Coefficient Giving

Frontiers in Disease Prevention

Prepared by Metaculus on June 11th, 2026

Background

Metaculus is a forecasting platform that uses collective intelligence predictions to inform key decisions for individuals and organizations. This report was commissioned by Coefficient Giving to surface independent forecasts on the timing and trajectory of the most consequential disease prevention technologies in development today.

A total of 15 Metaculus Pro Forecasters, among the most accurate forecasters on the platform, contributed their forecasts and reasoning to this report. Pros leveraged only publicly available information and did not have access to internal sponsor data. The aggregate forecasts in this report are constructed by equally weighting each Pro's forecast.

In addition to narrative reasoning, Pros provided a list of key factors that contributed to each forecast. Metaculus consolidated these factors across Pros and sent the full list back to each forecaster. Each Pro then assigned importance ratings to each factor on a scale of 0 to 100, where 0 is least important and 100 is most. The median rating is included in the top key factors table for each question and in the full list in Annex A. Pro reasoning for their forecasts on each question is included in Annex B.

Forecasting topics

Tuberculosis

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (MTB) bacteria, which spreads through the air and primarily affects the lungs. TB killed 1.23 million people in 2024 and is in the top 10 leading causes of death worldwide, especially affecting lower and lower-middle income countries. The only approved TB vaccine, Bacillus Calmette-Guérin (BCG), has been in use for over a century but offers limited protection to adolescents and adults, the populations driving most transmission. M72/AS01E and MTBVAC are both TB vaccines currently in development.

Malaria

Malaria kills about 600,000 people a year globally and is primarily spread through bites from mosquitoes, when they are infected with a malaria-causing Plasmodium parasite species. Current mitigation efforts involve usage of bed nets to prevent bites at night, application of insecticides, and (more recently) vaccines for children. However, insecticide resistance among mosquitoes is a growing problem.

Gene drive mosquitoes are a proposed genetic intervention using CRISPR-based biased inheritance to spread a trait through wild Anopheles mosquito populations and either crash mosquito numbers or render them unable to transmit malaria. Three main research programs are currently active: Target Malaria (Burkina Faso, Uganda, Mali), Transmission Zero (Tanzania), and the University of California Malaria Initiative (São Tomé and Príncipe, Equatorial Guinea). The technology was first demonstrated in laboratory settings in 2011 but has not yet been released in any open environment.

Microneedle patches

Microneedle or microarray patches are small skin patches covered with microscopic needles that deliver vaccines into the upper layers of the skin. Proponents argue they could simplify mass vaccination by removing the need for syringes, improving heat stability, and enabling self-administration in low-resource settings. Australia's Vaxxas and the US-based Micron Biomedical dominate the late stage pipeline. Both have major institutional backing from the Gates Foundation, the EU, BARDA, and the WHO.

The views and forecasts expressed in this report are those of Metaculus and its forecasting community and do not necessarily reflect the positions or opinions of Coefficient Giving.

Executive Summary

Across the ten forecasting questions in this report, Pro Forecasters consistently distinguish between programs constrained by science (early efficacy, unproven mechanisms) and those constrained by everything that comes after (manufacturing scale-up, regulatory pathways, political will, commercial deal-making).

For the M72 tuberculosis vaccine, Pros project roughly 45% Phase 3 efficacy, modestly below the Phase 2b headline of 49.7% but well above the WHO's policy-relevance threshold, with median expected licensure in 2032. However, there is one big complication. M72 relies on a proprietary GSK ingredient also used in Shingrix, the company's $4B/year shingles vaccine. GSK has declined to spend the ~$200M needed to scale manufacturing for the TB vaccine that will earn far less. Tech transfer plus bridging studies could add 2+ years to any post-licensure rollout, which is why even an optimistic licensure could mean limited supply into the mid-2030s or beyond, resulting in a median forecast of 168 million vaccinated by 2040, but with a 34% chance of <200k.

MTBVAC is the fast follower with a fundamentally different commercial logic. Its Phase 2b IMAGINE trial in adults is widely seen as a long shot (Pros estimate ~35% efficacy with a negative lower confidence bound), but the parallel Phase 3 in newborns could position it as a direct Bacillus Calmette-Guérin (BCG) replacement, with an established global market of ~100 million infants per year. The forecast for MTBVAC vaccinations has a median of 226 million by 2040, with a strong infant Phase 3 result driving the right tail, and failure in both indications driving a long left tail toward zero.

When it comes to gene drive mosquitoes for malaria control, the technology is essentially ready. Pros consistently identify political incentives as the binding constraint, with regulators facing career risk for approval but no comparable reward for success. Forecasts cluster in 2036 for first open-environment release, with meaningful probability past 2040, and the corresponding question on formal bans suggests that bans will likely follow rather than precede actual releases.

Microneedle patches could be rolled out relatively soon, with Pros estimating June 2032 for first approval. The technology has been validated in human trials, two companies (Vaxxas and Micron Biomedical) have meaningful manufacturing investment behind them, and the regulatory pathway is well understood. The main consideration is whether Vaxxas's seasonal flu program or Micron's measles-rubella patch crosses the finish line first.

Across all questions, disagreement among forecasters is driven by judgment calls about regulatory speed, political risk tolerance, and how much weight to give institutional momentum versus historical base rates. Where success depends on a single decision-maker or a single political moment (the GSK adjuvant deal, a country approving the first gene drive release), forecasters take a cautious approach..

Key Takeaways

- **M72** is on track to become the first new TB vaccine licensed in over a century. Pros forecast **licensure around February 2032** with **~45% Phase 3 efficacy**, but GSK's unresolved adjuvant supply standoff is likely to delay rollout. Pros forecast **168 million people** vaccinated by 2040, with a 34% chance of <200k.
- MTBVAC's path forward for adults and adolescents hinges on the current Phase 2 trial, for which Pros **estimate a 35% efficacy** result, with a median lower 95% confidence bound **less than zero**. Ultimately its widespread use depends more on the infant Phase 3 trial as a BCG replacement; Pros forecast a median **226 million people** vaccinated by 2040, but with a long left tail toward zero.
- Gene drive mosquito releases are not technically constrained. Pros consistently identify political incentive asymmetry as the binding constraint, with regulators facing career risk for approval. The first release is forecast for **April 2036**, but formal bans are likely to follow, projected in **April 2038**.
- Microneedle patch vaccines are closest to delivering real-world impact, with Pros forecasting first approval in **June 2032**. Manufacturing scale-up is the main hurdle between licensure and patients, but forecasters do not anticipate additional multi-year delays from supply or commercial disputes.

