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# Economic impact of thermostable vaccines

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ABSTRACT

*Background:* While our previous work has shown that replacing existing vaccines with thermostable vaccines can relieve bottlenecks in vaccine supply chains and thus increase vaccine availability, the question remains whether this benefit would outweigh the additional cost of thermostable formulations.
*Methods:* Using HERMES simulation models of the vaccine supply chains for the Republic of Benin, the state of Bihar (India), and Niger, we simulated replacing different existing vaccines with thermostable formulations and determined the resulting clinical and economic impact. Costs measured included the costs of vaccines, logistics, and disease outcomes averted.
*Results:* Replacing a particular vaccine with a thermostable version yielded cost savings in many cases even when charging a price premium (two or three times the current vaccine price). For example, replacing the current pentavalent vaccine with a thermostable version without increasing the vaccine price saved from $366 to $10,945 per 100 members of the vaccine's target population. Doubling the vaccine price still resulted in cost savings that ranged from $300 to $10,706, and tripling the vaccine price resulted in cost savings from $234 to $10,468. As another example, a thermostable rotavirus vaccine (RV) at its current (year) price saved between $131 and $1065. Doubling and tripling the thermostable rotavirus price resulted in cost savings ranging from $102 to $936 and $73 to $808, respectively. Switching to thermostable formulations was highly cost-effective or cost-effective in most scenarios explored.
*Conclusion:* Medical cost and productivity savings could outweigh even significant price premiums charged for thermostable formulations of vaccines, providing support for their use.


## 1. Introduction

While our previous work has shown that replacing existing vaccines with thermostable vaccines can relieve bottlenecks in vaccine supply chains and thus increase vaccine availability [1], the question remains whether this benefit would outweigh the additional cost of thermostable formulations. All World Health Organization (WHO) prequalified vaccines currently require storage in refrigerators or freezers as exposure to higher temperatures may result in the denaturation of the proteins in the vaccine rendering them impotent. However, many vaccine supply chains in low- and middle-income countries have shortages in refrigerated (or even lower temperature) storage and transport capacity to accommodate all of the vaccine doses that must eventually make it to the population [2,3]. Making certain vaccines thermostable would allow these vaccines to be stored outside refrigerators or freezers, thus freeing up space for vaccines that still require cooler or cold temperatures. More vaccine doses reaching the population can protect more mothers and children from infectious diseases, thus saving medical costs and productivity losses. However,

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**Table 1**
Vaccine characteristics.

| Vaccine | Benin | | | | | Bihar, India | | | | | Niger | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Doses per person* | Doses per vial* | Packed volume per dose vaccine (mL)† | Packed volume per dose diluent (mL)† | Price per vial (USD)‡ | Doses per person§ | Doses per vial§ | Packed volume per dose vaccine (mL)§ | Packed volume per dose diluent (mL)§ | Price per vial (USD)§ | Doses per person** | Doses per vial** | Packed volume per dose vaccine (mL)† | Packed volume per dose diluent (mL)† | Price per vial (USD)‡ |
| BCG | 1 | 20 | 1.2 | 0.7 | 1.6 | 1 | 10 | 1.2 | 0.7 | 0.52 | 1 | 20 | 1.2 | 0.7 | 1.6 |
| Measles (M) | 1 | 10 | 3.5 | 4 | 2.8 | 2 | 5 | 5 | 4 | 0.83 | 1 | 10 | 3.5 | 4 | 2.8 |
| Oral polio (OPV) | 4 | 20 | 1 | 0 | 2.6 | 5 | 20 | 1 | 0 | 1.24 | 4 | 20 | 1 | 0 | 2.6 |
| Pneumococcal conjugate (PCV) | 3 | 1 | 12 | 0 | 5.52 | 3 | 5 | 5 | 0 | 17.1 | 3 | 1 | 12 | 0 | 5.52 |
| Pentavalent | 3 | 2 | 11 | 0 | 3.88 | 3 | 10 | 5.3 | 0 | 21.86 | 3 | 1 | 16.8 | 0 | 2.32 |
| Rotavirus (RV) | 2 | 1 | 17.1 | 0 | 1.88 | 3 | 10 | 3.2 | 0 | 10.36 | 2 | 1 | 17.1 | 0 | 1.88 |
| Tetanus toxoid (TT) | 2 | 10 | 3 | 0 | 0.8 | 4 | 10 | 3 | 0 | 0.21 | 2 | 10 | 3 | 0 | 0.8 |
| Yellow fever (YF) | 1 | 10 | 2.5 | 6 | 11.9 | – | – | – | – | – | 1 | 10 | 2.5 | 6 | 11.9 |
| Hepatitis B (HepB) | – | – | – | – | – | 1 | 10 | 3.8 | 0 | 0.52 | – | – | – | – | – |
| Diphtheria-tetanus-pertussis vaccine (DTP) | – | – | – | – | – | 2 | 10 | 3 | 0 | 0.41 | – | – | – | – | – |
| Inactivated polio (IPV) | – | – | – | – | – | 1 | 10 | 2.46 | 0 | 10.36 | – | – | – | – | – |
| Japanese encephalitis (JE) | – | – | – | – | – | 2 | 5 | 3 | 2.9 | 0.93 | – | – | – | – | – |

