

The Invisible Graveyard: Quantifying the Mortality Cost of FDA Efficacy Lag

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Abstract

This study quantifies the cumulative mortality and morbidity costs associated with the Unitary Pre-Market Approval (UPMA) model mandated by the 1962 Kefauver-Harris Amendments. By enforcing efficacy testing prior to market entry, the current regulatory framework imposes an average “Efficacy Lag” of 8.2 years (90% CI: 4.84 years-11.5 years) post-safety verification. Using data from the Tufts Center for the Study of Drug Development (CSDD) and the WHO Global Burden of Disease (GBD) database, we estimate two distinct mortality costs: (1) Historical mortality (1962-2024): approximately 102 million people died waiting for approved drugs during their approval delays, representing a lower bound excluding drugs never developed due to cost barriers; (2) Future timeline shift: an additional 416 million will eventually die because the disease eradication timeline has been pushed back by 8.2 years (90% CI: 4.84 years-11.5 years). Combined, these represent 8.77 billion Disability-Adjusted Life Years when adjusted for morbidity, with a cumulative economic deadweight loss of approximately \$1.32 quadrillion (90% CI: \$676 trillion-\$2.14 quadrillion) (2024 USD), reflecting 8.77 billion DALYs valued at the standard WHO cost-effectiveness threshold of \$150,000 (90% CI: \$100,384-\$198,679)/DALY. The societal cost of Type II Regulatory Errors (delayed access to effective therapies) exceeds the averted cost of Type I Regulatory Errors (market access for ineffective therapies) by a factor of 3,389 (90% CI: 1,811-5,734).

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Version note. This document is an archival snapshot. Latest interactive version: <https://papers.acceleratedmedicine.org/invisible-graveyard.html>. Citable DOI: <https://doi.org/10.5281/zenodo.18356231>.

1 The Short Version

A drug is proven safe. It might cure your disease. The FDA says you cannot have it yet because they need 8.2 years (90% CI: 4.84 years-11.5 years) to confirm it works (the 1962 Kefauver-Harris Amendments). You die during those 8.2 years (90% CI: 4.84 years-11.5 years). The drug is then approved and given to people who are not you, because you are dead. This has happened 102 million times since 1962. It is called “consumer protection.” Two distinct mortality costs:

1. **Historical deaths (1962-2024):** 102 million people died waiting for approved drugs during their approval process - a **lower bound** excluding drugs never developed due to cost barriers
2. **Future timeline shift (under cascade assumption):** 416 million additional deaths will occur because the entire disease eradication timeline is pushed back by 8.2 years (90% CI: 4.84 years-11.5 years)

The ratio: Type II errors (blocking effective drugs) cost 3,389 (90% CI: 1,811-5,734) more lives than Type I errors (approving dangerous drugs) prevent.