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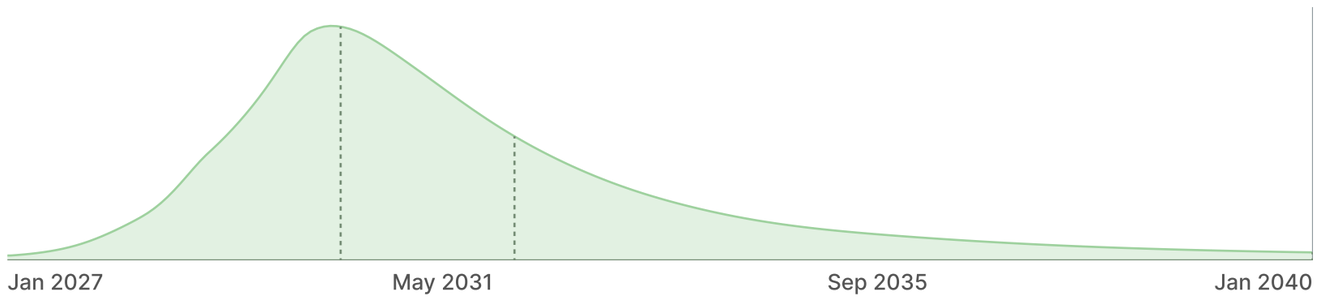
1

When will the M72 tuberculosis vaccine receive a license from a WHO-listed regulator?

Feb 2032
↔ (02 May 2030 – >Dec 2039)



M72/AS01E is a TB vaccine candidate from GSK and the Gates Medical Research Institute, now in a Phase 3 trial with 20,000 participants. If approved, it would be the first new TB vaccine in more than a century, and the first ever to protect adults and adolescents (BCG is given to infants). The earlier Phase 2b trial showed roughly 50% efficacy at three years, and the WHO estimates an effective M72 rollout could prevent 76 million new TB cases over 25 years.

Pro Forecasters' median forecast for licensure lands in early 2032, but with a 28% chance of licensure past December 2039. The forecast hinges on whether Phase 3 replicates Phase 2b efficacy and how quickly a WHO-listed regulator moves once data are in hand.

Forecasters at the earlier end of the range lean on the strength of the Phase 2b readout, the early completion of Phase 3 enrollment in April 2025, and public confidence from TB vaccine expert and vaccine study co-PI Willem Hanekom (who said in March 2026 he'd "eat his hat" if Phase 3 isn't positive). GSK's own February 2026 demand forecast assumes approvals begin in 2029, supporting a compressed 12 to 18 month review given unmet need.

More cautious forecasters point to a wide Phase 2b 90% confidence interval (12% to 71%), the poor historical track record of TB vaccines in adults, and a roughly 60% Phase 3-to-approval base rate. Additionally, South Africa's regulatory agency, the most likely first-mover regulator, isn't a WHO Listed Authority (WLA), pushing the realistic path through the EMA or Indonesia's equivalent (a WLA since December 2025).

Pro Perspective

"The major causal influence is the efficacy result of the trial. If the vaccine fails to prove significant efficacy, it will probably not go to market within the question time frame. If it shows high promise, the licensing process may be sped up. If the trial does not fail, its degree of success may still affect timelines. A borderline efficacious vaccine may lose momentum and take longer. On the other hand a highly effective vaccine may be rushed to the market."

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
The efficacy results from the phase 3 trial	→ Mixed or neutral	**85**
1-2 years are expected to pass from results to eventual approval	↓ Lengthens timeline	**77**
Reasonable risk of Phase 3 failure or other setbacks still leaves a meaningful probability of no approval by 2040	↓ Lengthens timeline	**75**
Phase 3 trials expected to conclude mid-2028	→ Mixed or neutral	**75**

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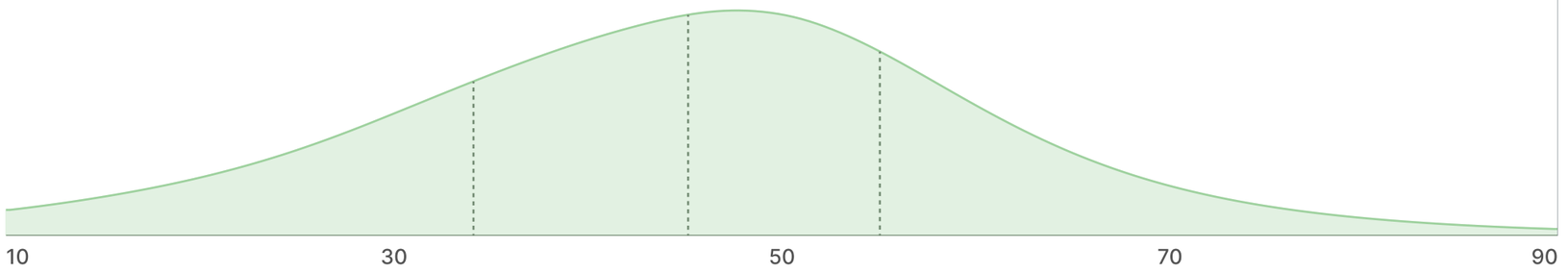
KEY FACTOR	DIRECTION	MEDIAN RATING
Phase 2b efficacy results are very promising	↑ Shortens timeline	70
The historical base rate of success of TB vaccines is extremely low	↓ Lengthens timeline	65
Phase III trials fail fairly frequently	↓ Lengthens timeline	63
Existing trial is large and well-funded making further trials likely unnecessary	↑ Shortens timeline	60
Efficacy usually drops between Phase II and Phase III clinical trials	↓ Lengthens timeline	60
Likely to be the first new TB vaccine for children and adults. MTBVAC is not far behind, but this is first being studied for infants.	↑ Shortens timeline	57

2

What vaccine efficacy will the M72 tuberculosis vaccine show in the Phase 3 Gates MRI trial?

45.2%
↔ (34.1 – 55.0)



M72/AS01E is in a Phase 3 trial that hit its 20,000-participant enrollment target ahead of schedule across 54 sites in South Africa, Kenya, Malawi, Zambia, and Indonesia. The earlier Phase 2b trial reported 49.7% efficacy at three years against active pulmonary TB, the best result for any TB vaccine candidate since BCG.

The median phase 3 efficacy forecast lands at 45.2% (50% prediction interval [34.1%, 55.0%]), anchored on the 49.7% Phase 2b finding but adjusted slightly downward to account for shrinkage as trials move from Phase 2 to Phase 3. Most disagreement is about how big the drop will be, not whether there will be one.

Forecasters at the higher end anchor close to the Phase 2b result, noting that the Phase 3 uses a stricter case-confirmation endpoint under which Phase 2b efficacy was higher (~68% in sensitivity analysis) and that the Gates Medical Research Institute (MRI) wouldn't have funded a $550M trial on shaky data. They also note that the trial co-PI has publicly expressed strong confidence in a positive readout, though this is tempered by the fact that the trial is quadruple-masked and his access to unblinded efficacy data should be limited. Several Pros also noted that the much larger Phase 3 sample (20,000 vs 3,300) and the move from 32 to 110 cases should narrow the confidence interval by roughly a factor of 1.85, tightening precision around whatever the true effect is.

Pro Perspective

“The main pull downward is regression to the mean. The Phase 2b had very few events (13 vs 26 cases) and a very wide confidence interval. Small trial results can be misleading.”

