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Advances in vaccine stability monitoring technology

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Abstract

Electronic time–temperature indicator (eTTI) monitors can be programmed to exactly follow the stability characteristics of vaccines with a high degree of realism. The monitors have a visual output, enabling vaccine status to be assessed at a glance, and can also output more detailed statistical data. When packaged with vaccine vials in groups of about 10 vials per box, the eTTI can remain with a vaccine throughout most of the vaccine's lifetime. The monitors can detect essentially all cold-chain breaks, and can detect issues, such as inadvertent freezing, that are presently not detected by other vaccine stability monitors such as Vaccine Vial Monitors (VVM).

Keywords: Vaccine; Stability; Cold-chain

1. Introduction

Vaccines are designed to present foreign antigens to the immune system in a way that elicits a strong and lasting immune response. To do this, vaccines often present the vaccine antigen in a form that is non-covalently bound to vaccine adjuvants, such as aluminum salts [1,2].

As a result, vaccines are often very temperature sensitive. Higher temperatures can cause denaturation and degradation of the vaccine's protein or carbohydrate-based antigens [3]. Temperatures below freezing can often produce ice crystal formation that may either denature the antigen, or alternatively alter the structure of the vaccine–adjuvant complex. Thus, to be effective, vaccines must be stored within a relatively narrow temperature range.

Due to the temperature-sensitivity of vaccines, the process of distributing vaccines to patients is complex and somewhat fragile. At the manufacturer and national storage facility level, logistics personnel employ sophisticated tracking and well-regulated refrigeration systems to ensure that the vaccines are properly handled. As the vaccine passes to regional and local storage depots, however, the chances for problems tend to grow because the process may not be as well controlled [4–6]. At the local level, vaccines are usually monitored by manual methods that require office personnel to make a paper record of the vaccine storage conditions on a daily or twice-daily basis. This use of manual tracking methods increases the chance of human error [7]. Compounding the problem is the fact that refrigeration systems at the local level are often not designed or certified for vaccine storage.

From a failure modes effects analysis (FMEA) and human factors standpoint [8,9], current vaccine cold-chain practices have a number of problems. These problematic aspects are (1) the engineering challenges of maintaining refrigeration equipment that can meet the narrow vaccine storage temperature requirements; (2) the fact that thermally deteriorated vaccine is difficult to detect; and (3) the many human factors issues created by the need for manual record keeping and manual records transfer.

The first engineering FMEA issue is caused by the limitations of present-day refrigeration technology. This is because there is often only a small difference between the lower end of the proper storage temperature (e.g. 2 °C) and the upper end of the improper storage temperature (e.g. 0 °C). This is a challenging goal for refrigeration engineers [10].

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The narrower the gap is between the lower end of the proper storage temperature and the upper end of the improper storage temperature, the greater the engineering challenges become. Refrigerators are feedback-controlled systems, which by necessity must be allowed some freedom to fluctuate both below and above the desired set point. The smaller the allowed range of fluctuation, the greater the engineering challenges, and the greater the likelihood that a given refrigeration unit will fail to meet these challenges.

The second major FMEA problem is detection—in this case detecting thermally damaged vaccines. In the 1990s, the World Health Organization, recognizing the severity of vaccine cold-chain problems, took a first step towards addressing some of these issues by mandating that WHO vaccines incorporate chemical time–temperature indicator labels (Vaccine Vial Monitors, or "VVM") onto vaccine vials. Initially VVM were required for Oral Polio Vaccine (OPV), and later this mandate was extended to all vaccines [11,12]. These VVM indicators, which cost only about seven cents a unit, contain a chemical that becomes darker in response to heat over time. This indicator is printed as a small square against a larger circular background, which itself has a preprinted reference color. By modifying the chemistry, the rate in which the chemical gets darker as a function of time and temperature can be adjusted. The color of the preprinted background square can also be increased or decreased. As a result (assuming that the vaccine has a relatively simple time–temperature deterioration curve), the VVM can be set to approximately track the time–temperature sensitivity curve of materials with simple, Arrhenius decay, time–temperature degradation characteristics.

The VVM system was, and is, well suited for OPV and other vaccines that deteriorate with simple Arrhenius kinetics, and which are tolerant to freezing. However, VVM are not perfect, and are not appropriate for, all situations. One of the biggest weaknesses is the VVM's inability to monitor more complex time–temperature stability situations, such as sensitivity to freezing. This is because the chemically based VVM indicator dye system continues to get darker, even under proper refrigeration, but does not get darker or register a color change if the vaccine is frozen. Thus, VVM can monitor stability problems caused by high temperatures, but often are less accurate at monitoring stability problems caused by low temperatures [13].

As a result, when VVM are used with freezing sensitive vaccines, there is a disconnect between "looking fresh" and "being fresh". If the vaccine has been accidentally frozen, the VVM will continue to look fine, but the vaccine may be inactive. This leads to the third major FMEA problem, human factors.

