays a significant role in survival of childhood across the globe. (Sachdeva, S. and Datta U. 2010) Major cause of morbidity and mortality among children as well as mother of developing countries are diseases like polio, measles, and hepatitis. These diseases are controlled and prevented by Vaccines under the immunization programs. (Hinman, A. 1999) Thus Immunization is one of the best and effect methods to control and prevent the childhood diseases. Immunization against a disease is achieved with the help of a potent vaccine to be vaccinated to the recipient in potent form. (Agrawal, D. K. 2005) India, itself contributes biggest Universal Immunization Program (UIP) across the nation where the most beneficiaries (almost 30.2 million pregnant women and 27 million infants) covered, the proportion of vaccines used is very high where the workers involved across 29 state boundaries and 6 Union Territories. (Mishra, N., and Kumar, S. 2016) The entire cost for the program is more than Rs. 2000 crores which is used to against the vaccine preventable diseases in children. (Hanjeet, K. et. al. 1996)

The program is mainly focused on six deadly Vaccine Preventable Diseases (VPD) i.e. Hepatitis B, Tetanus, Tuberculosis, Diphtheria, Pertussis, Polio and Measles. Apart from these diseases, Japanese Encephalitis (JE) is also included in Universal Immunization Program to protect the children in India. The channel of providing the Immunization services is well organized and vast. The health district hospitals, primary health centers are the integral part of infrastructure dealt with the immunization action plan along with the community health centers (CHC) and many sub-centers also. (Ministry of Health & Family Welfare, Government of India. 2003 and Baldiwala, Q. 2001)

To attain the successful immunization, an organized and well-planned cold-chain storage systems has developed consisting of State, District in associationship of Government Medical Supply Depots (GMSD), PHC/ CHC vaccine storage points and Regional/Divisional centers. Vaccine stores and. The backbone of the immunization program is the cold chain to ensure the quality and right quantity reaches to the affected children, women, and other population. A predefined system of the logistic is essential for storing and transporting the vaccines. Primarily the vaccines reached to the main stores i.e. Government Medical Store Depots (GMSDs) and it is used to maintain the stock for maximum of 3 months. Karnal, Chennai, Mumbai and Kolkata are 4 Government Medical Store Depots in India. The flow of vaccines is from vaccine stores of the states to through divisional to district and finally it reaches at last storage center of CHC or PHC. (Srinivasan R. 2005) These methods are generally used to keep and distribute the vaccines by maintaining

its potency throughout is expressed “cold chain.” Other names like vaccine supply chain, or the immunization supply chain are also used synonymously for cold chain. This consists of a chain of storage and transport links, all of which are designed to retain the vaccines at controlled or ambient temperature to the reach of vaccine to target recipients. (Srinivasan R. 2005)

Vaccine Adverse Event Reporting System (VAERS) presented data till Dec 2014 and found that the cases for hospitalization are **1244**; cases of people reporting a disability are **416**; **122** reported deaths; reported life-threatening cases are **388** . The following data presents the year and different reported cases of disability, hospitalization, deaths, or life-threatening illness presented on and the reason behind these are some spurious or deteriorated vaccines might be responsible. The deterioration is due to improper storage, inadequate handling and unorganized/uncontrolled transportation of temperature sensitive products under bad cold chain. (*Dr. Bob 2014*)

Now one can understand how serious concerns are associated with the immunological products control, management, storage, and transportation to the target reach. So, cold chain management plays a remarkable role in entire immunization program and an error in coordination of vaccines leads to result even death of children, mother, patients, or other population after immunization. Thus, its challenging to preserve the vaccines under optimum temperatures for longer period during the transit. (Thakker, Y. et. al1992 and Bell, K. N. 2001) Vaccines are wasted upto certain extent during the implementation of the immunization program and different states have different wastage rate which depends on the cold storage capacity and the available infrastructure. The vaccines are categorized on basis of their sensitivity whether it is freeze sensitive or heat sensitive. On basis of the sensitivity, the immunological products are stored, handled, and transported from one place to another till the immunization. (Nagdeve D and Bharti D. 2006)

2. LITERATURE REVIEW

An alarming rise in the deaths of children after vaccination has put this issue under the scanner of the Union Health Ministry, Govt. of India and triggered off ripples of apprehension among the public. Times of India covered the a news of 128 children who died in 2010 and reason behind the death was adverse effects observed post immunization. The number of deaths has escalated over the past three years from 111 in 2008, 116 in 2009, 128 in 2010, 156 in 2014 and 197 in 2016. According to media sources, the numbers only appear to be climbing upwards. Sources in the logistics industry and the medical fraternity are analyzing the cause of death and indicate that among other reasons, neglect of cold chain facilities could be a possible reason for such deaths. (Umit, K.,

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Milstien, J. 2014) Last year a shocking news published in Times of India dated 1 July 2016 stated about the National Immunization Program and Cold Chain Management stating that 25 per cent of the vaccines which contributes a huge proportion, go waste before the reach to doctors and followed by to the patients. Out of these, many vaccines may lose the potency or efficacy completely due to poor control and logistics management for the cold chain.

It is a major challenge for the public health agencies and government mainly in the surrounding areas where supply chain logistic and infrastructure are in poor shape to control the cold chain management. (www.logistics week.com July 2015) To overcome the problem, Ministry of Health is now taking initiatives to put in action increasingly/additionally to manage the supply chain in a better way. More than 27,000 cold chain points have been planned in intention to store and distribute of the vaccines. The world's largest vaccination drive is Universal Immunization Program (UIP) which is planned to introduce a rigorous and real time electronic vaccine intelligence network (EVIN) to simplify the vaccine stock supervision and monitoring of cold chain temperature with the help of mobile technology. Majority of vaccines are heat sensitive and the potency of vaccines are maintained 2-8 °C.