More conservative forecasters emphasize three downward pulls: the “winner's curse” (selection bias from advancing only promising Phase 2 candidates); population heterogeneity from adding Indonesia and Malawi, which have different TB strain distributions and baseline immunity profiles than Kenya and South Africa; and the broader pattern that Phase 3 efficacy tends to come in 5 to 15 percentage points below Phase 2.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
Phase 2b result of 49.7% efficacy sets a strong baseline for the Phase 3 efficacy estimate	↑ Increases estimate	**90**
Typical Phase 2b-to-Phase 3 vaccine efficacy attrition	↓ Decreases estimate	**85**
Larger heterogeneity of participant population in Phase III clinical trials often leads to a lower measured efficacy at the end of the study	↓ Decreases estimate	**67**
Very wide Phase 2b confidence interval (2-74%) means the true efficacy could be well below 50%	→ Mixed or neutral	**65**

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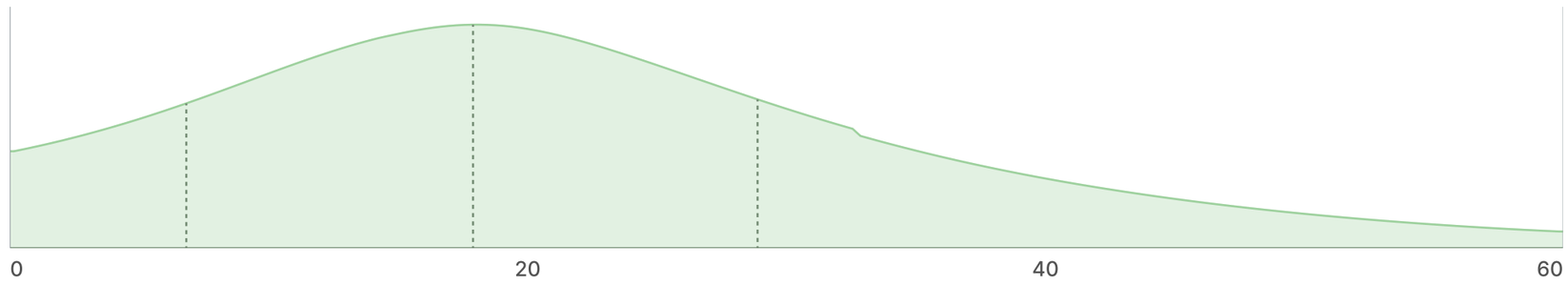
KEY FACTOR	DIRECTION	MEDIAN RATING
Historical base rate of only 50-60% of candidate drugs successfully clearing Phase III clinical trials	→ Mixed or neutral	57.5
The Phase 3 uses a stricter endpoint definition which showed higher efficacy (~68%) in Phase 2b sensitivity analysis	→ Mixed or neutral	55
Small sample size of 110 cases	↓ Decreases estimate	50
Increasing the number of events from 32 to 110 should decrease the CI by 1.85	↑ Increases estimate	50
Much larger Phase 3 sample size (20k participants across 5 countries) should make the result more stable and closer to real world performance	→ Mixed or neutral	50
Uncertainty to account for wide CI and Phase 3 having a larger pool	↓ Decreases estimate	50

3

What will be the lower 95% confidence bound for the vaccine efficacy of the M72 tuberculosis vaccine in the Phase 3 Gates MRI trial?

17.9%
↔ (6.8 – 28.9)



M72/AS01E's Phase 3 trial hit its 20,000-participant enrollment target ahead of schedule. It's event-driven, meaning the analysis runs once 110 laboratory-confirmed cases of pulmonary TB have accumulated, roughly three times the case count of the Phase 2b trial, which reported 49.7% efficacy with a wide 95% confidence interval of 2.1% to 74.2% based on just 39 cases. The lower bound is a conservative test of whether the vaccine has any real effect: if it sits above zero, the data are inconsistent with the vaccine doing nothing, and if it sits above a clinically meaningful number like 30%, the data are inconsistent with the vaccine being marginally useful.

Pro Forecasters's median estimate for the lower bound lands around 18%, with a 50% prediction interval from 7% to 29% and an 18% probability of <0. The forecast is largely mechanical: it follows from each Pro's central efficacy estimate combined with the expected narrowing of the confidence interval as the trial accumulates roughly three times more cases than Phase 2b.

Pro Perspective

"A lower bound below 10% would be surprising; it would only happen if Phase 2 was very lucky in its case mix. On the other hand, anything above 40% would also be a surprise given the still relatively limited number of cases studied in Phase 3."

Disagreement is mostly about how much shrinkage to expect and how much probability mass to leave on a lower bound at or below zero. Forecasters on the higher end point to the math: shrinking the Phase 2b confidence interval in proportion to the greater number of cases gives a distance to the lower-bound from the median of about 28.6 percentage points. Based on the forecasted central estimate of ~49%, that implies a lower bound around 21%. Some also pointed to the stricter Phase 3 case definition, under which Phase 2b's sensitivity analysis showed roughly 68% efficacy with a 95% confidence interval lower bound of 25%, arguing the same endpoint applied to Phase 3 would push the lower bound higher still.

Forecasters on the lower end keep more probability mass on scenarios where true efficacy is well below 49%, in which case the lower bound could plausibly land below 0%. One Pro noted that standard error scales multiplicatively with the risk ratio, so as median efficacy drops, the lower-bound distance shrinks non-linearly. Several others kept a wide left tail to absorb the roughly 20% to 30% probability that Phase 3 fails outright or shows much weaker efficacy than Phase 2b suggested, which would push the lower bound to zero or below.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
The lower bound depends on the median, so this question is heavily derivative of the other question	→ Mixed or neutral	**80**

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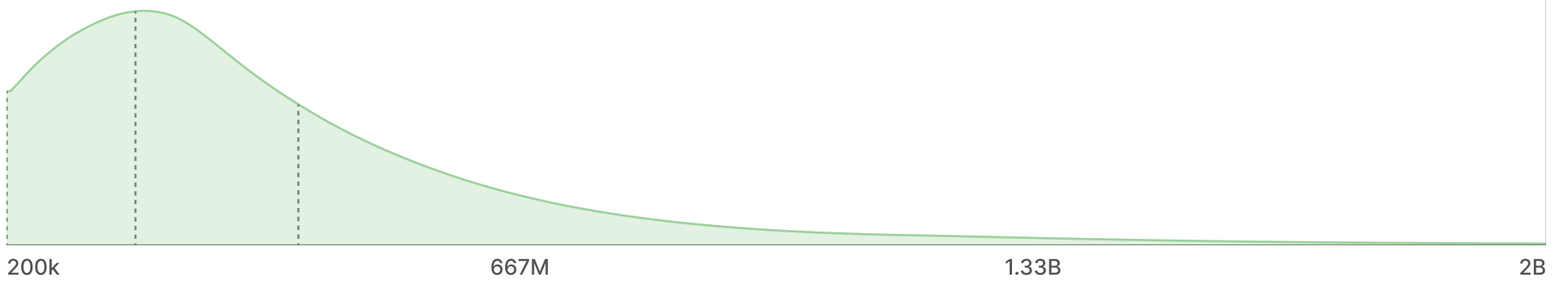
KEY FACTOR	DIRECTION	MEDIAN RATING
The larger trial size should narrow the confidence intervals	↑ Increases estimate	75
Efficacy estimates often drop during Phase III trials due to the sampling of a more heterogeneous population	↓ Decreases estimate	67.5
Phase 2 efficacy of 49.7% points to a likely considerable increase in the lower bound once more cases are observed	↑ Increases estimate	65
The "winner's curse" — Phase II results selected for advancement are often at the optimistic end of the true efficacy distribution due to statistical noise	↓ Decreases estimate	65
Very large confidence interval from the study	→ Mixed or neutral	60
Regression to the base rate on TB vaccine trials	↓ Decreases estimate	60
It's unclear whether the Phase 3 uses the same case definition as the Phase 2b primary analysis or the stricter one	→ Mixed or neutral	40
Some additional complexity if we consider how much over 110 the final number of cases analyzed will be	↑ Increases estimate	30
Significant deviation of the results from normal distribution	→ Mixed or neutral	27.5

4

How many people worldwide will have completed vaccination with the M72 tuberculosis vaccine before 2040?