From the human factors standpoint, vaccine transport personnel can hardly be expected to be experts in vaccine stability and the fine points of VVM chemistry. They tend to read the VVM labels, assume that the labels are correct, and make the logical conclusion that lower temperatures are better. As a result, in order to make the vaccines look "still fresher", some personnel may be tempted to lower the temperature of their refrigerators closer to freezing. As a result, the refrigerators, which were probably hard-pressed to maintain a $5\,^{\circ}C \pm 3\,^{\circ}C$ temperature range to begin with, are now asked to maintain $2\,^{\circ}C + 6\,^{\circ}C - 0\,^{\circ}C$ setting. This, unfortunately, is beyond the control capability of most real-world refrigeration units.

The FMEA motivation behind the VVM concept, improving the reliability of the vaccine cold-chain by increasing the ability of workers to promptly detect deteriorated vaccines, was absolutely correct in theory. The real life problems are caused by the fact that the VVM do not accurately track true vaccine time–temperature stability for all vaccines [14]. If improved time–temperature indicators could be developed that more accurately tracked vaccine stability, then the present harmful practice of storing vaccines at low temperatures to avoid triggering chemical VVM could be prevented. This change would allow the original FMEA logic behind the VVM mandate—detect improper vaccine storage conditions, to be finally realized. All types of improper vaccine storage would now be detected.

At present, WHO and other vaccine agencies are attempting to work around the limitations of current VVM by recommending that additional freeze monitoring devices be used [15]. For example, WHO recommends that a Freeze-Watch^{TM} indicator be placed in the middle of all cold-boxes during transport of freezing sensitive vaccines, and additionally that all cold-sensitive vaccines be evaluated for possible freezing damage using the shake-test. This informal use of additional devices and ad-hoc detection schemes has a number of problems, however, and does not stand up well to FMEA analysis. These problems are:

1: Presently available freezing indicators are difficult to customize to match a particular vaccine's cold sensitivity. Only two configurations are available, one of which warns at $0\,^{\circ}C$ for 1 h, and one of which warns at $-4\,^{\circ}C$ for 1 h. Vaccines have more complex freezing damage time–temperature stability profiles, however. Since the freeze-watch cannot be customized to match the profile of a particular vaccine, the freeze-watch indicators tend to be unrealistic, and may have credibility issues in the field.
2: Because only a single freeze-watch indicator is used in the center of the box, possible freezing damage to vaccines located on the periphery of the box may go undetected.
3: Each freeze-watch indicator monitors only a tiny part of the cold-chain—that is, transport between one cold-chain storage facility to the next.
4: Because the freeze-watch indicators are not permanently fixed to the vaccine packaging, the indicators may be overlooked or accidentally discarded when the vaccines are unpacked. As a result, accidental freezing may go undetected.
5: The shake-test for accidental vaccine freezing, although better than nothing, is not particularly reliable. A recent

publication suggests that there is a lack of standardization in shake-test procedures. In a recent survey, only 37–60% of Indian physicians in a vaccine-handling training course could correctly identify frozen vaccines using this method [16]. An earlier article in a Spanish journal also commented on the insensitivity of the shake-test [17]. A 1996 Canadian article, which also studied this issue, concluded: "*the 'shake test' is not a satisfactory means to detect freezing-induced damage. The only reliable means to determine if vaccines have been inadvertently frozen and thawed is to place temperature monitoring devices beside them during transport*" [18,19].

2. Time for a new approach?

Rather than try to work around the defects of present VVM, would it be possible do utilize some of the many advances in modern electronics to design a better vaccine stability monitoring system? If so, what would a better system be like?

An ideal next-generation vaccine time temperature stability monitor might have the following characteristics:

1: Fit the vaccine's true time–temperature stability curve at all temperature ranges.
2: Travel with the vaccine from the time of initial packaging until final use in the field.
3: Have a lifetime as long as the vaccine's lifetime.
4: Allow workers to instantly see vaccine status at a glance.
5: For deteriorated vaccines, explain why (when and how) the deterioration occurred.

As it turns out, this is now possible, and, in fact, is now available on a demonstration basis. Modern electronics has pushed the cost of microprocessors down to a few cents per unit. Similarly, there have been advances in other areas of electronics, such as paper-thin batteries, low-cost radiofrequency (RFID) chips, low-energy visual displays such as liquid crystal displays (LCD), and more recently even flexible printed visual displays. As a result, it is now possible to construct sophisticated time–temperature indicators (based on modern electronics) that are capable of accurately monitoring vaccine stability in a cost effective manner [20]. Here the technology behind these modern electronic time–temperature indicators (eTTI) is discussed in detail, and its possible utility in improving the integrity of the vaccine cold-chain is examined.

3. The physics of electronic stability monitoring

The issues and procedures for establishing the basic stability properties of a vaccine have been discussed in previous publications [21,22]. For the purposes of this discussion, it is assumed that the time–temperature stability of the vaccines in question has been determined at a number of different temperatures, and that these stability data have been reviewed and are considered to be accurate.