Dr Amin Kaba, a pediatrician at Saifee hospital, Mumbai, emphasized about the cold chain that most of the health care professionals are not having ample knowledge of cold chain facilities or even logistics and don't understand how this could impact the health sector. Many health care professionals/doctor's stores medicines in the door of the refrigerator in their clinics but if vaccines are stored in the door of refrigerators; it causes the vaccine to lose its potency. However, Dr. Kaba mentioned that it would not cause death — there are other factors too. The change in color of VVM reflects whether vaccine should be used or not if the quality of the vaccine has declined. Dr Usha Agboatwala, a Pediatrician at Mazagaon, Mumbai, says, "its critical to maintain the cold chain. If a vaccine is not properly preserved it becomes useless."She also highlighted the state government's preference for cheaper vaccines and the lack of a regulatory body to institute stringent quality control guidance to the stakeholders and it may be a possible reasons for such deaths. Other probable reasons for such deaths are poor immunity power of the children, improper administration of vaccines and acute malnourishment of young children who are unable to tolerate the vaccine dose.

The largest number of deaths has been registered in Maharashtra. "Services in Maharashtra have been on the decline. In southern states, no quality check is there because situation is different and diligence is greater in the province. Even Gujarat is better than Maharashtra in this regard and the deaths are occurring largely due to mismanagement of cold chain practices from production to the

last mile. Generally, the inefficiencies exist at the last leg of a vaccine's life cycle. (United Nations/AGECC 2010) The chances of errors in the last leg of distribution, storage and time lapse before vaccination at outreach points because this step is less monitored. But the production and the first leg of distribution may still be well-controlled and monitored. Any lacunae in the protocol would also impact quality and efficacy of the vaccine. The pharmaceutical companies have taken various efforts to ensure the quality of the vaccines. Hence it is vital to comply cold chain temperature as per the recommendation and avoid the cold chain breach. (United Nations/AGECC 2010)

The cold chain at the peripheral levels controlled and engaged by people i.e health workers to preserve the equipment and temperature. (Mallik s, et al. 2011 and Aggarwal, A, et. al. 1995) Adverse reactions and/or missed opportunities to vaccinate are the clinical outcomes resulting from cold chain break which denotes an inadequacy in "cold chain maintenance". Goel et al reported that it is an unsatisfactory maintenance of the cold chain apparatus in their evaluation of cold chain system in Chandigarh. (Goel, N. K, et. al. 2004) Prior to reach the doctors and patients, about 25% of the vaccines may lose their potency due to inadequate quality supply chain and logistics management system before the administration to the patients (Bachani, D. 1990 and Ortega, M. P., et. al. 2002)

Government and public health agencies is facing lot of temperature control related issues to address the immunization coverage, when supply chain logistics and set-ups are in poor shape. Thus a cold chain management is vital and crucial step to ensure quality or efficacy of vaccines or any other biologicals also. (Dr. Bob 2014)

The total wastage volume of vaccines is of 25% for all kind of vaccines with exception of BCG which wastes goes upto 50% as per Immunization Technical Support Unit (ITSU). (Dr. Bob 2014)

In United States, severe vaccine adverse reactions have been reported so far to the Centers for Disease Control between 3,000 and 4,500. These are not mild reactions but severe reactions resulting hospitalization or in the intensive care units (ICUs) or death stated or cause a permanent disability as stated by by Dr. Bob Sears, a pediatrician (California), said on CNN (2 Feb 2015). Cold chain preservation is systematic and a continuous process to maintain temperatures between +2°C to +8°C to ensure their potency, efficacy while in transit, the storage process for vaccines from the manufacture point up to the beneficiary should be controlled and recorded in timely manner. (Srinivasan R. 2005)

Environment conditions (such as temperature, heat, relative humidity, and light) affects the vaccines deadly if not controlled properly and it is the

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utmost need to monitor the transferring, storing, handling, and holding areas throughout which the biologicals/vaccine passes. To avoid any negligence during the cold management, the monitoring processes should enable the alarming of temperature excursion (control and monitoring tools) during the time of day and night. The data generated during the transit, should be archived much safely, data should be available on time and inspected out regularly. (Le Tailec, D., et al. 2009)

2. METHODOLOGY OF VACCINE BIOLOGICAL INTIGRITY

The methodology explains different crucial steps to ensure the biological integrity of vaccines w.r.t. efficiency and potency. After compliance, of all requisite, one can ensure the potency of the vaccine till the child/mother immunization.

2.1 Vaccine storage temperature and compliance

The temperature range between 36° F and 46°F (previously between 35° F and 46° F) is being recommended by the **Advisory Committee on Immunization Practices (ACIP)**. All the manufacturer inserts stated the Celsius temperature range (between 2°C and 8°C) which remain unchanged for vaccines. Throughout the proper vaccine storage and their handling plays a significant role to eradicate and prevent many common vaccine-preventable diseases. Many patients are being revaccinated because of storage and handling errors and significant financial loss due to wasted vaccine. Community losses confidence about to vaccinate their Children because the vaccines quality has been compromised during the handling.

The storage conditions of refrigerated vaccines lie between 2°C /36°F and 8°C/46°F. Vaccines are stored in between -50° C/-58°F and -15°C/+5°F in the deep-freezer without any kind of excursions where the thermostat is an alternative tool to control and assure the appropriate frozen temperatures. (Aggarwal, K. et. al. 2002) Transportation of vaccine is based on the type of vaccines because vaccines are more prone towards the heat and freezing. Sensitivity to heat and freezing are crucial steps for immunological products management. These vaccines are categorically placed as per the heat sensitivity as given in figure 1.1

On basis of heat sensitivity, vaccines are generally grouped into six categories. (Samant, Y., et. al. 2007) The vaccines are categorized into six categories on basis of sensitivity to heat. The groups are A, B, C, D, E, F starting from most sensitive to heat (group-A) towards the less sensitive to heat (group-F). Primarily the heat stability is applicable and relevant for

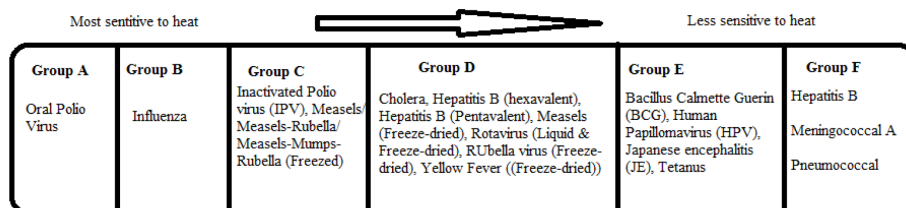


Figure. 1: Types of Vaccines based on heat sensitivity.

freeze-dried vaccines only to unopened vials but the potency of the vaccines might be decreased rapidly after reconstitution.