* *Source:* Benin CMYP [17].
† *Source:* WHO Vaccine Volume Calculator; WHO Prequalified Vaccines Database [18].
‡ *Source:* cMYP Costing Tool 3.6; UNICEF Product Menu [19].
§ *Source:* Personal communications with INCLEN.
** *Source:* Niger cMYP [20].

thermostable formulations of vaccines may cost more than current formulations. Therefore, our HERMES Team used computational simulation modeling to evaluate the impact of replacing different types of vaccines with thermostable formulations in the Republic of Benin; the state of Bihar, India; and Niger.

## 2. Methods

### 2.1. HERMES models of Benin; Bihar, India; and Niger

Our team used our previously described HERMES (Highly Extensible Resource for Modeling Event-Driven Supply Chains) software to construct and run detailed discrete-event simulation models of the Expanded Program on Immunization (EPI) and Universal Immunization Program (UIP) supply chains (representing all vaccines, storage and immunization locations, storage devices, vehicles, ordering and shipping policies and processes, and associated costs) for the Republic of Benin [4,5] (4 levels: 1 national store, 7 region/department stores, 80 communes, 763 health posts); the state of Bihar, India [5] (4 levels: 1 state store, 7 division stores, 13 of 38 district stores, 161 of 533 PHCs); and Niger [1,3,6,7] (4 levels: 1 national store, 7 regional stores, 42 districts, 644 integrated health centers).

Table 1 lists the current and newly introduced vaccines and their characteristics for each location. All models used 2013 population estimates and reported costs are in 2016 US dollars ($US).

### 2.2. Comparing standard versus thermostable formulations of each vaccine

In the baseline scenario for each of the three supply chains, all vaccines represent presentations currently available plus introduced vaccines, with each vaccine requiring either refrigeration or freezing depending on the temperature susceptibility profile of that specific vaccine. Making a vaccine thermostable meant that the vaccine could remain outside cold storage without suffering degradation. Thermostable formulations would have the same overall shelf life and the same physical presentation (e.g., doses per vial, packaged volume) otherwise. Different experiments varied the price of thermostable vaccines from the current vaccine price (i.e., no price premium for a thermostable version of the vaccine) up to 300% of the current vaccine price.

Each experiment consisted of running the supply chain simulation for the course of one year. As the simulation proceeded, logistics costs accrued for labor, storage, transport, and buildings. The formula for total logistics costs for each supply chain is below:

$$Cost_{total} = Cost_{labor} + Cost_{storage} + Cost_{transport} + Cost_{building}$$

where

$$Cost_{labor} = \sum_{personnel} Cost_{per\ employee}$$

$$Cost_{storage} = \sum_{storage\ units} Cost_{per\ storage\ unit}$$

$$Cost_{transport} = \sum_{transport\ routes} Cost_{per\ transport\ route}$$

$$Cost_{building} = \sum_{buildings} Cost_{per\ building}$$

The formulas for each of the cost components are given below:

Labor Costs

$$Cost_{per\ employee} = Cost_{employee's\ annual\ salary\ and\ benefits} \times \%\ of\ time\ dedicated\ to\ vaccine\ logistics$$

Storage Costs

$$Cost_{per\ storage\ device\ unit} = Cost_{storage\ unit\ energy\ usage} + Cost_{storage\ unit\ maintenance} + Cost_{storage\ depreciation}$$

Transport Costs

$$Cost_{per\ transport\ route} = Cost_{per\ km} \times distance\ traveled + Cost_{per\ diems\ for\ route}$$
$$Cost_{per\ km} = Cost_{vehicle\ maintenance\ per\ km} + Cost_{vehicle\ depreciation\ per\ km} + Cost_{fuel\ per\ km}$$
$$Cost_{fuel\ per\ km} = Cost_{fuel\ per\ liter} / fuel\ efficiency\ of\ vehicle_{km\ per\ liter}$$

Building Costs

$$Cost_{per\ building} = (Cost_{annual\ depreciation} + Cost_{annual\ utilities}) * \%\ of\ building\ utilized\ for\ logistics$$