Once a set of accurate vaccine stability data has been established at various temperatures, the steps needed to construct an accurate electronic time–temperature stability monitor can begin. The physics of electronic stability monitoring is based on the concept that a vaccine's time–temperature stability lifetime is a cumulative function. That is, each minute after a vaccine is initially produced, the vaccine slowly deteriorates according to some function of temperature. When the deterioration reaches a point where too much of the vaccine has deteriorated to be immunologically effective (determined by experimental studies), then the vaccine is no longer good.

Mathematically, this approach computes vaccine stability as an integral of time versus a function of temperature, that is:

$$\text{Stability} = B - \int_0^{\text{Time}} P(\text{temp})\mathrm{d}t \quad (1)$$

Here P(temp) is a function that describes how quickly the vaccine deteriorates at a given temperature, and the $\int_0^{\text{Time}} \mathrm{d}t$ is simply a sum (integral) of all the temperatures that the vaccine has experienced up until the present moment "Time" in its lifetime, starting at time = 0. "B" is the number of deterioration "stability points" allowed before the vaccine is no longer considered good.

The P(temp) function is based on physical chemistry. Although vaccine labeling typically contains instructions such as "store between 2 °C and 8 °C, do not freeze", we all realize that storage at 9 °C will not make a big difference in vaccine storage lifetime, but storage at 30 °C probably will. We also realize that for vaccines that tolerate freezing, storage at temperatures below 0 °C will not adversely hurt the lifetime, and even may be beneficial. By contrast, for freeze sensitive vaccines, storage at −5 °C may cause the vaccine to immediately lose its effectiveness. How can an electronic stability monitor be programmed to understand these effects?

The key here is to incorporate the experimentally determined stability data into the P(temp) equation. For example, for temperatures above zero, the vaccine's temperature sensitivity can be accurately reproduced by mathematically "connecting the dots" from experimentally determined vaccine stability data obtained at defined temperatures, (e.g. 4–8 °C, 25 °C, 30 °C, 40 °C). This can usually be done using multiple Arrhenius equations to cover this range in multiple steps, where each equation is of the form:

$$k = A\mathrm{e}^{(E_\mathrm{a}/RT)} \quad (2)$$

Here, multiple versions of Eq. (2) are used to compute the P(temp) function between the experimentally determined data points. (In this Arrhenius equation, "k" is the rate of deterioration, A is an experimentally determined variable, E_a is an experimentally determined variable, R is a constant, and T is the temperature in K.)

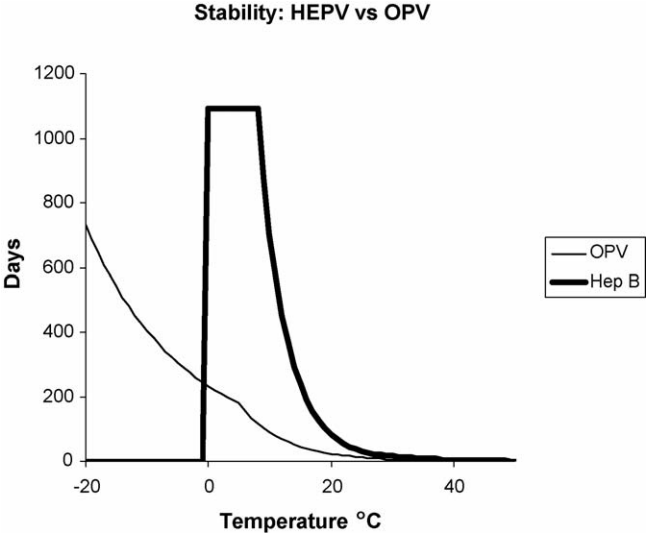


Fig. 1. A graph showing the relative time–temperature stability of hepatitis B vaccine and Oral Polio Vaccine, based on the 1998 WHO study [24]. The OPV vaccine has a relatively simple exponential decay curve with no major inflection points. By contrast, the hepatitis B vaccine has a phase change at −0.5 °C and becomes unstable below this point. Note the flat plateau between 0 °C and 8 °C, which represents the fact that the stated lifetime of hepatitis B at 2 °C is the same as 8 °C.