The light sensitive vaccines are liable to degrade when exposed to light and the freeze sensitive vaccines are liable to degrade when reaches to the freezing state. (Pande, R.P. 2003) Thus it's always essential to protect the potency of the vaccines to provide an ambient temperature during the storage and transport.

There are the UIP guidelines for light and temperature which are to be followed during the cold chain management as given in the table 2 and its mandatory to control the temperature as described. Any temperature excursion (above and below) is enough to damage the potency of vaccines by understanding the above groups of the vaccines. (Samant, Y. 2007)

Table 1. Cases of cases of disability, hospitalization, deaths, or life-threatening illness.

	Year	Number of reported cases of disability, hospitalization, deaths, or life-threatening illness
Vaccine Adverse Events year-wise	2014	1737
	2013	1837
	2012	1934
	2011	2045
	2010	2570
	2009	2701
	2008	2465
	2007	2289
	2006	1477

Table 2. List of freeze and light sensitive vaccines.

VACCINES	
Freeze sensitive	Light sensitive
DTap-hepatitis B-Hib-IPV (hexavalent)	Few vaccines are light sensitive and lose their potency when they are exposed to it i.e. sunlight/artificial light. Light sensitive vaccines are heat sensitive also.
Cholera	
Hepatitis B (Hep B)	
Hib (Liquid)	BCG
Influenza, Rotavirus (liquid & freeze dried)	Measles-mumps-rubella
Inactivated poliovirus (IPV)	Measles-rubella
Human Papillomavirus (HPV)	Measles
Pneumococcal, Tetanus, DT, Td	Rubella

Table 3: Temperature limitations of vaccines.

Vaccine	PHC	Light and Heat Exposure	Cold temperature exposure	Temperature (°C)
Heat and light sensitive vaccines				
Measles vaccine		Light and Heat sensitive	No damage under freezing	+2°C to +8 °C
OPV* vaccine		Sensitive to heat		
OPV* vaccine		Relatively heat stable, but sensitive to light		
Freezing Sensitive Vaccines				
Hepatitis B vaccine		Relatively heat stable	Freezes at -0.5°C (Should not be frozen)	+2°C to +8 °C
TT** vaccine		Relatively heat stable	Freezes at -3°C (Should not be frozen)	
DT*** vaccine		Relatively heat stable	Freezes at -3°C (Should not be frozen)	
DPT**** vaccine		Relatively heat stable	Freezes at -3°C (Should not be frozen)	

*OPV : Oral Polio Vaccine; **TT: Tetanus Toxoid, ***DT: Diphtheria and Pertussis, ****DPT : Diphtheria, Pertussis and Tetanus

The temperature excursions can be avoided by using 1. Excellent refrigeration units; 2. Excellent thermometers; 3. Rapid notification of issues before they become problems; 4. Excellent staff & excellent guidance which is most important but most variables.

2.2. Cold chain Management (CCM)

The cold chain management (CCM) is defined as the surrounding controlled temperature used to maintain and distribute vaccine under optimal conditions to protect its quality throughout. Three components are the main basis of an effective and reliable cold chain and these are:-

- An expertised and well trained professional/staff/worker.
- Equipments of reliable features like well calibrated or proper storage capacities.
- Precise and validated vaccine monitoring system

It is continuous process of control the storage and transporting the vaccines at the desired temperature series from manufacturing premise to the point of use. CCM is the need of hour and a vast cold chain infrastructure required to deliver potent, efficacious, and effective vaccine to last users like patients/ mothers/children/adolescent girls etc. from the manufacturer to the primary vaccine stores. (Levinson 2012 and Wirkas, T., et al. 2007)

2.3. Levels of cold chain system

Different levels of CCM are a decentralized management system in which areas are categorized on Primary, Intermediate and Peripheral level.

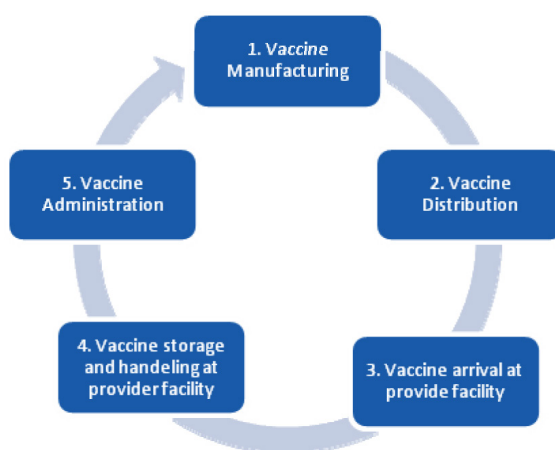


Figure 2: Cold Chain Flow Chart.

Table 4. Levels of Vaccine reach.

Levels		Management
Primary level	National	At national level, the freezers, cold rooms, cold boxes freezer rooms, refrigerators, refrigerated trucks used for bulk vaccine transportation.
Intermediate Level	Province/District	At district level cold boxes, cold/freezer rooms, freezers, refrigerators and sometimes refrigerated trucks are used for bulk vaccine transportation.
Peripheral level	health center/ health post	Generally, room refrigerators are used for health centers and Cold boxes, Gel Packs also applicable to sustain the viability of vaccines.