In addition, the formula for total procurement costs is given below:

$$Cost_{procurement} = \sum (Cost_{vaccine\ A} \times vials\ procured_{vaccine\ A}) + (Cost_{vaccine\ B} \times vials\ procured_{vaccine\ B}) \ldots + (Cost_{vaccine\ Z} \times vials\ procured_{vaccine\ Z})$$

When a vaccine was made thermostable, running the model determined how many additional vaccinations occurred. The following formula translated the additional vaccinations into infections averted:

$$Vaccine\text{-}preventable\ infections\ (VPI)\ averted = (Doses\ administered_{Thermostable\ Scenario} - Doses\ administered_{Baseline}) \times (Vaccine\ efficacy \times Disease\ incidence)$$

The following formulas then determined the medical costs saved, disability-adjusted life years (DALYs) averted, and productivity losses averted from the infections prevented:

$$Direct\ medical\ costs\ saved = VPI_{Averted} \times Average\ medical\ cost\ per\ infection$$
$$DALYs\ averted = VPI_{Averted} \times Average\ DALYs\ per\ infection$$
$$Productivity\ losses\ averted = DALYs_{Averted} \times GNI\ per\ capita$$

We ranged these results from low to high with a base case scenario. Each input for incidence, medical costs per case and DALYs per case was pulled from the literature (Table 2). When ranges were not available from the literature, we varied the average incidence and medical cost per case by 50% and the average DALYs per case by 20% and used these as low and high inputs.

Additionally, we calculated the incremental cost-effectiveness ratio (ICER) of stabilizing a vaccine compared to not stabilizing using the following formula:

$$ICER = ((Logistics + procurement + medical\ costs\ incurred\ in\ thermostable\ scenario) - (logistics + procurement + medical\ costs\ incurred\ in\ baseline\ scenario))/(DALYs\ incurred\ in\ baseline\ scenario - DALYs\ incurred\ in\ thermostable\ scenario)$$

Cost-effectiveness is defined as an ICER ratio <3x GDP per capita, while highly cost-effective is <1x GDP per capita. GDPs per capita were $762 for Benin, $1598 for India, and $359 for Niger in 2015 US dollars ($) [8].

All reported results for logistics costs, procurement costs, vaccine availability, and doses administered represent the mean. When not reported the standard deviation was 1% or less.

**Table 2**
Model inputs for disease parameters.

| Disease | Location | Vaccine efficacy (%) | Incidence per 1000 | Direct medical cost per case | DALYs per case | Refs. |
|---|---|---|---|---|---|---|
| Diphtheria | Benin | 94 (87–100) | 6 (3–9) | $95 ($42–$147) | 23 (18–28) | [21–23] |
| | Bihar | | 6 (3–9) | $71 ($32–$111) | 23 (18–28) | |
| | Niger | | 6 (3–9) | $97 ($43–$151) | 23 (18–28) | |
| Hepatitis B | Benin | 85 (75–95) | 50 (25–75) | $3591 ($2467–$4714) | 2 (1–2) | [23–27] |
| | Bihar | | 50 (25–75) | $2705 ($1859–$3551) | 2 (1–2) | |
| | Niger | | 50 (25–75) | $3686 ($2533–$4839) | 2 (1–2) | |
| Hib | Benin | 98 (95–100) | 4 (2–6) | $138 ($69–$208) | 7 (6–9) | [23,28] |
| | Bihar | | 4 (2–6) | $89 ($44–$133) | 7 (6–9) | |
| | Niger | | 4 (2–6) | $128 ($64–$192) | 7 (6–9) | |
| JE | Bihar | 80 (70–90) | 0.02 (0.01–0.02) | $293 ($84–$1662) | 15 (12–18) | [23,29–31] |
| Measles | Benin | 98 (95–100) | 0.2 (0.1–0.2) | $26 ($13–$38) | 8 (6–9) | [23,32] |
| | Bihar | | 0.2 (0.1–0.2) | $16 ($8–$24) | 8 (6–9) | |
| | Niger | | 0.2 (0.1–0.2) | $26 ($13–$39) | 8 (6–9) | |
| Pertussis | Benin | 80 (70–90) | 64 (48–96) | $54 ($0–$272) | 0.3 (0.2–0.3) | [23,33–35] |
| | Bihar | | 64 (48–96) | $36 ($0–$180) | 0.3 (0.2–0.3) | |
| | Niger | | 64 (48–96) | $51 ($0–$253) | 0.3 (0.2–0.3) | |
| Pneumococcal disease | Benin | 80 (58–90) | 6 (5–11) | $95 ($42–$147) | 5 (4–6) | [22,36–39] |
| | Bihar | | 6 (5–11) | $71 ($32–$111) | 5 (4–6) | |
| | Niger | | 6 (5–11) | $97 ($43–$151) | 5 (4–6) | |
| Rotavirus | Benin | 81 (74–87) | 84 (72–97) | $16 ($5–$19) | 0.3 (0.2–0.4) | [40–42] |
| | Bihar | | 84 (72–97) | $10 ($3–$12) | 0.3 (0.2–0.4) | |
| | Niger | | 84 (72–97) | $17 ($6–$20) | 0.3 (0.2–0.4) | |
| TB | Benin | 40 (0–80) | 0.1 (0.1–0.1) | $101 ($75–$193) | 8 (6–9) | [23,43–45] |
| | Bihar | | 0.1 (0.1–0.1) | $75 ($56–$144) | 8 (6–9) | |
| | Niger | | 0.1 (0.1–0.1) | $96 ($71–$183) | 8 (6–9) | |
| Tetanus | Benin | 98 (95–100) | 1 (0.1–1) | $8708 ($4354–$13,063) | 26 (21–31) | [23,46–48] |
| | Bihar | | 1 (0.1–10) | $6561 ($3281–$9842) | 26 (21–31) | |
| | Niger | | 1 (0.1–1) | $8941 ($4470–$13,411) | 26 (21–31) | |
| Yellow fever | Benin | 94 (90–98) | 0.02 (0.01–0.03) | $179 ($152–$232) | 2 (2–3) | [23,49,50] |
| | Niger | | 0.02 (0.01–0.03) | $179 ($152–$232) | 2 (2–3) | |