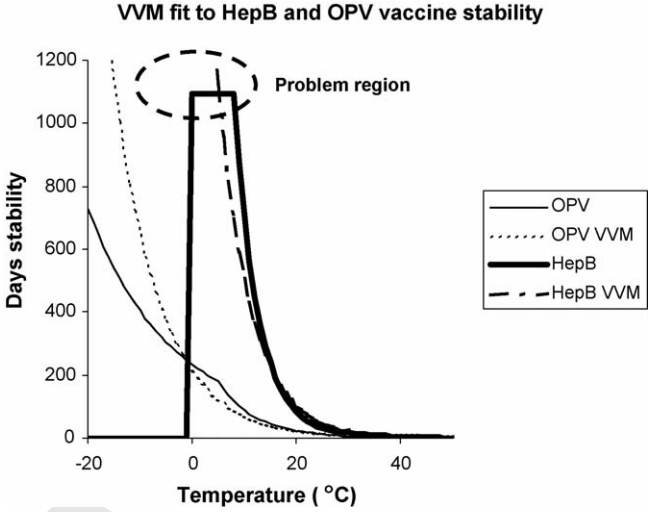


Fig. 2. A graph showing how the hepatitis B and OPV stability data can be fit using a simple Arrhenius-type exponential decay model, similar to that used in chemical VVM. As can be seen, although the fit between the OPV vaccine data and the exponential decay model isn't perfect, it is quite good above 0 °C, and generally tracks the OPV vaccine at freezing temperatures. By contrast, although the fit between the hepatitis B data and the exponential decay model is also fairly good above 0 °C, there is a large discrepancy in this fit below 0 °C. The Arrhenius model used in the VVM indicates that the vaccine is good when, in fact, freezing has damaged the vaccine.

Using modern computer spreadsheets, it is a relatively simple matter to determine the proper A and E_a values to make the Arrhenius equation fit the observed experimental data at various time points, such as 8 °C and 25 °C. Once this is done, these same spreadsheets can accurately predict what the likely vaccine stability properties will be at in-between temperatures, such as 9 °C or 24 °C. Clearly 9 °C will be much like 8 °C, 24 °C will be much like 25 °C, and so on.

As an example, consider the stability properties of two vaccines, one of which is sensitive to freezing (hepatitis B), and one of which is resistant to freezing (Oral Polio Vaccine). A table summarizing the stability of these two vaccines at various temperatures, using data from a 1998 WHO study [23] is shown below.

A figure showing a graph of this stability data is shown in Fig. 1.

One drawback of chemical VVM is that VVM attempt to fit the entire vaccine stability range using only a single Arrhenius equation. The results obtained using this VVM type approach with hepatitis B and OPV vaccines is shown in Fig. 2.

As can be seen in Fig. 2, the indicator dye chemistry used in present VVM works well for some vaccines, but not well with other vaccines. VVM match the stability characteristics of vaccines with simple exponential decay curves fairly well. Thus, OPV, which has an exponential-like decay curve, is fit fairly well by VVM. By contrast, hepatitis B vaccine, which has a more complex stability curve, does not work as well with chemical VVM. Although the VVM fit is adequate at higher temperatures, there is a major discrepancy between the stated VVM stability and the real hepatitis B vaccine stability at lower temperatures. As a result, the chemical VVM fails to warn about the instability of hepatitis B vaccine below freezing.

The poor ability of VVM to match the stability characteristics of freeze-sensitive vaccines creates a number of human factors problems. The OPV VVM reinforces the belief that there is no downside to lower temperatures. Indeed, the OPV VVM teaches that lower temperatures are preferable, because the OPV VVM continues to change color at 2–8 °C. Is it any wonder that cold-chain personnel, when confronted with VVM that fail to warn about freezing damage, tend to accidentally freeze cold-sensitive vaccines? Thus, an important goal of electronic time–temperature stability indicators is to avoid this problem by exactly reproducing the stability characteristics of vaccines that have complex time–temperature stability curves.

4. Programming eTTIs to match the stability of hepatitis B and OPV vaccine

Using the stability data from Table 1, and filling in the gaps in the data with suitable Arrhenius curves, P(temp) functions can be computed for both hepatitis B vaccine and OPV vaccine. These P(temp) functions are shown in graphical form in Fig. 3.

These P(temp) functions in turn can then be incorporated into stability Eq. (1) to produce hepatitis B and OPV stability Eqs. (3) and (4), shown below.

Table 1
Experimentally determined vaccine stability data

	Hepatitis B	Oral Polio Vaccine
Lifetime at −20 °C	0 days	2 years
Lifetime at −0.5 °C	0 days	(freeze-thaw tolerant)
Lifetime at 5 °C (2–8 °C)	3 years	6 months
Lifetime at 22–25 °C	30 days	12 days
Lifetime at 37 °C	7 days	1.9 days
Lifetime at 45–50 °C	45 °C, 3 days	50 °C, 3 h

An example hepatitis B vaccine stability equation is:

$$\text{HepB} = 157,608 - \int_0^{\text{Time}} P(\text{temp})_{\text{HepB}} \quad (3)$$

An example Oral Polio Vaccine stability equation is:

$$\text{OPV} = 106,228 - \sum_0^{\text{Time}} P(\text{temp})_{\text{OPV}} \quad (4)$$

Fig. 4 shows the results of these calculations. As can be seen, the fit between the eTTI stability and the experimentally determined vaccine stability data is essentially perfect. In actuality, the fit is often even better than the example in the graph, because in this example, the digital signal error of the electronic time–temperature indicator was slightly increased above optimum values in order to make the differences between the vaccine and the eTTI large enough to be visible.