Various kinds of equipments for transportation and storage of the vaccines under the cold temperature are used to fulfill the need of different level needs. These equipments assist to maintain the integrity of the vaccines providing the vaccine ambient temperature to sustain its potency and allow the immunization program in effective manner. (Matthias DM et al. 2007) These different levels are:

2.4 Monitoring the cold chain

Many vaccines are very heat resistant and might be shipped without insulation from manufacturers to the end users at PSCs. But they might be deteriorated at or above the temperature of +48°C. To control and assess the excursions of the temperature a special device is required to monitor the transit and delivery temperatures.

For each shipment, an individual indicator is included and the staff must know how temperatures are monitored and understand how to interpret temperature readings from the instrument to avoid damage of vaccines. (Burgess, M.A., and McIntyre P.B. 1999) It is true for cold chain equipment that any machinery performance will always be good if it is effectively monitored and controlled by personnel. Cold chain system should be monitored regularly, to safeguard the vaccines. (Afsar A and Kartoglu U. 2006)

The vaccine integrity like potency/efficacy and its overall effectiveness maintained and it should be kept in its safe temperature range to achieve the desired therapeutic results as suggested. One must understand the basics of monitoring the vaccines during the storage and transportation as given below:

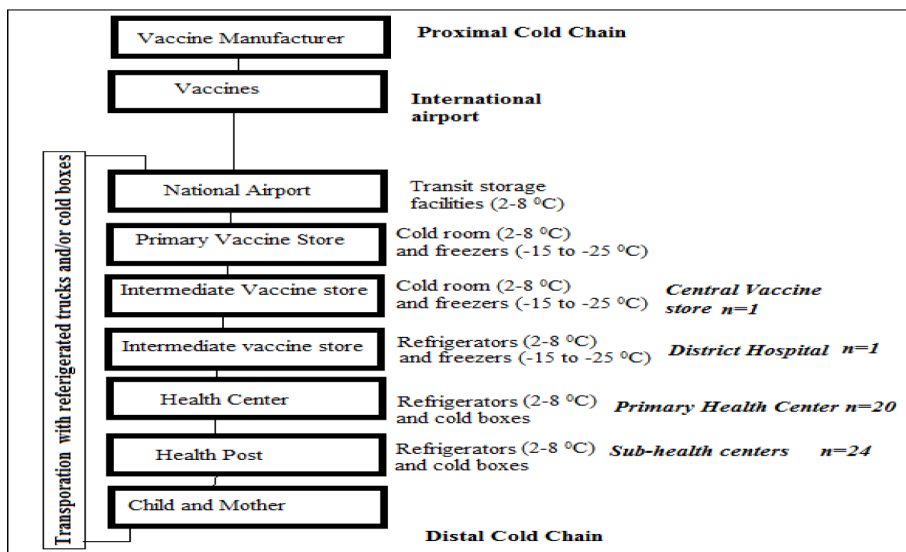


Figure 3: Cold chain maintenance flow chart as per WHO protocol.

Table 5: Recommended temperature ranges of Vaccines.

Vaccine Types	Stages of cold chain	Temperature (°C)	
		Max.	Min.
Hepatitis B and DTP	All		
DT, TT	Storage	+ 8°C	+ 2°C
Diluent	Point of Use		
Diluent	Transport		
Diluent	Storage	Ambient	+ 2°C
DT, TT	Transport	+ 40°C	+ 2°C
OPV, Measles, Yellow fever, BCG*	All	+ 8°C	-20°C

*BCG : Bacillus Calmette-Guerin

2.4.1 Vaccine Impairment

Vaccine impairment is the result of the inadequate handling of the immunological product during the handling, storage, shipment, or use. There are many ways to assess the biologicals/vaccines whether to use or not to use. One criteria is to evaluate the physical appearance of the vaccine but the physical appearance

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of many vaccines may remain unchanged even after it is damaged. Therefore, it is essential to know about the loss of potency due to either exposure to heat or cold to protect the vaccine from impairment.

2.4.2 Heat Damage

Vaccines are heat sensitive hence damaged by temperatures stored more than +8°C. It might be damaged exposed to heat in a short period like keeping vaccines in a closed container but exposed to the sun or a small amount of heat for a long period for example recurrent opening of lid of ILR during the exposure of heat. The risk of contamination for reconstituted BCG, measles, and Japanese Encephalitis (JE) vaccines is high due to their high sensitivity towards the heat and light. Because to these reasons, BCG uses time is very short and should be used within 4 hours of its reconstitution while JE vaccine should not be used after 2 hrs of reconstitution. (Jain, R., et. al. 2003)

2.4.3 Heat Damage evaluation: The Vaccine Vial Monitor(VVM):






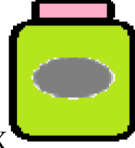


VVM is described as a label which is placed on a vial of vaccine to register cumulative heat exposure over the time and because VVM is composed of a heat-sensitive material which changes in its coloration on exposure of light/heat. (Chudasama, R..K., et. al. 2009)

The main factors which affects the coloration of inner square are temperature and time which causes the color changes from lighter to darken on inner square of the VVM gradually and irreversibly. It's essential to ensure the status of the VVM, before opening a vial. But it does not mean that potency of the vaccines can be measured directly by VVM. VVM only gives evidence about the factors responsible for potency like heat exposure over a period. The exposure to freezing (responsible for degradation of freeze-sensitive vaccines) cannot be measure by the VVM. (Jezek J. et al. 2009 and Schondorf, I., et. al. 2007) Therefore, the monitoring of the vaccine or immunological products handling is a crucial step in NIP where the VVM has a great role to assess the use or not to use the vaccines.

2.4.4 Electronic Vaccine Intelligent Network (eVIN)

United Nations Development Program (UNDP) control the overall the immunization program and strengthen the Universal Immunization Programme (UIP) with the appropriate designing and implementing an Electronic Vaccine Intelligence Network (eVIN). The entire eVIN system works in association with the Ministry of Health and Family Welfare, Government of India. The improved policy-making in procurement, vaccine delivery and planning for new antigens is the integral part of the eVIN. The success program can be

Table 6: Representation of VVM check.