**Table 3**
Net cost of replacing each vaccine with a thermostable formulation.

| Replacing the following vaccine with a thermostable formulation | In this location | Price of thermostable version is… | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Equivalent to the price of the current non-thermostable version | | | Twice the price of the current non-thermostable version | | | Three times the price of the current non-thermostable version | | |
| | | Resulted in the following costs per 100 people in the target population*,§ | | | | | | | | |
| | | Base case | Low | High | Base case | Low | High | Base case | Low | High |
| Pentavalent | Benin | $(2172) | $(4686) | $(684) | $(1962) | $(4477) | $(475) | $(1753) | $(4268) | $(265) |
| | Bihar | $(1139) | $(2908) | $(366) | $(1072) | $(2842) | $(300) | $(1006) | $(2776) | $(234) |
| | Niger | $(4884) | $(10,945) | $(1424) | $(4646) | $(10,706) | $(1186) | $(4407) | $(10,468) | $(947) |
| Pneumococcal conjugate vaccine (PCV) | Benin | $(370) | $(969) | $(51) | $216 | $(383) | $534 | $802 | $202 | $1121 |
| | Bihar | $(151) | $(408) | $(57) | $(69) | $(326) | $24 | $11 | $(245) | $106 |
| | Niger | $(918) | $(2434) | $(99) | $(352) | $(1868) | $467 | $214 | $(1302) | $1032 |
| Rotavirus vaccine (RV) | Benin | $(375) | $(804) | $(115) | $(243) | $(672) | $17 | $(111) | $(540) | $149 |
| | Bihar | $(131) | $(209) | $(80) | $(102) | $(180) | $(51) | $(73) | $(152) | $(23) |
| | Niger | $(1065) | $(2392) | $(294) | $(936) | $(2263) | $(165) | $(808) | $(2135) | $(37) |
| Tetanus toxoid (TT) vaccine | Bihar | $ (166) | $(1040) | $ (55) | $ (166) | $(1040) | $ (54) | $ (165) | $(1039) | $ (53) |
| | Niger | $(245) | $(598) | $(48) | $(239) | $(593) | $(42) | $(233) | $(587) | $(36) |
| Measles vaccine | Bihar | $(107) | $(261) | $(50) | $(104) | $(258) | $(47) | $(101) | $(256) | $(44) |
| | Niger | $(222) | $(523) | $(50) | $(199) | $(499) | $(27) | $(175) | $(476) | $(3) |
| DTP | Bihar | $(990) | $(2294) | $(356) | $(989) | $(2293) | $(355) | $(988) | $(2292) | $(354) |
| Hepatitis (Hep B) | Bihar | $(157) | $(275) | $(67) | $(157) | $(274) | $(66) | $(156) | $(274) | $(66) |
| Oral polio vaccine (OPV) | Niger | $(96) | $(205) | $(34) | $(78) | $(187) | $(16) | $(60) | $(169) | $2 |
| Bacillus calmette–Guérin (BCG) | Niger | $(157) | $(374) | $(35) | $(144) | $(361) | $(22) | $(131) | $(347) | $(8) |
| Yellow fever (YF) | Niger | $(119) | $(344) | $9 | $(19) | $(244) | $108 | $80 | $(145) | $208 |

* Base costs use the average input for medical costs per case, incidence, and DALYs per case. Low costs use the high input for medical costs per case, incidence, and DALYs per case, while high costs use the low input for medical costs per case, incidence, and DALYs per case.
§ Parentheses represent negative numbers, in this case, cost savings.