In this simplified example, it is assumed that the *P*(temp) value is taken every hour, and freeze-thaw effects are not calculated. In real life, it is preferable to compute the temperature more often, such as every few minutes, and also deduct the effects of freeze-thaw cycles (if any), from the overall stability equation lifetime as well.

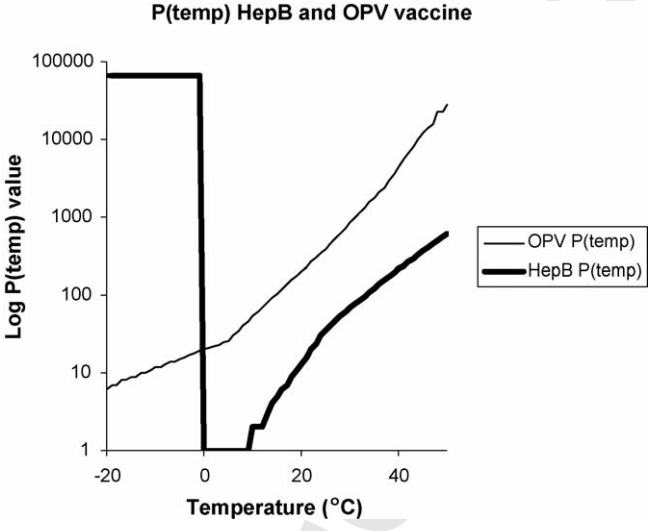


Fig. 3. A graph showing the stability *P*(temp) function vs. time for hepatitis B and OPV vaccine. The *P*(temp) values cover a wide numeric range, and thus this graph shows the log of the *P*(temp) value in order to allow the entire *P*(temp) numeric range to be easily visualized. Here, the *P*(temp) value is computed to fit the vaccine stability data from Table 1, assuming that the stability integration (Eqs. (3) and (4)) is done on an hourly basis. Lower *P*(temp) values indicate a longer stability lifetime, and higher *P*(temp) values indicate a shorter stability lifetime. Note that the OPV lifetime increases below 0 °C, while hepatitis B lifetime abruptly drops to zero below 0 °C.

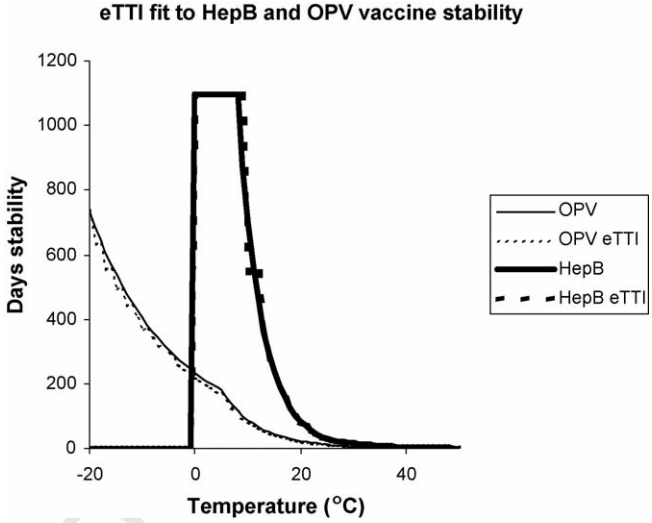


Fig. 4. Electronic time–temperature indicator stability data output. Here the eTTI continually computes the hepatitis B and OPV stability Eqs. (3) and (4) using the *P*(temp) function from Fig. 3, and tells the user when the values of Eqs. (3) and (4) reach zero. Because the *P*(temp) value can be customized to exactly fit the experimental stability data, the fit between the eTTI stability output and the real experimental data is excellent for both vaccines.

To implement this type of function in an electronic time–temperature indicator, a modern low-cost, low-power programmable processor is used. Although many microprocessors or microcontrollers can be used for this purpose, one particularly good choice is the Texas Instruments MSP430 microprocessor/microcontroller series. This microprocessor is available in volume for under 50 cents a unit, can do sophisticated 16-bit arithmetic calculations.

The microprocessor in turn is put into a low-cost case or tag with a temperature measuring thermistor (usually costing a few cents per unit), a low-power liquid crystal display, and a battery. The overall tag is not much larger or more expensive than a digital watch, which is made in the tens or hundreds of millions yearly for only $1–3 a unit. In addition to visual output, which gives immediate feedback to users in the field, numeric output may also be obtained by incorporating a low-cost infrared light emitting diode (LED) or RFID transmitter in the unit [24]. For ultra-low cost applications, a data transmitting LED can be added for only a few cents per unit, and this data can be downloaded via a special RS232 computer cable equipped with a photodiode detector. This cable can be produced for only a few dollars. All users can immediately read the unit via the visual LCD display. Users using a data cable and a computer may download supplemental tracking and statistical data.