Square	Mark (Yes/No)	Description
	 ✓	The vaccine may be used till the inner square is lighter than the outer circle but check expiry date, it is over or not. If vaccine expiry is over, then color of the square doesn't matter.
	 ✓	Vaccine can still be used if the inner square is still lighter than the outer circle with expiry date of vaccine has not passed.
	 X	Discard Point: When the color of the inner square matches with outer circle and there is no difference in outer circle and square box coloration. Then avoid to use the vaccine.
	 X	Beyond the discard point: this is a critical condition for vaccine and If the coloration of the inner square is darker than the outer circle, it is strongly recommended not using the vaccine.

observed that it must be designed and implemented to achieve the targeted vaccine deliveries with the optimum temperature control and potency in all districts (371 districts of India).

The eVIN system is enable to get the real time information on cold chain temperatures and vaccine stocks along with the flows of vaccine in all the districts of Madhya Pradesh, Rajasthan and Uttar Pradesh that count approximately 160. It's capable enough to keep the record of more than 10,500 vaccine stores and cold chain points in more than 12 states at one time. More than 2 million transactions of the vaccine data can be logged online at a time without any stuck-up of eVIN server. It has many advantages that it really strengthened entire immunization program of the state by arraying the managers who control the vaccine and cold chain in the districts to approximate the need of vaccines, to oversee the cold chain handlers across the district in coordination with cold chain technicians. This eVIN is standardized and authorized by the Government of India at every cold chain point to facilitate the efficient vaccine record-keeping through providing distribution register

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and standard stock. It also supports to the UIP to guide and coordinating the vaccine and immunization research network (VIRN) and Scientific Advisory Group (SAG). (UNDP).

The efficiency of the eVIN is such a way that it has been selected as a “best practice” at the National Summit on Good, Replicable and Innovative Practices and recognized as one of the premier scalable models in health care system. It is also considered as one of the best digital innovation under the Ministry of Health and Family Welfare, Govt. of India at the India International Trade Fair 2016. It developed in such a way to ensure the precise monitoring of the temperature by installing nearly temperature loggers to record the excursions during the storage, handling and transit.

3. EQUIPMENTS/DEVICES USED TO CONTROL TEMPERATURE

Various equipment are recommended for the storage of vaccines under the set temperature conditions around the year. The equipment differs in their capacity, size, and temperature control systems at different levels.

Equipment's are of electricity driven and electric supply is needed to maintain the recommended temperature, while others are non-electricity driven and it has advantage over the electricity driven is than the temperature can be maintained in absence of electricity supply also. On this basis, it can be categorized into electrical and non-electrical equipment's. (Kartoglu, U. et. al 2010)

3.1. Electrical equipment's: -

a) *Walk-in-Coolers (WIC)*

State and Regional/Divisional Stores permit to preserve used Walk-in-Coolers to store the bulk vaccines between +2°C to +8°C. These are used for vaccines, like DT, Hepatitis B, TT, DPT, Measles, BCG. Coolers have two identical units and generator along with in emergency. These coolers equipped with the alarm systems to alarm time to time at the excursions and temperature recorder to record the temperature overall as well. These may get activated if the temperature of the cooler exceeds more than +10°C. The coolers are equipped at different regional centers and have capacity to store vaccines 25% surplus for approximately 4-5 districts and stock for the districts they cater.

b) *Walk-in-Freezers (WIF)*

Whenever the bulk of oral polio vaccine (OPV) required to be stored then these freezers are on the priority. It also has additional advantage of preparing the ice packs at different state stores. These are capable enough to maintain

a temperature around (-) 20 °C or below. These freezers are available in dimension of 16.5 x 32 m³. These freezers are having the additional power back-up facility with standby two alike cooling units.

c) *Deep Freezer*

Deep Freezers are distributed with top opening lids under national immunization program to maintain the integrity of the biologicals. It may control the temperature between -15 to -25°C and generally used to store the OPV and used to prepare the freezing ice packs. It also has a great advantage to cover the temperature range of -15°C to -25°C for 18 & 26 hours at ambient temperatures in case of power failure if not opened. The Deep Freezer is having special insulation, to control the inside temperature from (-) 25°C to (-) 15°C. About 4-5 deep freezers have been provided to all districts whereas the small deep freezer kept at the PHCs.

d) *Ice Lined Refrigerator (ILR)*

The efficiency of the Ice Lined Refrigerators is more and cold air holding capacity is more than a normal freezing units having an opening at front. It is capable to keep vaccine in safe mode for 24 hour with a very little energy consumption of 8 hours. Smaller ILR to PHC headquarters are equipped with the larger ILR while the district headquarters should have equipped with bigger ILRs. The manufacturing of the ILRs is very simple and walls are composed of lining of water containers (ice packs or tubes) and held by the frame. These refrigerators are very much safe for the vaccines due to its property to maintain the inside temperature of the refrigerator at a safer level, if the electricity supply fails.

e) *Solar Refrigerators*

Solar refrigerators work on the principle of normal compression refrigerators but a photovoltaic refrigerator has the greater levels of insulation which surrounds the compartments of storage to maximize its energy efficiency.

f) *Domestic Refrigerators*

These are useful to maintain the cabinet temperature between 2 to 8°C as needed. It is good to load the refrigerators correctly to preserve the optimum temperature for vaccines and diluents. Universal Immunization Program (UIP) always prefers the refrigerators (in the rural places where the availability of deep freezers or other equipment are not available).