**Table 4**
Incremental cost-effectiveness ratio (ICER) of replacing each vaccine with a thermostable formulation.

| Replacing the following vaccine with a thermostable formulation | In this location | Price of thermostable version is… | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Equivalent to the price of the current non-thermostable version | | | Twice the price of the current non-thermostable version | | | Three times the price of the current non-thermostable version | | |
| | | Resulted in the following costs per 100 people in the target population | | | | | | | | |
| | | Base Case | Low | High | Base Case | Low | High | Base Case | Low | High |
| Pentavalent | Benin | $(601) | $(744) | $(385) | $(462) | $(674) | $(10) | $(323) | $(603) | $365 |
| | Bihar | $(449) | $(526) | $(212) | $(330) | $(477) | $114 | $(211) | $(429) | $441 |
| | Niger | $(592) | $(730) | $(370) | $(544) | $(706) | $(243) | $(496) | $(682) | $(116) |
| Pneumococcal conjugate vaccine (PCV) | Benin | $(59) | $(289) | $546 | $1,365 | $393 | $3,937 | $2,790 | $1,076 | $7,329 |
| | Bihar | | $(75) | $357 | $895 | $259 | $2,123 | $1,721 | $594 | $3,890 |
| | Niger | $(218) | $(392) | $232 | $157 | $(210) | $1,132 | $532 | $(29) | $2,031 |
| Rotavirus Vaccine (RV) | Benin | $(229) | $(412) | $128 | $148 | $(206) | $945 | $525 | $(0) | $1,761 |
| | Bihar | $(169) | $(167) | $(182) | $218 | $75 | $455 | $605 | $316 | $1,091 |
| | Niger | $(354) | $(506) | $(70) | $(264) | $(458) | $131 | $(174) | $(410) | $333 |
| Tetanus Toxoid (TT) Vaccine | Bihar | $(626) | $(397) | $(1,382) | $(617) | $(395) | $(1,346) | $(608) | $(394) | $(1,309) |
| | Niger | $(435) | $(559) | $(169) | $(415) | $(550) | $(101) | $(396) | $(540) | $(33) |
| Measles Vaccine | Bihar | $(840) | $(602) | $(1,447) | $(774) | $(578) | $(1,273) | $(709) | $(554) | $(1,100) |
| | Niger | $(405) | $(565) | $(70) | $(321) | $(522) | $144 | $(237) | $(479) | $359 |
| DTP | Bihar | $(727) | $(728) | $(705) | $(725) | $(727) | $(701) | $(724) | $(727) | $(697) |
| Hepatitis (Hep B) | Bihar | $(3,410) | $(4,212) | $(4,804) | $(3,395) | $(4,203) | $(4,760) | $(3,381) | $(4,193) | $(4,716) |
| Oral Polio Vaccine (OPV) | Niger | $(604) | $(691) | $(505) | $(418) | $(597) | $(30) | $(232) | $(502) | $446 |
| Bacillus Calmette–Guérin (BCG) | Niger | $(428) | $(582) | $(87) | $(358) | $(547) | $95 | $(289) | $(512) | $278 |
| Yellow Fever (YF) | Niger | $(208) | $(489) | $501 | $292 | $(234) | $1,777 | $792 | $20 | $3,053 |

Black represents highly cost-effective (< GDP/capita) and gray represents cost-effective (<3x GDP/capita). Annual GDPs per capita are $762 for Benin, $1,598 for India, and $359 for Niger in 2015 US dollars ($).[6]

Black represents highly cost-effective (<GDP/capita) and gray represents cost-effective (<3x GDP/capita). Annual GDPs per capita are $762 for Benin, $1598 for India, and $359 for Niger in 2015 US dollars ($) [6].

## 3. Results

### 3.1. Current situation with no vaccines thermostable (Baseline)

Our simulation runs of the current vaccine supply chains yielded the following results over the course of one simulated year: in Benin, 5,294,835 doses were administered resulting in 80% overall vaccine availability (the vaccine availabilities fall within the ranges of WHO/UNICEF-estimated per vaccine coverage in Benin 2013, 64–92%, with the vaccine availability at each location consistent with observed geographic variability) [9]; in Bihar, 14,506,033 doses and 50% availability; and in Niger, 7,302,396 doses and 46% availability (which falls within the WHO/UNICEF-estimated per vaccine coverage in Niger 2013, 38–71%) [10]. Our team did not have Bihar, India, WHO/UNICEF-estimated vaccine coverage data. Validation of all three country models also consisted of comparing model results with actual stock data and wastage rates provided by in-country partners.