168M People
↔ (<200k – 379M)



The WHO projects global demand for TB vaccines will exceed 3 billion regimens between 2030 and 2040, with procurement costs of $5 to $8 billion over the decade and no earmarked funding yet in place.

Pro Forecasters span a wide range, with a median of 168 million people, but the distribution tail leans left, with a 34% probability of <200k people. The forecast primarily hinges on whether GSK and the sponsor resolve a long-running standoff over adjuvant supply.

Forecasters at the higher end anchor on or above GSK's commissioned demand forecast, which projects ~210M people vaccinated in the base case and ~301M in the upside scenario, assuming rollout starts in 2029 and reaches 89 countries by 2039. This group reasons that M72 will effectively monopolize adult TB vaccination for most of the 2030s (MTBVAC is the main competitor, but it primarily targets infants), and they trust the sheer scale of unmet need to drive uptake once the vaccine is available.

Pro Perspective

“There is still the unresolved question of whether (and when) a commercial partnership is reached that would allow for the mass-production and rollout of M72. It is unclear how long it will take to reach an agreement with GSK on supply of the adjuvant or indeed whether an agreement can even be struck with them.”

Forecasters on the lower end emphasize three compounding risks. First, a significant probability the vaccine isn't licensed at all, given Phase 3 trial risk. Second, the GSK adjuvant deadlock: GSK seems hesitant to make the investment to scale manufacturing for the vaccine because a proprietary necessary ingredient earns about $4B per year through Shingrix, and GSK has not yet made a licensing deal to allow commercialization. Even once a deal is made, tech transfer plus bridging studies could add 2+ years before rollout. And finally, delivery realities: adults require active outreach, the two-dose schedule means meaningful drop-off (e.g. HPV two-dose completion in sub-Saharan Africa is only ~20%), and the median time from licensure to first Gavi introduction is 5.4 years. A few Pros also flagged that GSK's forecast assumes recommendations will extend to people without latent TB infection, which were barely tested in Phase 3 and could shrink the addressable population by roughly 3x if excluded. There is also disagreement about India and China rollout, two countries with significant TB burden but unclear uptake decisions.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
The vaccine could fail to ever be approved	↓ Decreases estimate	**90**
Results of the Phase 3 trial	→ Mixed or neutral	**90**

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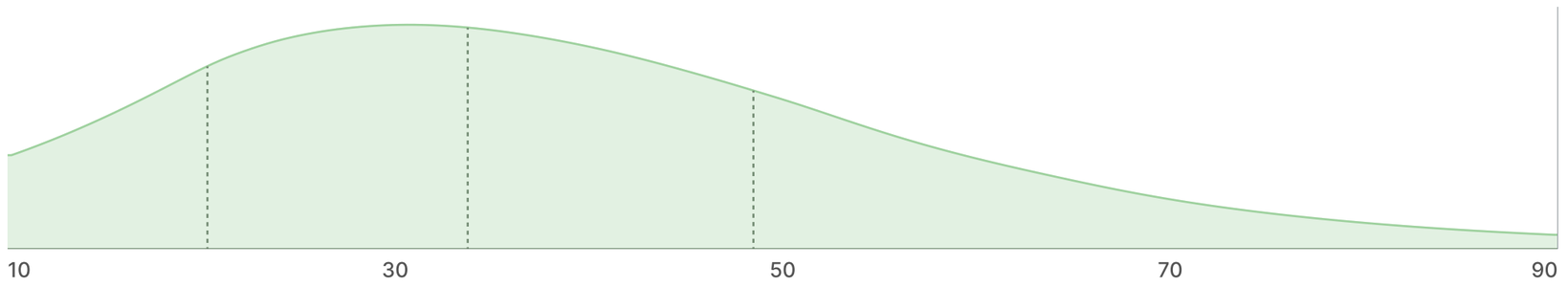
KEY FACTOR	DIRECTION	MEDIAN RATING
Assumed regulatory approval around 2030 provides a long window for distribution to accumulate before 2040	↑ Increases estimate	71
Alternatives to the M72 vaccine could reduce uptake, especially further into the 2030s	↓ Decreases estimate	70
M72 is the clear frontrunner — it has the largest Phase 3 trial, the most robust Phase 2b efficacy data, and the most powerful funders	↑ Increases estimate	66
M72 has very promising results compared to other prospective TB vaccines	↑ Increases estimate	65
Existing forecasts point to wide range but ~500M total adult TB vaccine demand during the period	↑ Increases estimate	65
Which other vaccines are available for adolescents and adults, and when do they become available? If M72 has a monopoly for a number of years it will likely reach a much larger number of people than in a scenario in which e.g. MTBVAC is approved around the same time	↓ Decreases estimate	64
TB-specific historical base rate: extremely poor until recently — no new TB vaccine has been approved in 100 years	↓ Decreases estimate	62
Only 50-60% of candidate drugs successfully clear Phase III clinical trials	↓ Decreases estimate	62

5

What vaccine efficacy will the MTBVAC tuberculosis vaccine show in the IMAGINE phase 2 clinical trial?

35.3%
↔ (21.1 – 50.4)



MTBVAC is a live-attenuated TB vaccine candidate developed at the University of Zaragoza, designed to provide broader and more durable protection than BCG, particularly in adults. The IMAGINE Phase 2b trial began vaccinating participants in early 2026 across sites in Kenya, Tanzania, and South Africa, and is the first efficacy trial for MTBVAC in adults with latent TB infection.

Pro Forecasters mostly land below the WHO's 50% policy-relevance threshold, with an aggregate median at 35.3% (50% prediction interval [21.1%, 50.4%]). The forecast reflects deep skepticism that earlier MTBVAC immunogenicity signals will translate to clinical efficacy, given the TB vaccine field's long history of failed Phase 2 to Phase 3 translation.

Forecasters on the lower end point to structural concerns. MTBVAC is a whole-cell vaccine like BCG, which loses much of its protective effect in adults pre-exposed to non-tuberculous mycobacteria, a common phenomenon in the regions where IMAGINE is running. BCG revaccination showed strong Phase 2 immunogenicity but failed to replicate efficacy in Phase 3, a cautionary precedent.