At this time, it is difficult to give an exact estimate of what such units would cost at high production volumes (e.g. hundreds of thousands or millions of units). This is because electronics costs vary greatly depending upon the production

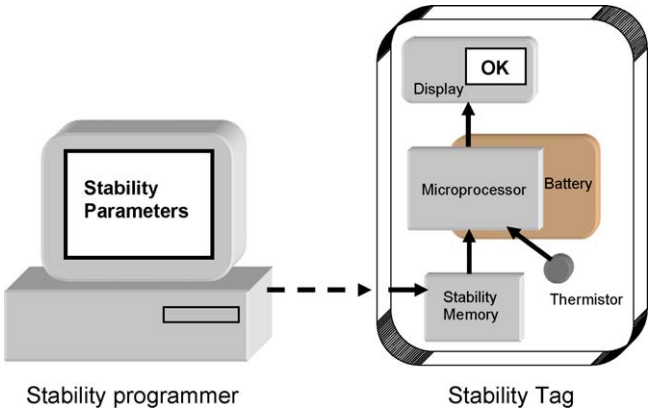


Fig. 5. Schematic drawing showing an electronic time temperature indicator (stability tag) on the right, as well as a drawing showing how this tag is programmed on the left. To use this tag, the vaccine stability parameters are calculated, and then downloaded from a stability programmer computer to the stability tag. These parameters correspond to the P(temp) and "B" values from Eqs. (3) and (4). After the stability tag is initialized, the battery powered microprocessor continually computes the P(temp) value using temperature data from the thermistor, and continually displays if the result of the stability equation (such as Eqs. (3) and (4)) is positive (in which case the vaccine is OK), or negative (in which case the vaccine has expired due to using up its stability lifetime).

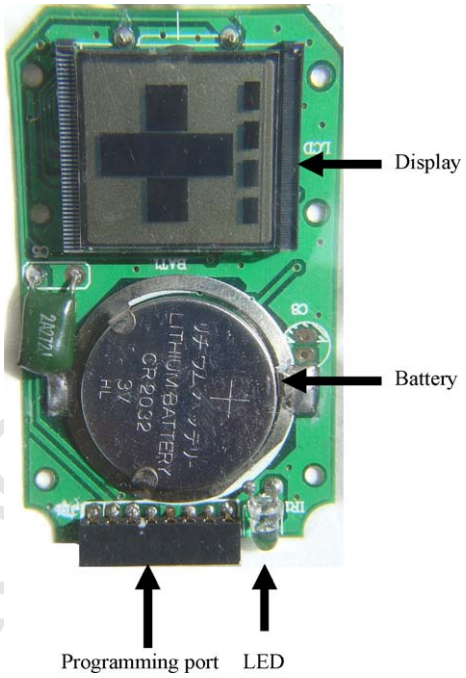


Fig. 6. Electronic circuit board for a LifeTrack™ demonstration vaccine electronic time–temperature stability monitor. The circuit board contains a coin-sized battery, which can power the unit for about 4 years. The board also contains a liquid crystal display which is continuously on, and which allows the status of the vaccine to be instantly read. The board also contains a programming plug (bottom) and an infrared light emitting diode (LED) which enables statistical stability data to be output to an outside computer, at user request, using a low-cost RS232 cable equipped with an infrared detector. RFID output could also be done using an RFID output chip.

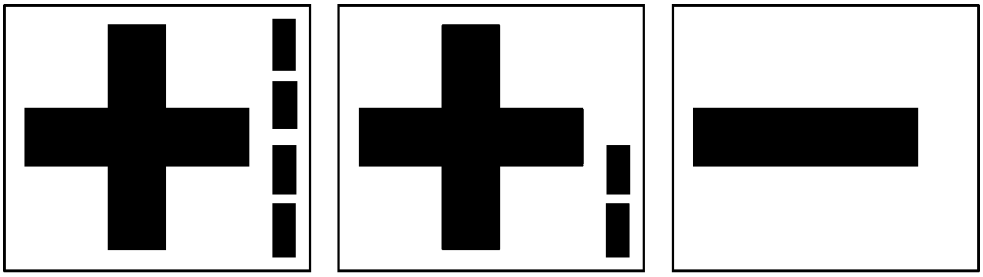
volume and the specific design of the device. The demonstration LifeTrack units discussed in this paper, which were produced in low production volumes (e.g. batches of a few 1000 units), and which did not have a cost-optimized design, had a production cost of about $5.00 a unit. It is anticipated that at high volumes, and with a cost-optimized design, the costs would be considerably less than this.

A schematic diagram of an eTTI tag is shown in Fig. 5, and a photograph of a LifeTrack™ demonstrator eTTI circuit board is shown in Fig. 6. An example of a LifeTrack visual output is shown in Fig. 7. In this example, the eTTI has a large ± display that immediately shows at a glance if the vaccine is still good or not. This unit also has a supplemental bar-graph display that shows what percentage of the vaccine's lifetime is still remaining.