Table 3 shows the cost impact of making each vaccine thermostable (per 100 persons in the target population) and Table 4 shows the ICER values across each thermostable scenario, vaccine cost, and location.

### 3.2. A thermostable pentavalent vaccine (Penta)

Making the Pentavalent vaccine thermostable improved overall vaccine availability in Benin to 86%, averting 7427 (4192–12,242) infections and 17,012 (6304–33,399) disability-adjusted life years (DALYs). At current vaccine price, procurement costs increased by $812,000 (as indicated in Section 2, where not reported, standard deviation is <1%), while logistics costs decreased by $9000, medical costs by $11,033,000 ($3,232,000–$25,662,000) and productivity losses by $14,290,000 ($5,295,000–$28,055,000), resulting in $24,521,000 ($7,724,000–$52,914,000) total savings. In Bihar, overall vaccine availability improved to 56%, averting 40,117 (22,011–67,874) infections and 96,518 (35,110–237,604) DALYs. At current price, procurement costs increased by $7,383,000, while logistics costs decreased by $6000, medical costs by $50,694,000 ($14,832,000–$132,262,000) and productivity losses by $154,429,000 ($56,176,000–$380,166,000), resulting in $197,746,000 ($63,631,000–$505,052,000) total savings. In Niger, overall vaccine availability improved to 69%, averting 62,268 (36,761–100,002) infections and 130,382 (49,117–256,131) DALYs. At current price, procurement costs increased by $6,473,000, while logistics costs decreased by $230,000, medical costs by $83,454,000 ($24,438,000–$193,321,000) and productivity losses by $50,849,000 ($19,156,000–$99,891,000), resulting in $128,059,000 ($37,350,000–$286,969,000) total savings.

As shown in Table 4, thermostabilized Penta was cost-saving or highly cost-effective at all modeled price points (current, 2x, and 3x). In most cases, the reduction in medical costs generated savings above the increase in associated procurement costs. Only when Penta was priced at 3x the current price, using the low estimate for disease incidence and medical costs, were the costs greater than the savings per DALY averted. Even in this scenario, however, Penta thermostability was highly cost-effective.

### 3.3. A thermostable pneumococcal conjugate vaccine (PCV)

Making PCV thermostable improved overall vaccine availability in Benin to 86%, averting 2194 (1398–3476) infections and 4643 (1950–9688) DALYs. At current vaccine price, procurement costs increased by $1,621,000, while logistics costs decreased by $9000, medical costs by $1,885,000 ($546,000–$4,415,000) and productivity losses by $3,990,000 ($1,638,000–$8,138,000), resulting in $4,174,000 ($572,000–$10,941,000) total savings. In Bihar, overall vaccine availability improved to 56%, averting 5488 (3482–9626) infections and 17,171 (8025–42,343) DALYs. At current price, procurement costs increased by $3,542,000, while logistics costs decreased by $6000, medical costs by $2,346,000 ($673,000–$6,726,000) and productivity losses by $27,474,000 ($12,840,000–$67,749,000), resulting in $26,284,000 ($9,977,000–$70,940,000) total savings. In Niger, overall vaccine availability improved to 58%, averting 19,762 (12,654–30,952) infections and 39,553 (16,488–81,584) DALYs. At current price, procurement costs increased by $9,104,000, while logistics costs decreased by $163,000, medical costs by $17,577,000 ($5,108,000–$40,929,000) and productivity losses by $15,426,000 ($6,430,000–$31,818,000), resulting in $24,062,000 ($2,598,000–$63,806,000) total savings.

Thermostable PCV was cost-saving or highly cost-effective in each location at its current price (Table 4). At 2x current price, PCV remained highly cost-effective or cost-effective when the average and high inputs for incidence, medical costs and DALYs were used. However, given the high price of the vaccine, doubling the price, using low inputs for incidence, medical costs and DALYs, led to PCV no longer being cost-effective in Benin and Niger.

### 3.4. A thermostable rotavirus vaccine (RV)

Making RV thermostable improved overall vaccine availability in Benin to 86%, averting 5339 (3969–7126) infections and 3962 (1829–7254) DALYs. At current price, thermostability increased procurement costs by $707,000, while decreasing logistics costs by $9000, medical costs by $1,605,000 ($463,000–$3,687,000) and productivity losses by $3,328,000 ($1,536,000–$6,093,000), resulting in $4,235,000 ($1,302,000–$9,083,000) total savings. In Bihar, overall vaccine availability improved to 55%, averting 37,045 (29,069–46,656) infections and 12,827 (7799–20,549) DALYs. At current price, procurement costs decreased by $1,118,000, logistics costs by $6000, medical costs by $1,039,000 ($292,000–$2,299,000) and productivity losses by $20,523,000 ($12,478,000–$32,878,000), resulting in $22,687,000 ($13,895,000–$36,302,000) total savings. In Niger, overall vaccine availability improved to 53%, averting 43,950 (31,858–59,207) infections and 37,550 (16,754–69,980) DALYs. At current price, procurement costs increased by $3,928,000, while logistics costs decreased by $149,000, medical costs by $17,060,000 ($4,948,000–$39,199,000), and productivity losses by $14,645,000 ($6,534,000–$27,292,000), resulting in $27,926,000 ($7,704,000–$62,713,000) total savings.