Pro Perspective

“It sounds like the IMAGINE trial was designed as a Hail Mary. The statistical power is only enough to detect an obvious >50% efficacy. Anything below that and it's a wash.”

Forecasters on the higher end use M72's 49.7% Phase 2b result as a rough ceiling for what's plausible in a successful TB vaccine in this population, and adjust down a few points for MTBVAC's lack of human efficacy data. Some also pointed to MTBVAC's improvements over BCG (it retains nearly all M. tuberculosis antigens, including two BCG lacks) and the encouraging Phase 1b/2a immunogenicity results. A few Pros noted that the trial's 60-70% powering target is more of a budget constraint than a probabilistic estimate (a study powered to detect lower efficacy would need many more participants), so the higher end leaves more right-tail mass.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

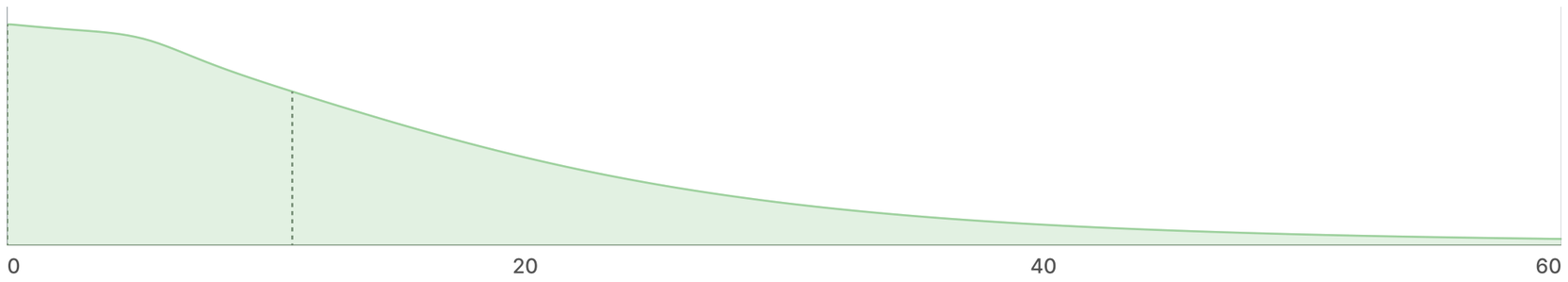
KEY FACTOR	DIRECTION	MEDIAN RATING
Historical base rates for TB vaccines are poor; few candidates succeed or show strong efficacy	↓ Decreases estimate	**75**
For TB vaccines, strong immunogenicity or animal results do not reliably translate into human efficacy	↓ Decreases estimate	**70**
The trial's small final analysis size (~35 TB cases) means high statistical noise and a wide range of possible efficacy estimates	→ Mixed or neutral	**70**

KEY FACTOR	DIRECTION	MEDIAN RATING
Because MTBVAC is BCG-like / whole-cell, it may inherit some of BCG's adult-efficacy limitations, especially in tropical or mycobacteria-exposed populations	↓ Decreases estimate	65
M72's ~50% Phase 2b result is the main benchmark/reference point, and it could be treated as an upper anchor for MTBVAC	↓ Decreases estimate	60
There is still no direct human efficacy evidence for MTBVAC in adults/ adolescents; current evidence is mostly immunogenicity rather than protection	↓ Decreases estimate	60
TB is intrinsically hard to vaccinate against; even natural infection does not generate strong protective immunity	↓ Decreases estimate	60
Early preclinical and Phase 1/2a results are promising, with good immunogenicity/safety and signs MTBVAC may outperform BCG immunologically	↑ Increases estimate	55
MTBVAC may outperform BCG because it improves on the BCG platform and adds missing immunodominant antigens	↑ Increases estimate	40
Expert commentary, especially around Willem Hanekom, appears more enthusiastic for M72 than for MTBVAC	↓ Decreases estimate	39

6

What will be the lower confidence bound for the vaccine efficacy of the MTBVAC tuberculosis vaccine in the IMAGINE Phase 2 clinical trial?

<0%
↔ (<0 – 11%)



The IMAGINE Phase 2b trial is the first efficacy trial for MTBVAC in adults with latent TB infection, with sites in Kenya, Tanzania, and South Africa. It's event-driven, triggering analysis once 35 pulmonary TB cases accumulate across roughly 4,300 participants. The lower bound of the confidence interval is a conservative measure of whether a vaccine has any real effect: above zero means the data rule out no benefit, and above a clinical threshold means they rule out merely marginal benefit. The trial is powered to deliver a positive lower bound only if true efficacy lands near 60-70%.

Pro Forecasters' predictions are very low, with aggregate at less than 0%. The forecast is largely mechanical: it follows from each Pro's central efficacy estimate (~34%), the small case count, and the trial's design choice to power detection only at the 60-70% efficacy level. Most Pros put 20% to 50% of their distribution on a lower bound below zero, meaning the trial fails to demonstrate statistical significance.

Forecasters on the higher end look to the M72 Phase 2b comparison: M72 had a 49.7% median with a 2.1% lower bound, and IMAGINE is slightly larger (4,300 vs 3,300 participants). They argue that if MTBVAC's median lands anywhere near M72's, the lower bound could similarly hover just above zero. One Pro made a counter-intuitive point worth flagging: enrolling adults with latent TB infection boosts the absolute case count at trial sites, which narrows the CI and can lift the lower bound even when the median drops.

Pro Perspective

"A vaccine efficacy above 50% would be required to push the lower confidence bound above zero. For a Phase 2 trial, even 95% confidence that the vaccine does something would be a resounding success."

Forecasters at or near zero point to base rates and case counts.
Across four comparable Phase 2b vaccine trials in difficult infectious diseases (M72, Imbokodo, HVTN 702, Step), three had negative lower bounds and only M72 cleared zero, by two points. A vaccine would need roughly 50% median efficacy to push the lower bound above zero with only 35 cases, and most Pros forecast MTBVAC's median well below that. The majority allocated 40% to 67% of their distribution to a negative lower bound, resulting in non-significance as the overall median outcome.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

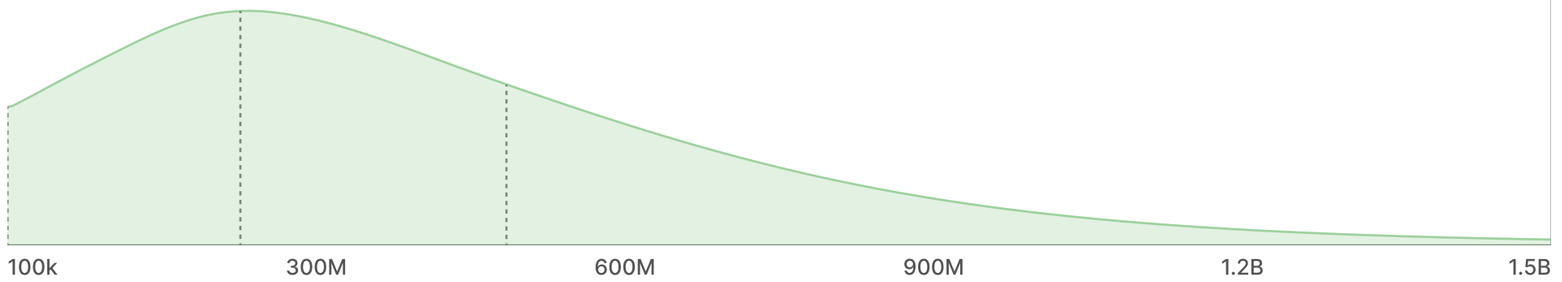
KEY FACTOR	DIRECTION	MEDIAN RATING
The lower confidence bound is mostly a direct consequence of the underlying efficacy point estimate; the relationship is nonlinear, but higher/lower VE generally raises/lowers the bound	→ Mixed or neutral	**90**
Only about 35 endpoint TB cases mean wide confidence intervals and a substantial risk of a low or negative lower bound	↓ Decreases estimate	**85**