The units can be programmed to keep an ongoing record of temperatures experienced by the tag from the time of initial vaccine packaging until the time the tag is read, similar to an airplane crash recorder. In the event of vaccine stability failure, the tag preserves a record of the temperatures experienced just before the failure, as well as the time elapsed since the failure. This allows users to determine exactly when and how the cold-chain failures occurred (e.g. 40 °C temperatures experienced for 5 h, 3 weeks ago), and take appropriate corrective action. Previous studies have shown that this type of immediate feedback can greatly improve the reliability of the cold-chain [26]. An example of this type of "crash analysis" output from a LifeTrack unit is shown in Fig. 8.

Even in volume, electronic time–temperature indicators are likely to cost a few dollars each, which will tend to make them too expensive to incorporate into individual vials. At the same time, the eTTI tags will have the most value if the tags stay with the vaccine from the time of initial manufacture up until the time that the vaccine is used.

Individual vaccine vials are usually placed into secondary packaging (boxes) of 10–50 vials per box. These boxes are usually labeled with the same vaccine lot number that is printed on the vaccine vial labels. The vaccine boxes are then usually placed in larger shipping cartons, which can contain between 10 and 50 boxes of vaccine (a total of 300–500 vials per shipping carton). The individual vaccine vials stay with the vaccine boxes through essentially all of the steps in the cold-chain, from manufacturer to final use. As a result, electronic time–temperature indicators securely affixed to lot-coded vaccine boxes would provide essentially all of the benefits of the present VVM system, and would additionally allow more precise temperature monitoring and detailed analysis of cold-chain failure. This method would reduce the cost of the electronic TTI to about 15–30 cents per vial. This is still more expensive than VVM, which cost about 7 cents a unit, but is within reason. Here, the higher eTTI cost is divided by the number of vaccine vials in the box. A diagram of this configuration is shown in Fig. 9. To improve accuracy, the thermocouple in the TTI can be mounted fac-



Fresh 50% life remaining Expired

Fig. 7. Diagram of the visual output from the LifeTrack™ electronic time–temperature indicator shown in Fig. 6. When the vaccine is fresh, a large "+" is visible, and all four stability lifetime bars are shown. As the vaccine ages and loses shelf life, this progressive loss is shown by the smaller number of stability bars. At 50% of remaining lifetime, only two stability bars are shown. The large "+" at 50% lifetime, however, lets users know that the vaccine is still good. When the stability lifetime is fully exhausted, the display changes to a large "−" sign, letting users know that the vaccine is not good. The remaining lifetime stability bars are optional. These can be omitted, or alternatively replaced with a numeric remaining-stability lifetime display, or other display, as desired.

ing the inside the box, or even in the box interior (on a short probe).

In many situations, eTTI and VVM may co-exist. eTTI can be used at the carton level to insure that the vaccines have traveled through the majority of the cold-chain in an intact state. VVM, attached to the individual vials, may then monitor the final stage at the local level, where cartons are opened and the individual vials distributed to local health-care workers.

5. Benefits to the vaccine field

eTTI could provide a number of benefits for the vaccine field. The immediate and accurate vaccine stability feedback that the eTTI would provide would allow weak links in the cold-chain to be quickly detected [25]. This could produce a rapid improvement in the worldwide vaccine cold-chain system. These improvements could also result in significant cost reductions due to less wasted vaccine, and could also

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Thu Apr  6 15:03:06 2006

OPV       , ID Code: 12345123451234

Security code: 39577,  Checksum: 6127 vs 6127 OK

Status: EXPIRED

Hours elapsed since LifeTrack start: 3736
Hours run before expiration: 2407, Average temperature: -6.3 +/- 19.9 C
Hours run since expiration:  1329, Average temperature: 23.5 +/- 0.9 C


Temperature logger (degrees C):
Logger frequency: 12.0 hours, total logger time: 1200.0 hours

Temperatures recorded before expiration:

[- 2534.0 hr.]  -19,  -20,  -20,  -20,  -20,  -19,  -19,  -19,  -20,  -19,
[- 2414.0 hr.]  -19,  -19,  -20,  -15,  -18,  -19,  -19,  -20,  -19,  -19,
[- 2294.0 hr.]  -18,  -19,  -20,  -20,  -20,  -19,  -19,  -19,  -19,  -18,
[- 2174.0 hr.]  -18,  -20,  -19,  -20,  -19,  -20,  -19,    5,   23,   23,
[- 2054.0 hr.]   25,   24,   24,   23,   23,   23,   23,   22,   24,   25,
[- 1934.0 hr.]   24,   25,   23,   23,   24,   23,   22,   22,   24,   23,
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[- 1574.0 hr.]   23,   24,   24,   23,   23,   23,   24,   23,   23,   24,
[- 1454.0 hr.]   22,   22,   22,   21,   21,   23,   23,   24,   23,   23,