At each price point (current, 2x, and 3x) and location, thermostable RV was cost-saving, highly cost-effective, or cost-effective (Table 4).

### 3.5. A thermostable tetanus toxoid vaccine (TT)

Making TT thermostable improved overall vaccine availability in Bihar to 56%, averting 4067 (2418–8413) infections and 12,991 (3178–90,492) DALYs. At current price, procurement costs decreased by $3,387,000, while logistics costs decreased by $4000, medical costs by $4,737,000 ($1,000,000–$32,505,000) and productivity losses by $20,786,000 ($5,085,000–$144,787,000), resulting in $28,913,000 ($9,476,000–$180,684,000) total savings. In Niger, TT thermostability improved overall vaccine availability to 55%, averting 3195 (1998–4913) infections and 7773 (2261–16,532) DALYs. At current price, procurement costs increased by $551,000, while logistics costs decreased by $8000, medical costs by $3,926,000 ($925,000–$9,785,000) and productivity losses by $3,031,000 ($882,000–$6,447,000), resulting in $6,415,000 ($1,265,000–$15,690,000) total savings.

At each price point (current, 2x, and 3x) in Bihar and Niger, thermostable TT was cost-saving or highly cost-effective (Table 4).

### 3.6. A thermostable measles vaccine (M)

Making M thermostable improved overall vaccine availability in Bihar to 57%, averting 3843 (2387–6119) infections and 7658 (2883–20,624) DALYs. At current price, procurement costs decreased by $3,259,000, logistics costs by $4000, medical costs by $3,167,000 ($908,000–$9,155,000) and productivity losses by $12,253,000 ($4,613,000–$32,998,000), resulting in $18,683,000 ($8,784,000–$45,416,000) total savings. In Niger, overall vaccine availability improved to 56%, averting 4039 (2578–6151) infections and 7322 (2866–14,346) DALYs. At current price, procurement costs increased by $959,000, while logistics costs decreased by $27,000, medical costs by $3,897,000 ($1,134,000–$9,039,000) and productivity losses by $2,856,000 ($1,118,000–$5,595,000), resulting in $5,821,000 ($1,320,000–$13,702,000) total savings.

At each price point (current, 2x, and 3x) in Bihar and Niger, thermostable M was cost-saving or highly cost-effective (Table 4).

### 3.7. A thermostable diphtheria-tetanus-pertussis vaccine (DTP)

Making DTP thermostable improved overall vaccine availability in Bihar to 54%, averting 29,829 (15,159–50,851) infections and 73,871 (26,784–171,121) DALYs. At current price, procurement costs decreased by $4,196,000, logistics costs by $4000, medical costs by $49,473,000 ($14,691,000–$120,398,000) and productivity losses by $118,194,000 ($42,854,000–$273,794,000), resulting in $171,867,000 ($61,746,000–$398,392,000) total savings. At each price point (current, 2x, and 3x) in Bihar, thermostable DTP was cost-saving (Table 4).

### 3.8. A thermostable hepatitis B vaccine (Hep B)

Making Hep B thermostable improved overall vaccine availability in Bihar to 53%, averting 3341 (983–5923) infections and 5455 (1807–8212) DALYs. At current price, procurement costs decreased by $4,323,000, logistics costs by $4000, medical costs by $14,275,000 ($4,355,000–$30,267,000), and productivity losses by $8,729,000 ($2,891,000–$13,139,000), resulting in $27,329,000 ($11,573,000–$47,732,000) total savings. At each price point (current, 2x, and 3x) in Bihar, thermostable Hep B was cost-saving (Table 4).

### 3.9. A thermostable oral poliovirus vaccine (OPV)

Making OPV thermostable improved overall vaccine availability in Niger to 49%, averting 1480 (949–2252) infections and 2524 (987–4972) DALYs. At current price, procurement costs increased by $329,000, while logistics costs decreased by $407,000, medical costs by $1,447,000 ($421,000–$3,358,000) and productivity losses by $984,000 ($385,000–$1,939,000), resulting in $2,509,000 ($883,000–$5,375,000) total savings. At each price point (current, 2x, and 3x) in Niger, thermostable OPV was cost-saving, highly cost-effective, or cost-effective (Table 4).