KEY FACTOR	DIRECTION	MEDIAN RATING
Historically, TB vaccines and comparable Phase 2b trials often produce results consistent with no effect or negative lower bounds	↓ Decreases estimate	73
M72's Phase 2b result is the main analogue: despite about 50% efficacy it had only about a 2% lower bound, and MTBVAC is often expected to perform worse than M72	↓ Decreases estimate	68
A somewhat larger trial than M72, and any final analysis with more than 35 cases, would modestly narrow the interval and raise the lower bound	↑ Increases estimate	60
Preclinical and Phase 1b/2a results are encouraging; stronger immune response than BCG and broader antigen coverage suggest at least some non-zero efficacy	↑ Increases estimate	55
There is no direct human efficacy evidence for MTBVAC and few strong analogues, leaving wider uncertainty around the lower bound	↓ Decreases estimate	51
BCG revaccination and broader TB vaccine experience suggest that immunogenicity does not reliably translate into protection; a BCG-like platform may inherit adult-efficacy limitations	↓ Decreases estimate	50
The study was powered assuming roughly 60–70% efficacy; if efficacy is that high, a non-negative lower bound becomes plausible, but weaker efficacy makes statistical significance unlikely	→ Mixed or neutral	50
Hanekom is mildly bullish and expert community views seem somewhat more optimistic	↑ Increases estimate	35

7

How many people worldwide will have completed vaccination with the MTBVAC tuberculosis vaccine before 2040?

226M People
↔ (<100k – 485M)



Unlike M72 (which targets adults), MTBVAC is being developed for two distinct markets. A Phase 3 trial in newborns is testing it as a replacement for the century-old BCG vaccine, and the Phase 2b IMAGINE trial is evaluating efficacy in adolescents and adults with latent TB infection. MTBVAC is a single-shot, live-attenuated vaccine without the adjuvant supply concerns facing M72, and Biofabri has signed manufacturing tech-transfer agreements with partners on three continents. A demand forecast published in October 2025 projects 120 million courses of TB vaccination in the first five years after introduction, stabilizing around 90 million annually by 2040.

Pro Forecasters span a wide range from <100k to 485M people vaccinated, with median at 226M. The forecast hinges almost entirely on the infant Phase 3 trial: if MTBVAC succeeds as a BCG replacement, the global infant market is already ~100M people per year and supply chains exist. If it doesn't, M72 dominates the adolescent/adult market and MTBVAC reaches comparatively few people.

Forecasters on the higher end treat MTBVAC's neonatal Phase 3 as the dominant pathway. If it shows superior safety and efficacy to BCG (Phase 1b/2a data are encouraging), it could substitute into existing infant immunization programs across Africa, India, and Southeast Asia, with Bharat Biotech's tech-transfer covering 70+ countries. These forecasters put higher probability on infant Phase 3 success and expect meaningful market capture by 2040. Some also factored in scenarios where M72 stalls on the GSK adjuvant deadlock, opening the adolescent/adult market to MTBVAC as a contingency.

Pro Perspective

“Over 100 million babies receive BCG every year, and the supply chains already exist. If MTBVAC proves superior in the Phase 3 infant trial, swapping it in could happen quickly, and the numbers could be huge.”

Forecasters on the lower end point to several drags. First, there is a 17% to 50% probability that the vaccine isn't approved anywhere. Second, MTBVAC may not be rolled out in some high-burden countries at all: there are concerns that as a live-attenuated vaccine, MTBVAC isn't safe for immunocompromised people, including the ~2 million people in South Africa with undiagnosed HIV. Third, the M72 head start likely costs MTBVAC the adolescent/adult market unless M72 fails. Fourth, recent demand forecasts may be systematically optimistic: COVAX overestimated COVID vaccine deliveries by ~42%, and several Pros noted that UN population estimates in key TB markets (Nigeria, DRC) are likely overcounted.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
The neonatal/infant indication is the clearest path to large numbers, because the existing infant TB-vaccine market is enormous and MTBVAC is already in Phase 3 there	↑ Increases estimate	**80**
TB vaccine development has a very poor historical base rate	↓ Decreases estimate	**80**

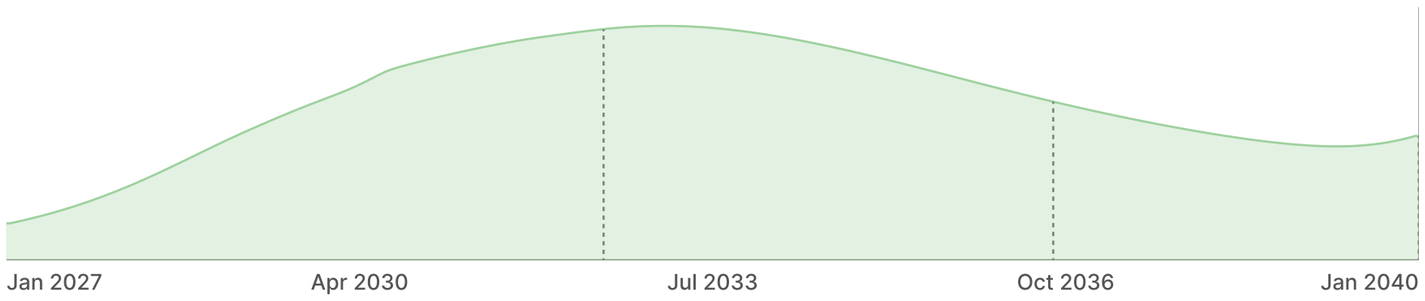
Frontiers in Disease Prevention

KEY FACTOR	DIRECTION	MEDIAN RATING
The underlying addressable market is very large (especially in Africa, India, and the infant segment), so even modest market share could translate into a large number vaccinated	↑ Increases estimate	75
The timing of Phase 3 readouts, approval, and scale-up matters enormously; a launch in the early 2030s leaves limited time to accumulate vaccinations by 2040	→ Mixed or neutral	72
Higher efficacy and a clear advantage over BCG are central; high efficacy supports approval and faster share capture, while low efficacy implies slower rollout or failure	→ Mixed or neutral	66
M72 and other late-stage or future vaccines could take meaningful share (especially in adults) and cap MTBVAC's total reach	↓ Decreases estimate	66
Even if approved, replacing cheap, familiar, century-old BCG programs may be slow because of policy conservatism, price sensitivity, switching costs, and hesitancy	↓ Decreases estimate	63
MTBVAC may have operational advantages: single dose, familiar live-vaccine manufacturing, existing infant-vaccine distribution channels, and possibly better market readiness than competitors	↑ Increases estimate	60
Country-level procurement, closed markets, missing financing, and shaky demand inputs could all reduce realized uptake relative to simple top-down market-size estimates	↓ Decreases estimate	51
Alternative vaccines, better therapies/diagnostics, or falling TB incidence could reduce the eventual addressable market for MTBVAC, especially later in the 2030s	↓ Decreases estimate	50

8

When will the first gene drive mosquito release intended to reduce malaria transmission occur?