3.2 *Non-electrical equipment's*

a) *Cold Box*

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These are big in size and insulated boxes available in different sizes- five, eight, twenty and twenty-two with number of ice packs. The ice packs are conditioned before the vaccine are placed and should be placed at covering the vaccines from all direction with the top lid. The Vaccines are to be covered and kept with a layer of pre-conditioned ice packs in vicinity of cold boxes. The vaccine vials of DT, TT, DPT, and Hep B shouldn't be in direct contact with the ice packs but when other vaccines like OPV/ BCG/Measles are also shipping then DT, TT, DPT, and Hep B should be surrounded by OPV/ BCG/Measles vaccines. The pre-conditioning of the ice-packs is mandatory and after 20-30 minutes of preconditioning, the vaccines are packed accordingly.

b) *Vaccine Carriers*

The small quantity carriers called vaccine carriers and these may be used to transport the 16-20 vials of vaccines to the sub-regional center. These carriers are composed of insulated material which is the main basis of determining the life of cold efficiency of the carrier. Maximum four ice packs are to be kept in the vaccine carrier as per label specified. Always pre-conditioned ice-packs are used and the lid of the carrier should be ensured that it has been closed tightly or not to prevent any kind of loss of energy during the transit. The vaccines like DPT, Hep B, DT, and TT are mandatory to keep in direct contact with the ice packs.

c) *Ice Packs and their use*

In cold chain, ice packs play its role significantly and used for ice lining in between the cold boxes. The deep freezer may generate the ice packs under the temperature range of (-) 15 to (-) 25°C. Each manufacturer has its own specifications of ice packs. There are the manufacturing guidelines which should be complied whenever the desired ice pack is to be used for vaccine/ biologicals during the shipment from one place to another.

3.3 Temperature monitoring devices

When the immunological products like vaccines are transported from one place to another then it is essential that the temperature change is bound to happen during the transition? The devices are useful to measure the changes in temperature thus recording the temperature of the biologicals/vaccines during transit and storage with the help of various type of thermometers and equipments is advantageous. These instruments record the temperature and explore the chart of date of dispatch to date of delivery along with the temperature variations. If any temperature excursions are observed and the potency of the vaccines are affected, then it would not be used further for

immunization. Thus, the temperature devices are essential to make the NIP successful. (Lewis, P.R et. al. 2001)

3.3.1 Dial Thermometers (DT)

These thermometers are used to measure and record the temperature of the products in the Ice Lined Refrigerators (ILRs). A moving needle is there in the device to determine and gives the indication about the temperature of vaccine/biologicals in the stipulated temperature range of -50°C to +50°C. (Lewis, P.R et. al. 2001)

3.3.2 Data Logger or Electronic Data Logger (EDL)

These data loggers play a significant role to record and store the data related to all temperature deviations (if any) during the transit of the boxes/ILR in which vaccines are stored. This electronic device is kept with the vaccine and it can record the vaccine temperature for 30 days or more as per design. An alarm system is built inside the logger and the safe range alarm alerts the handlers as soon as the temperature excursions occurs out of the stipulated ranges. (Lewis, P.R et. al. 2001)

3.3.3 Alcohol Stem Thermometers (AST)

The sensitivity of these kind of thermometers are quite high and with the reason they produce more precise, more reproducible and accurate results than dial thermometers. One advantage with the thermometer is that it may be used for deep freezers and ILRs also from -50°C to +50°C. (Lewis, P.R et. al. 2001)

This device is helpful to monitor the vaccines exposed to less than 0°C. This is composed of the electronic temperature measuring circuit with LCD display. Its alarm becomes on if the temperature goes below -0.5°C (for more than 60 minutes) and “good” status to “alarm” status will be displayed on the screen during the excursions of temperature. There is a specially provision that and it must be kept between freeze sensitive vaccines (Hepatitis B, DPT, TT, DT etc.). Here is a cross on it and once it changes the cross, it cannot be further re-used and will be eliminated, means it is only one time use and no one can change the readings also. (Lewis, P.R et. al. 2001)

4. METHODOLOGY OF VACCINE VIALS EVALUATION

The expiry dates of the products are the key factors to assess the utilization and no-utilization. Thus it plays a crucial role in the quality control and inventory control of the products (biologicals/vaccines/food products/drugs etc). The expiry date of vaccine as depicted in figure 4 are the guidelines indicated on the vials about to use or not to be used.

Vaccine may be used up to and including the expiration date

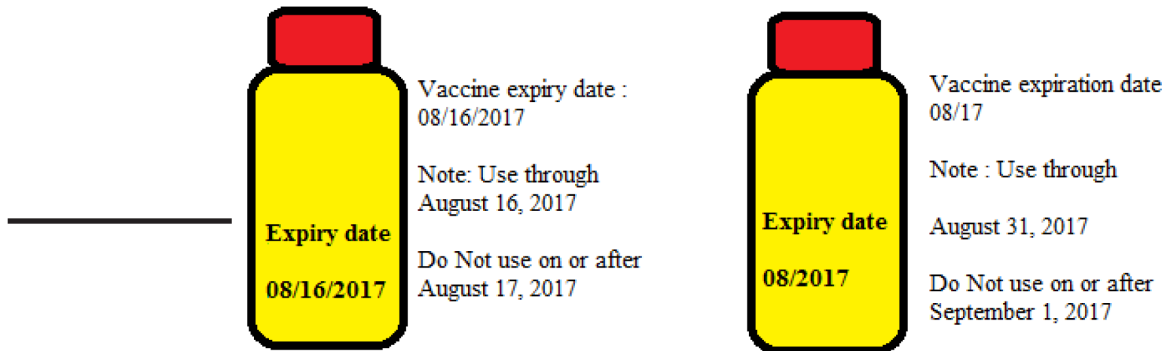


Figure 4: Vaccine expiry and its use.

There are different ways to depict the expiry dates but two procedures are adopted and there are 1. Year along with the month of expiry 2. Year with date and month of the expiry. When the date, month and year has mentioned as the expiry then the product should not be further used after that date, month in the year while if only month with the year mentioned in that case vaccines might be used till the last date of the month in that year as explained in the figure 4. (Kartoglu, U., et. al. 2010 ad Murhekar, et al. 2013)

Vaccines should be used on or before the expiration date—it is the date known as “**beyond use date**” (BUD). The basis of the calculation of BUD is depends on its opening and the person who opens first; entered the date of opening and its use beyond the date mentioned by him. Thus now the expiry date of the vaccine is replaced by this new date and it is the BUD for this opened vial or it may be used before the expiry date of the product. This new BUD information given by the person on the label of the vaccine vial should be initialed who made the change. (Stamatis D.H. 2003 and Kartoglu, U. et al. 2012)

Reconstituted vaccines have a limited period for their use and once the reconstitution of the vaccine done and diluent admixed with vaccine then the BUD should be mentioned. This period or BUD is labeled on the vial or on package insert so another person should aware to use or not to be used with the stipulated period. For example, if the label or package inserts of vaccine vials indicates to use the vaccine within 30 minutes, it must be used within the stipulated time otherwise vaccine must be discarded if not used by that time. This period of the vaccine utilization might only apply if the reconstituted vaccine is still present in the vial—not after it is drawn into a syringe—so check the package insert carefully.