### 3.10. A thermostable bacille calmette-guérin vaccine (BCG)

Making BCG thermostable improved overall vaccine availability in Niger to 55%, averting 2876 (1829–4399) infections and 5050 (1914–10,092) DALYs. At current price, procurement costs increased by $666,000, while logistics costs decreased by $16,000, medical costs by $2,809,000 ($817,000–$6,521,000) and productivity losses by $1,970,000 ($746,000–$3,936,000), resulting in $4,129,000 ($914,000–$9,807,000) total savings. At each price point (current, 2x, and 3x) in Niger, thermostable BCG was cost-saving or highly cost-effective (Table 4).

### 3.11. A thermostable yellow fever vaccine (YF)

Making YF thermostable improved overall vaccine availability in Niger to 55%, averting 3061 (1963–4657) infections and 5215 (2045–10,264) DALYs. At current price, procurement costs increased by $1,909,000, while logistics costs decreased by $16,000, medical costs by $2,979,000 ($867,000–$6,908,000) and productivity losses by $2,034,000 ($798,000–$4,003,000), resulting in $3,120,000 (–$228,000–$9,019,000) total savings. At current price, under all input conditions, thermostable YF was cost-saving or cost-effective in Niger (Table 4). However, when the price was 2x or 3x the current price, using low inputs for incidence, medical costs, and DALYs per case, a thermostable YF vaccine was not cost-effective. When the average and high inputs were used, thermostable YF was cost-effective at 2x and 3x the current price.

## 4. Discussion

Our results show that making vaccines thermostable can bring cost savings under a number of different circumstances including when a price premium is charged for the thermostable formulations. Logistics costs decreased because the introduction of thermostable vaccines relieved bottlenecks and in turn reduced the number of additional trips needed. However, with bottlenecks being reduced, vaccine costs increased since the system could then handle the ordering of more vaccine (although the increased costs from more vaccines were partially offset by reductions in wastage. The most substantial decrease occurred in medical costs and productivity losses decreased as more vaccines reached the target population and could then avert more cases of disease. Therefore, the net result was a decrease in overall costs. These findings help quantify the potential economic impact of thermostable vaccines, providing support for their development. Of course, the impact may vary depending on the severity of constraints in a supply chain and the burden of disease in the population. However, as previous studies have shown, many lower- and middle-income counties suffer from significant bottlenecks [1–3,11,12], while the burden of major vaccine-preventable disease remains high [13].

Thermostable vaccines are currently at a crossroads, which helped motivate this study. A decade ago, interest in thermostable vaccines grew until some suggested that thermostable vaccines would have limited value as long as other vaccines still required the cold chain [12]. In other words, the main value of thermostable vaccines seemed to be in their ability to obviate the need for any refrigerators and freezers. However, our previous study showed that there are additional benefits even when the cold chain remains: thermostable vaccines could help alleviate the constraints and bottlenecks of the supply chain by freeing up cold space that could then be used for other vaccines and items [1]. This current study then quantifies that value in economic, epidemiologic, and clinical terms.

Computational modeling can help guide the development of new technologies such as thermostable vaccines by showing their potential impact and value and how these may change based on changing characteristics and conditions. It can also help prioritize which types of vaccines should be the focus of such research and development. Currently, there are efforts to develop thermostable formulations of antigens such as influenza, polio, and rotavirus [14–16]. However, it is unclear which formulations of these may ultimately reach the market and when, since developing thermostable vaccines requires surmounting a number of technological challenges. For example, any new stabilizer, adjuvant, or excipient must not sacrifice the potency or safety of the vaccine. Regardless, our study suggests that the effort required to surmount such challenges may ultimately be worthwhile.

## 5. Limitations

No model can capture every aspect of a supply chain and factor that may affect the impact of a thermostable vaccine. Our experiments assumed that a thermostable formulation of a vaccine would otherwise have the same characteristics such as doses per vial, packaged volume, and efficacy. Our estimates of vaccine efficacy, infection rates, and the costs and DALYs associated with different vaccine-preventable diseases came from different studies identified from extensive searches of the literature. Each of these studies has associated limitations. When data were not available for a specific location, we used data from similar locations, transforming the data where appropriate (e.g., using purchase power parity to translate medical costs). Our study also did not consider other challenges in the supply chain and vaccines that may occur in the future.

## 6. Conclusions

Our study quantified the potential economic impact of thermostable vaccines. Replacing a particular vaccine with a thermostable version yielded cost savings in many cases even when charging a price premium of two or three times the current vaccine price. Savings in medical costs and productivity and in some cases logistics costs could outweigh even significant price premiums charged for thermostable formulations of vaccines. While developing thermostable vaccines will require overcoming technological challenges, our study suggests that the effort entailed may ultimately be worthwhile.

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