Apr 2036
↔ (Jun 2032 – >Dec 2039)



Gene drive mosquitoes are a proposed genetic intervention designed to spread through wild Anopheles populations and either crash mosquito numbers or render them unable to transmit the malaria parasite. Several organizations, most notably Target Malaria, Transmission Zero, and the UC Malaria Initiative, have active research programs in Burkina Faso, Uganda, Mali, Tanzania, São Tomé and Príncipe, and Equatorial Guinea. Public and political acceptance has been uneven; a 2025 police raid on Target Malaria's Burkina Faso partner, following a non-gene-drive male-biased mosquito release, suspended that program nationwide.

Pro Forecasters' median forecast is in April 2036, with an earlier confidence bound in June 2032 and meaningful probability mass past December 2039. The science is essentially ready, so the bottleneck is political and regulatory. The forecast hinges on which country (Tanzania, São Tomé and Príncipe, or Burkina Faso are the names most mentioned) becomes the first to grant approval, and whether the WHO's required three-stage phased rollout can move faster than the 12-15 years it's historically taken for comparable interventions like Wolbachia and sterile insect technique.

Forecasters at the earlier end point to several programs nearing readiness. Transmission Zero in Tanzania has presidential backing from Samia Suluhu Hassan, who has publicly championed gene drive research. The UC Malaria Initiative is making progress on São Tomé and Príncipe, a small island with only 1-7 mosquito species where environmental risk assessment is comparatively manageable. One Pro pulled a 12-14 year base rate from comparison classes (Oxitec OX513A, Wolbachia, sterile insect technique, approvals for genetically modified organisms [GMOs]). With the first gene drive in insects demonstrated in 2011, that base rate puts the implied date around 2029-2032 plus regulatory drag.

Pro Perspective

"The asymmetric political incentive structure dominates. There's no reward for success, but career risk for failure. That math doesn't push regulators toward approval, even when the disease burden is enormous."

More cautious forecasters point to the asymmetric political incentives, the Burkina Faso setback that showed how quickly approvals can reverse, and the structural fact that competing malaria interventions (vaccines, monoclonals) are improving fast enough that the case for an irreversible ecological intervention may weaken over time. Some allocated 15% to 30% probability to a "lone wolf" unauthorized release, though most considered this unlikely given the technical capability required and the backlash risk to legitimate research programs.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
Regulatory hurdles may delay release	↓ Lengthens timeline	**80**

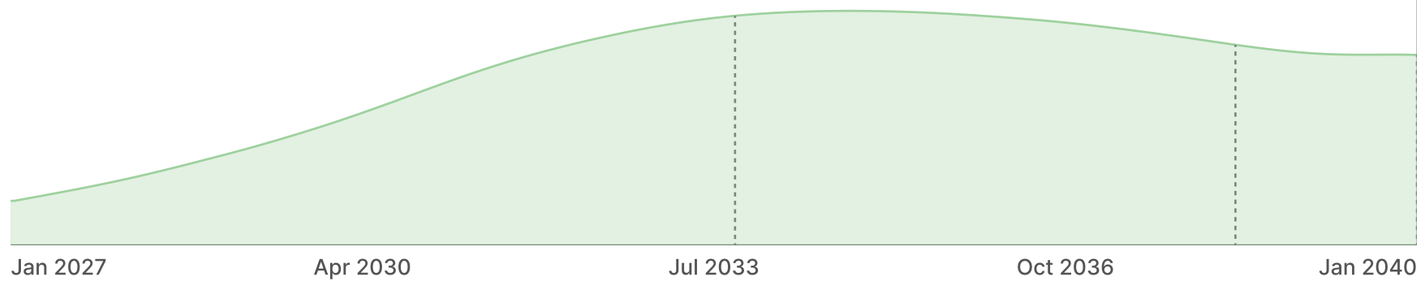
Frontiers in Disease Prevention

KEY FACTOR	DIRECTION	MEDIAN RATING
Gene drives can be scary and could face public opposition	↓ Lengthens timeline	75
WHO requires 3-staged phased approach, no country is even at stage 1	↓ Lengthens timeline	74.5
Enormous malaria burden creates strong incentive for action	↑ Shortens timeline	73
Many countries have trials in progress but only 1 needed	↑ Shortens timeline	70
Tanzania's president has publicly championed gene drive research and the country hosts an active programme	↑ Shortens timeline	70
In 2025, Target Malaria were 2-3 years behind initial schedule	↓ Lengthens timeline	65
No official timelines suggest low chance of quick release	↓ Lengthens timeline	65
Absence of national and international regulatory frameworks could cause complications	↓ Lengthens timeline	62.5
São Tomé and Príncipe has an ongoing project and is a good candidate as a small island	↑ Shortens timeline	62

9

When will new bans on the open-environment release of gene-drive mosquitoes cover 200 million people?

Apr 2038
↔ (Sep 2033 – >Dec 2039)



This question asks whether the political environment hardens into formal bans rather than just continued non-approval. Pre-existing GMO bans don't count, only new bans taking effect after March 18, 2026. Most countries currently rely on case-by-case regulatory approval (no permit, no release), which functions as a de facto ban without anyone needing to legislate. The 200-million population threshold can be cleared by a single large country (Nigeria, Brazil, or one of the other top-10-by-population jurisdictions) or a coalition of smaller ones.

Pro Forecasters converge on April 2037, with a wide prediction interval between September 2033 and after December 2039. The forecast hinges on whether ban activity is driven by a triggering event (an unauthorized or controversial release, an organized political movement, a disinformation cascade) or by general GMO regulation that incidentally captures gene drives. Most Pros considered preemptive bans rare in biotech: human reproductive cloning is the only clear precedent of a wide preemptive ban without a triggering event.

Forecasters on the earlier end flag a few potential triggers. First, broader GMO bans that would incidentally cover gene drives could accumulate if a charismatic leader makes it a populist issue in a country where no releases are even being considered. Second, neighboring-country dynamics: gene drives cross borders, so a country adjacent to a planned release may preemptively ban out of suspicion or for political signaling. Third, several smaller African countries banning together could combine to clear 200 million, especially if a single contested release triggers a regional cascade.

Pro Perspective

“Gene-drive mosquitoes cross borders. A country that bans them still gets the benefits from neighbors who don't, which makes the ban low-cost political signaling—exactly the kind of policy that can spread quickly.”