Logger expired on Fri Feb 10 05:03:06 2006 (local time), 1329 hours ago.
```

Fig. 8. Example of the type of statistical stability data that can be downloaded from a LifeTrack vaccine electronic time–temperature indicator. In this example, the LifeTrack unit is incorporated into a box of OPV vaccine. The OPV vaccine has been mishandled, and has expired unexpectedly early. The LifeTrack LCD display shows a "−", letting users know that the vaccine should not be used. When downloaded, the LifeTrack data shows what happened to the vaccine. The date the LifeTrack unit was downloaded, 6 April 2006, is shown at the top. The status of the vaccine is shown as EXPIRED. The lowest line shows that the vaccine expired on Friday, 10 February 2006 at around 5:00 a.m. in the morning. The logger data, with time points every 12 h, shows that the vaccine had been properly frozen until about 2090 h before the logger was downloaded on 6 April 2006. Thus, the vaccine was accidentally left outside the freezer about 87 days before 6 April 2006, which would have been around 9 January 2006.

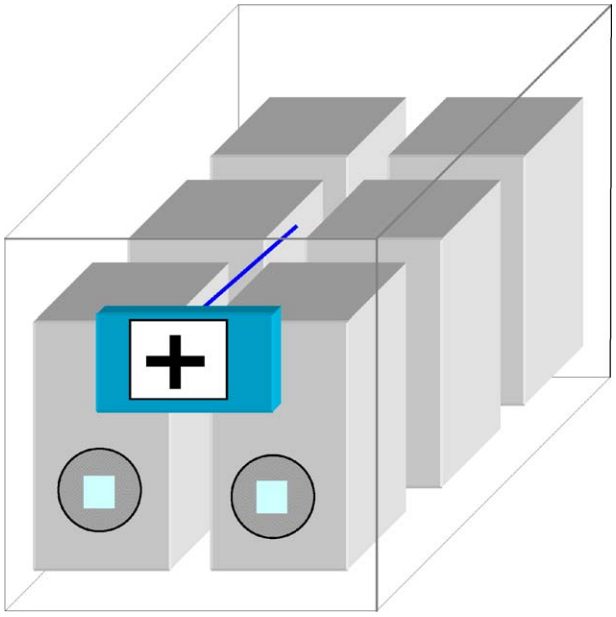

Fig. 9. Diagram showing the differences in packaging between a chemical VVM (circles) and an electronic time–temperature indicator. The VVM are attached to the individual vaccine vials. By contrast, the eTTI are attached to the vaccine box. The vaccine box will normally be printed with the same lot number that is printed on the individual vaccine vials. The vaccine vials stay associated with the vaccine box (with the attached eTTI) until shortly before use. As a result, although the eTTI is not attached to the individual vaccine vials, the eTTI remains with the vaccine vials through essentially all of the cold-chain links.

save lives due to a lower rate of inoculation with ineffective vaccines.

Some simple calculations show that by intelligent use, eTTI should be very cost effective. As previously discussed, costs can be substantially reduced by using the eTTI on a per-box basis. Additionally, not every vaccine box need be labeled. Costs can be reduced further by only labeling a certain percentage of the boxes, and using these labeled boxes as cold-chain "tracer" units.

The technology to implement such eTTI units is here today [26]. Demonstration quantities of LifeTrack units are currently available. These can be used by outside organizations to evaluate the concept, and to generate sufficient experimental data to determine if larger scale implementation is warranted. CliniSense welcomes such interest, and will cooperate with such studies. However, implementing this approach is more complicated than just attaching some electronic tags to some vaccine boxes. This effort will require coordination between national and international healthcare organizations, regulatory agencies, vaccine companies, and electronics manufacturers.

Although electronics vendors are quite willing to produce this type of electronic tag in high volumes, they will not make the necessary investment in production capability unless they are assured large orders from either national health agencies or vaccine companies.

Vaccine companies are in a good position to drive this change, and will likely do so if they see that there is enough demand from customers (usually national or international healthcare agencies) to warrant the expense and effort.

National or international healthcare agencies, which represent the ultimate vaccine customers, can play a very important role here. Here, cost effectiveness calculations will be important. ETTI will likely lead to vaccine cold-chain improvements, resulting in less wasted vaccine, reduced healthcare expenses and reduced mortality (from ineffective vaccinations). These agencies should ideally build these projections into various mathematical models, and compute if the calculated eTTI outcomes compare favorably with other alternative uses of scarce health-care funding.

One way to proceed may be through demonstration projects for the most problematic vaccines, such as DPT and hepatitis B. eTTI might then be gradually introduced as tracers randomly put on vaccine boxes, to flush out cold-chain issues. The data obtained from these initial studies can then be submitted to regulatory agencies to gain appropriate approvals and certification. As this approach gains acceptance, a larger number of vaccines would eventually follow.

6. Conclusion

In conclusion, although electronic time–temperature stability monitors represent a break from classic vaccine packaging technology, this approach offers a number of compelling benefits to the vaccine field. Modern electronics offers a way to substantially improve vaccine distribution, and allow healthcare workers worldwide to be confident in the effectiveness of the vaccines they are administering.

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Conflicts of Interest: Dr. Zweig is the CEO of CliniSense Corporation, a company that produces and licenses LifeTrack programmable time–temperature indicator technology.

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