Multidose vials are also having a specified period for use once vials have been entered with a needle. For example, the package says that the vaccine must be used within 28 days and discarded 28 days after it is entered. If the vial is entered on 06/Jan/2017, the BUD is 03/Feb/2017. The vaccine should not be used after 3 Feb and because it is BUD for the vaccine.

4. REGULATION GUIDELINES OF COLD CHAIN OR SUPPLY CHAIN

The regulatory bodies of the different areas like health, food, commerce, railway, water, law and many more plays a significant role for planning, designing, recording, collecting, reporting and execution of the guidelines under the purview or control of these agencies. Similarly, the regulatory of health system in every country across the globe has its own regulations to protect the right, safety, and wellbeing of human. As for as the immunization is concerned, it is an imperative need for the safety of the children and mothers specially when they deliver the babies to protect from the undesired diseases which may affect the health of the new born in future. Now question is that how the regulatory controls the health the public by providing the immunization or vaccination but it is challenge for the government or the stakeholders for the maintenance of the vaccine's integrity in terms of potency or efficacy. Therefore, it's an utmost need of the time to control the condition of the biologicals or vaccines during the phase of storage, handling and transportation. (Kurzatkowski W et al. and 2013 and Burton A, et al. 2009)

Thus Public and industry members strengthened the guidelines and requirements to meet the potency and quality of the product while distributing, storing and handling of temperature-sensitive immunological products. The spurious quality of immunological products will not be entertained by international organizations like WHO, vaccine cold chain have various global regulatory agencies and their requirements, Parenteral Drug Association etc. (Stamatis D.H. 2003 and Kartoglu, U. et al. 2012)

To address the issues related to the cold chain for immunological products or other biologicals, different regulatory bodies across the world are inclined to issue the regulatory oversight documents for guidance. Three type of institutions are accountable for the cold chain related compliance under these jurisdictions and these are 1. International Air Transport Association (IATA); 2. the International Conference on Harmonization; 3. National regulatory agencies of Member States (Health Canada, USFDA, EMA) issue guidelines for temperature control of drug products during storage and transportation. The International Conference on Harmonization of Technical Requirements

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for Registration of Pharmaceuticals for Human Use (ICH) and Food and Drug Administration (FDA) developed the key guidance on the supply chain management for temperature-controlled pharmaceutical and biotechnical products, including:

- ICH Harmonised Tripartite Guidelines Q6A and Q6B (Test Procedures and Acceptance Criteria for New Drugs and New Biotechnology). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products)
- ICH Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products
- FDA 483 observations on cold chain applications with suggested deviation offsets
- FDA CFR Title 21 203.32, 203.36, 211.150

The ICH guidelines are accepted by international community (US, Japan, and the European Union) and other developing countries also have faith for the standardization of pharmaceutical products. The FDA addresses three key regulations about cold chain and these are: (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products)

1. 21 CFR 203.32 “Prescription Drug Marketing – Drug sample storage and handling requirements.” It deals with the “Storage and handling conditions” and manufacturers, record distribution, and their representatives are bound to comply the labeling and compendia requirements.
2. 21 CFR 203.36 “requirement of shipping, houses, co-marketing agreements, and mailing services, with the third-party recordkeeping” in storing and shipping the drug samples. It must comply with the Prescription Drug Marketing Act (PDMA) and amendments with the recommendations relating to 21 CFR Parts 203 and 205.
3. 21 CFR 211.150 of Sub Part H: Holding and Distribution - “Distribution procedures” explained about the product shipment under appropriate conditions and optimum temperatures with requirements in the current edition of an official compendium, such as the United States Pharmacopeia/ National Formulary (USP/NF).”

Recently, various rigorous alterations and amendments to set the standards and putting forward the principles in pharmaceutical cold chain management were done to the guidelines including the ones from the United States Pharmacopeia, Health Canada, and the European Union. Thus an additional and growing requirements, list of documents, recommendations, legislation, and guidelines to cop-up the current regulatory environment is in cold chain management:

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- Centres for Disease Control and Prevention (CDC) Guidelines for Maintaining and Managing the Vaccine Cold Chain
 - The EU Guide to Good Manufacturing Practice, Annex 13
 - The US Code of Federal Regulations ■ US and European Pharmacopoeia
 - WHO Guidelines on the international packaging and shipping of vaccines
 - The Guidelines on Good Distribution Practice (GDP) of Medicinal Products

Cold Chain:
A Lynchpin
of National
Immunization
Program

The course of action in controlling the cold chain is revised about Good Storage and Distribution Practices for Drug Products, and the brand new for Good Distribution Practices – Supply Chain Integrity, Monitoring Devices – Time, Temperature and Humidity and United States Pharmacopoeia where it also announced the significant changes in the regulatory provisions. Pharmaceutical industry or other stakeholders should follow or not to follow depends on themselves only and there is no such obligation by law or act for the industry to comply these rules/guidelines/procedures strictly, it is the interest of their own to do or not to do. The most disadvantages on the guidelines is that only they described or explained about “what” must be done; but is has not been explained ‘how’ it could be done. To get the answer of how it could be done, WHO published 16 technical supplements on ‘Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products’ on best practices to support the harmonized and it can be considered a good development in this segment. (Afsar A, Kartoglu U. 2006)