Forecasters projecting later dates point to a structural reality: countries that don't want gene drives can simply decline to authorize them, so formal legislation requires unusual political pressure. Most countries inclined to ban GMOs already have done so (the wave peaked between 2000 and 2015, with Russia being the last large addition in 2016), and pre-existing bans don't count. The largest qualifying jurisdictions (China, USA, Brazil, Indonesia) have shown few signs of moving toward general GMO bans, and Nigeria, the only African country alone over 200M, has the highest malaria burden in the world and a strong incentive to keep options open.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
Possibility of unrelated GMO bans contributing	↑ Shortens timeline	**82**
The regulatory framing is approval-based, not ban-based	↓ Lengthens timeline	**75**

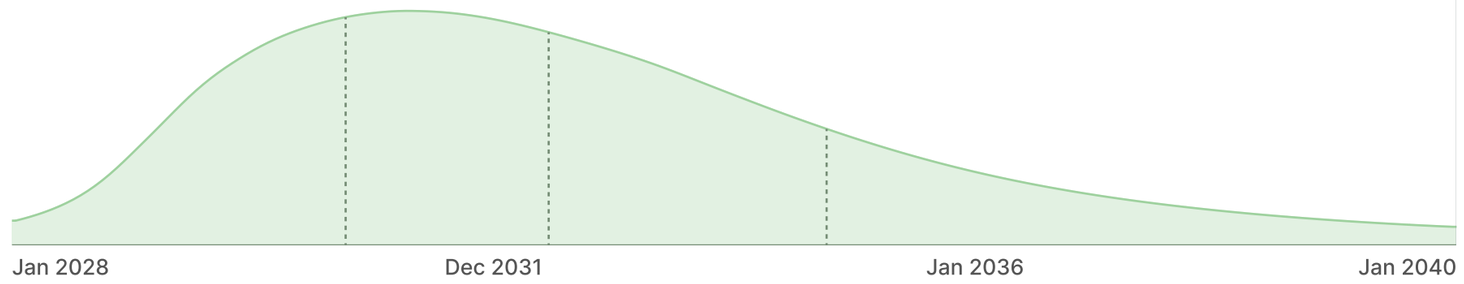
Frontiers in Disease Prevention

KEY FACTOR	DIRECTION	MEDIAN RATING
Enormous malaria burden disincentivises bans	↓ Lengthens timeline	73
Most anti-GMO countries already have bans which won't count	↓ Lengthens timeline	70
One ban or event could trigger cascading bans across many countries	↑ Shortens timeline	70
Possibility of just one large country being enough	↑ Shortens timeline	67
Bans are likely to be reactive	↓ Lengthens timeline	66
Easy to implement a ban	↑ Shortens timeline	65
200M is a high number required	↓ Lengthens timeline	62.5
Possibility of de-facto GMO bans not counting	↓ Lengthens timeline	62

10

When will a vaccine delivered by microneedle patches receive approval from a WHO-listed regulator?

Jun 2032
↔ (Oct 2030 – Oct 2034)



Microneedle or microarray patches are small skin patches covered with microscopic needles that deliver vaccines into the upper layers of the skin. Proponents argue they could simplify mass vaccination by removing the need for syringes, improving heat stability, and enabling self-administration in low-resource settings. Two companies dominate the late-stage pipeline. Australia's Vaxxas (high-density coated microarray patches) has a regulator-licensed manufacturing facility and is moving into Phase 2 for seasonal flu and measles-rubella in 2026-2027, with seasonal flu commercialization targeted for 2028. The US-based Micron Biomedical (dissolving microneedle technology) has stronger clinical data, including a positive Phase 1/2 measles-rubella trial in the Gambia with ~93-100% seroconversion, but its Phase 2 trial hasn't started yet. Both have major institutional backing from the Gates Foundation, the EU (a €250M consortium funding Vaxxas's flu program), Biomedical Advanced Research and Development Authority (BARDA), and the WHO.

Pro Forecasters cluster tightly between late 2031 and early 2033, with median at June 2032. The technology works in principle (Phase 1/2 immunogenicity data are encouraging), so the forecast hinges on manufacturing scale-up and Phase 3 timing. Vaxxas's seasonal flu program is the most plausible path to first approval, with Micron's measles-rubella vaccine following 1-2 years behind.

Pro Perspective

“The vaccines themselves are already approved. These trials are only testing a new delivery system, which has now been validated. The real bottleneck isn't safety or efficacy. It's manufacturing scale-up.”

Forecasters at the earlier end point to Vaxxas's manufacturing readiness, the EU's €250M consortium funding for seasonal flu, and the fact that Australia's regulatory agency is now on the WHO Listed Authorities list, which could provide a faster regulatory path than U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA). They also factored in the possibility that the technology gets first approval via a label expansion of an existing vaccine, which could short-circuit the standard Phase 3 timeline. Several Pros noted that because the antigens are already approved, Phase 3 trials are effectively immunogenicity bridging studies rather than full efficacy trials, which should narrow uncertainty and compress timelines.

More cautious forecasters emphasize manufacturing complexity. Microarray patch sterilization can't use standard methods (end filtration, heat, and radiation all degrade the vaccine), so producers have had to build aseptic processes from scratch. Regulators expect commercial-grade manufacturing to be in place by Phase 3, not just at launch, which means production scale-up needs to be largely solved before late-stage trials begin. The WHO's October 2025 Product Development for Vaccines Advisory Committee update flagged “significant manufacturing challenges” for the measles-rubella program without further detail, and Micron has gone notably quiet since June 2025 despite earlier signals of a 2027 commercialization target. A few Pros also flagged a non-trivial skin discoloration side effect observed in Micron's Phase 1/2 trial as a potential adoption issue at scale. Finally, some Pros flagged that competing delivery technologies (oral or nasal vaccines) could potentially make microneedle patches obsolete even before approval.

Most important key factors considered in forecasting

Rated by Pro Forecasters, where **0** is least important and **100** is most. Complete list included in Annex A: Key Factors.

KEY FACTOR	DIRECTION	MEDIAN RATING
Many competing companies means redundancy if a vaccine fails	↑ Shortens timeline	**75**
Phase 2/3 yet to happen	↓ Lengthens timeline	**75**
Multiple candidates (Micron and Vaxxas) already mid-stage and viable	↑ Shortens timeline	**75**
Micron's Phase 3 has not yet started, appears to be delayed	↓ Lengthens timeline	**74.5**
Multiple methods (dissolvable and solid microneedles) means multiple pathways to success	↑ Shortens timeline	**74**
The proof-of-concept stage has already been successfully passed	↑ Shortens timeline	**72**
US, EU, and Australia are all involved so more pathways to possible success and for resilience against potential political, supply chain, or regional disruptions	↑ Shortens timeline	**70**
Unknown future Phase 3 timing and duration	→ Mixed or neutral	**70**
Micron's Phase 2 data is promising	↑ Shortens timeline	**69**
Frontrunner vaccines set to have Phase 2 trials in 2027	↑ Shortens timeline	**68**