International Air Transport Association (IATA) has a great role and it harmonized the new regulation for time- and temperature-sensitive products or immunological/biological products for air transport. Still the more exhaustive and extensive revisions are needed to store, handle and the distribute the temperature sensitive products under cold supply chain, with more applied, more practical, more relevant than previous editions. Vaccine regulations for the cold chain is quite complex and multifunctional, which include the independent oversight of production, good control of the process and testing by a competent regulatory authority. The compliance of the regulatory and its activities initiated at the start of the vaccine development and it is continuous process throughout its entire life span. Guidelines developed by the WHO presenting the evaluation of the vaccine temperature stability by testing. The key component of the vaccine is the potency and efficiency control along with the evaluation pattern of the quality. (Levine, O.S., et al. 2011 and McColloster P.J. 2011) regulatory ensures that the characteristics of the vaccine quality should be tested before the marketing and loss of potency, as determined/assessed by a previously validated potency test, which may give the data on the loss of vaccine potency. The stability of the immunological products is

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serious concern, thus a procedure is required to assess a complete stability picture of vaccines. Current models never permit to determine or record the unplanned temperature excursions, and thus, the approach is to define limited conditions for planned temperature excursions (such as CTC use) and then assure a 'stability reserve' is requisite of the regulatory. (Levine, O.S., et al. 2011 and McColloster P.J. 2011)

DISCUSSION

As for as vaccines are concerned, these are required to be stored and supplied under the rigorous controlled conditions. It is essential that how the vaccines are stored and supplied to the end users with its appropriate integrity along with the potency. As for as the prophylactic prevention of diseases are concerned, immunization program is quite prominent to curb certain lethal diseases like tetanus, polio, diththeria, herpex, cervix cancer, hepatitis (Tembleque M.D.S., et.al. 2013) and many more. But the vaccines are manufactured at one place and transferred to another under the program. Vaccines are biological constituents and might degrade if not controlled under optimum temperature, heat, and moisture. These are the key environmental factors affects the potency of the vaccines adversely.

Many researchers already emphasized on reduction of vaccine potency during the storage and transportation if not controlled. Pediatricians focused on casual and unwillingness approach of some medical professionals towards the storage and administration of vaccines stating that doctors/nurses keep the vials in refrigerator doors which is not having an optimum temperature to maintain the biological activity of vaccines. It results into the less/no activity or adverse effects of the vaccines occurs. Various equipments like Walk-in-Freezers (WIF), Ice Lined Refrigerator (ILR), Walk-in-Coolers (WIC), Deep Freezer, Solar Refrigerators, Domestic Refrigerators, Cold Box, Vaccine Carriers, Ice Packs are in use to assist the vaccines to maintain the overall potency of the vaccines during storage, and transportation. Many monitoring devices i.e. Dial Thermometers, Electronic Data Logger, Electronic Data Logger, Alcohol Stem Thermometers, Alcohol Stem Thermometers are quite efficient to assess the transit temperature and moisture deviations during the storage and transportations to avoid any undesired adverse reactions. (Afsar A. and Kartoglu U. 2006) Here in this paper author also emphasized on the evaluation of vaccine expiry and how it could be calculated as to use and not to use if vial is beyond the use date (BUD). The vaccine potency and its utilization can be assessed with the color display of the vaccine content in the vial stating discard and beyond the discard point at the time of administration of the vaccine. (Stamatis D.H. 2003 and Kartoglu, U. et al. 2012)

Apart from that the regulations and guidelines framed time to time by the World Health Organization (WHO), ICH, Parenteral Drug Association, the International Air Transport Association (IATA) and the International Conference on Harmonization; Members state's National regulatory agencies (for example Health Canada, USFDA, EMA) to ensure the adequate biological efficacy of the vaccines. These regulatory organizations framing the guidelines and plays key role in cold chain management of vaccine to reach the Primary health care centers (PHCs) with the desired potency. (Levine, O.S., et al. 2011 and McColloster P.J. 2011)

Approximately, one-third of refrigerators had temperatures deviations or out of the range where the recommended range of 2-8 degrees centigrade is essential. The quality of the old refrigerators or coolers might show the inappropriate temperatures than newer ones. To protect and avoid the deviations during the storage, adequate information, knowledge, skill and practice for the handling and storage of vaccines required perfectly at primary health care centers or the physicians' offices. (Yuan, L. et.al. 1995)

Minimization of expiry risk of vaccines should be kept in mind and keep efforts to maintain the stock of the vaccine which required to be further used for next 1-3 months only. The order of the same kind of the vaccines are placed together to avoid any data related confusion during the storage and transportation. The expiry dates of the vaccines are evaluated and inspected a regularly way. The best method of doing this is that the older vaccines (having the expiry very near) should be moved to the front doors of the refrigerators and use these lots first. The date of the first withdrawn from the vaccine vial should be marked on the label of the multidose vial. The open vial of the vaccine must be discarded within 30 days (if not specified by the manufacturer for discard after the opening or follow the instructions as specified by the manufacturer) (Erica W. et. al. 2004)

The objective of the review paper is to address the compliance about the cold chain of the immunological products efficiently, logistic management, and overall maintenance of the immunological products like vaccines/antibodies during the storage, transportation and vial check or assessment at the time of administration to the end user child/mother at the Primary Health Care centers and it could be maintained across the nation without any deviation and negligence to avoid untoward medical occurrence due to vial content deterioration.

CONCLUSION AND IMPLICATIONS

The cold chain management (CCM) of immunological products is the utmost need of hour under Universal Immunization program (UIP) and National

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Immunization program (NIP). The paper itself described the techniques to control the immunological products/ biological products how it could be stored, shipped, handled, and administered safely to the end users without affecting the potency of vaccines. The equipment's used in the cold chain should be calibrated and having international standards to monitor the overall transit temperature of the vaccines to ensure the temperature control under the desired conditions. The regulatory guidance from the USA, Japan, European Union and ICH has developed the exhaustive document to make the successful execution of immunization program. Day to day observations and deleterious effect of vaccines due to storage and handling issues are elaborated in the review paper which reflects to manage the CCM effectively. Thus, the cold chain management prevail the overall process of immunization for implementation and achievement of immunization programs successfully across nation and worldwide as well.

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