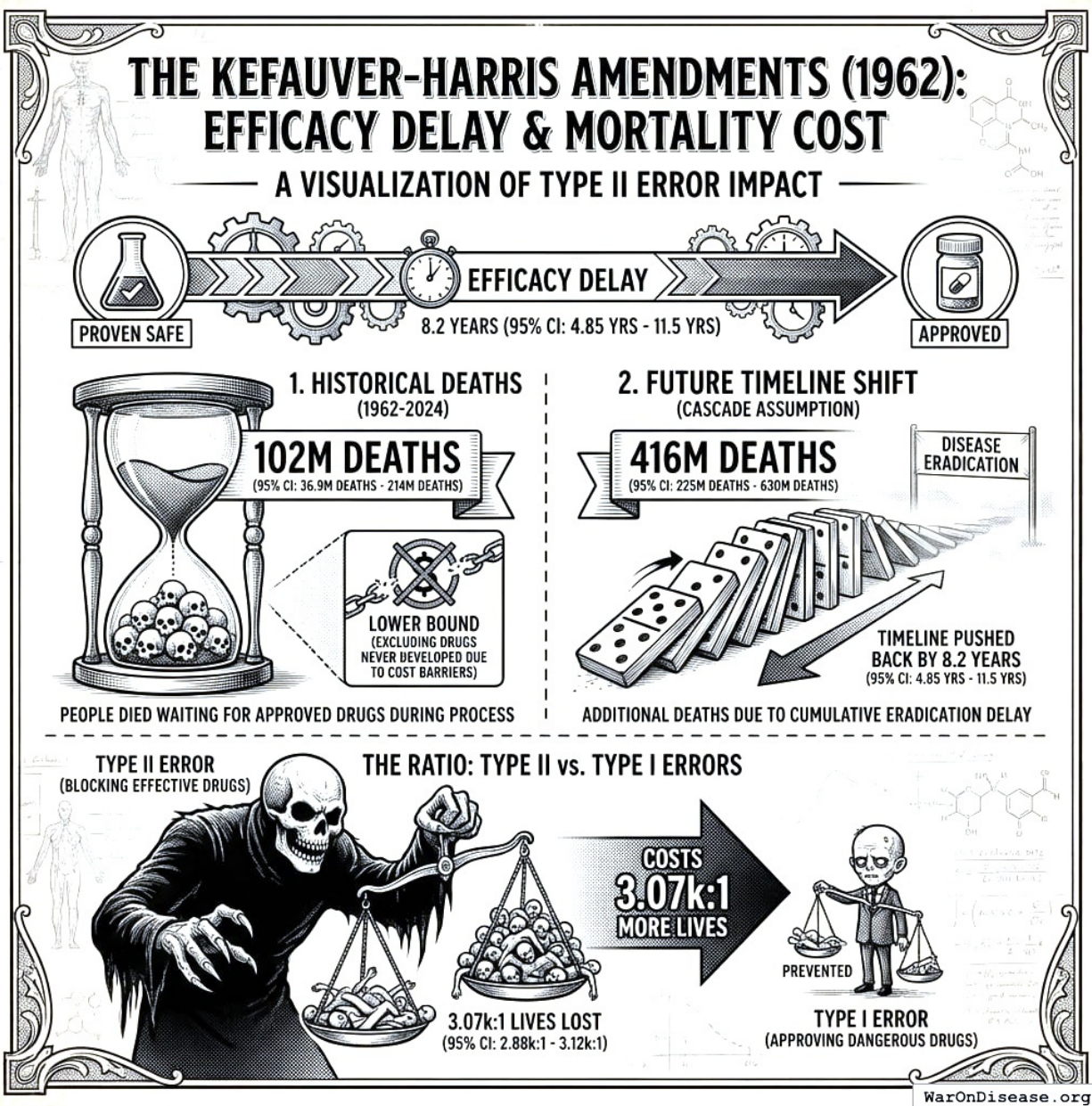


Figure 1: Approving a bad drug killed this many people historically. Delaying good drugs will kill 3,070 times more people in the future. We're very worried about the smaller number.

2 Abstract

This study quantifies the cumulative mortality and morbidity costs associated with the **Unitary Pre-Market Approval (UPMA)** model mandated by the 1962 Kefauver-Harris Amendments. By enforcing efficacy testing prior to market entry, the current regulatory framework imposes an average “Efficacy Lag” of **8.2 years (90% CI: 4.84 years-11.5 years)** post-safety verification.

Using data from the Tufts Center for the Study of Drug Development (CSDD) and the WHO Global Burden of Disease (GBD) database, we estimate two distinct mortality costs:

1. **Historical mortality (1962-2024):** Approximately **102 million people** died waiting for approved drugs during their 8.2 years (90% CI: 4.84 years-11.5 years) approval delays. This is a **lower bound** - it excludes drugs never developed due to cost barriers.
2. **Future timeline shift (under cascade assumption):** An additional **416 million** will eventually die because the entire disease eradication timeline has been pushed back by 8.2 years (90% CI: 4.84 years-11.5 years). When cures finally arrive, they arrive 8.2 years (90% CI: 4.84 years-11.5 years) later than they would have without efficacy requirements. During that delay, people die.

Historical Deaths Calculation:

$$\begin{aligned}
& Deaths_{lag,total} \\
&= Lives_{saved,annual} \times T_{lag} \\
&= 12.4M \times 8.2 \\
&= 102M
\end{aligned}$$

where:

$$\begin{aligned}
& Lives_{saved,annual} \\
&= \frac{LY_{saved,annual}}{T_{ext}} \\
&= \frac{149M}{12} \\
&= 12.4M
\end{aligned}$$

Monte Carlo Analysis: Total Deaths from Historical Progress Delays

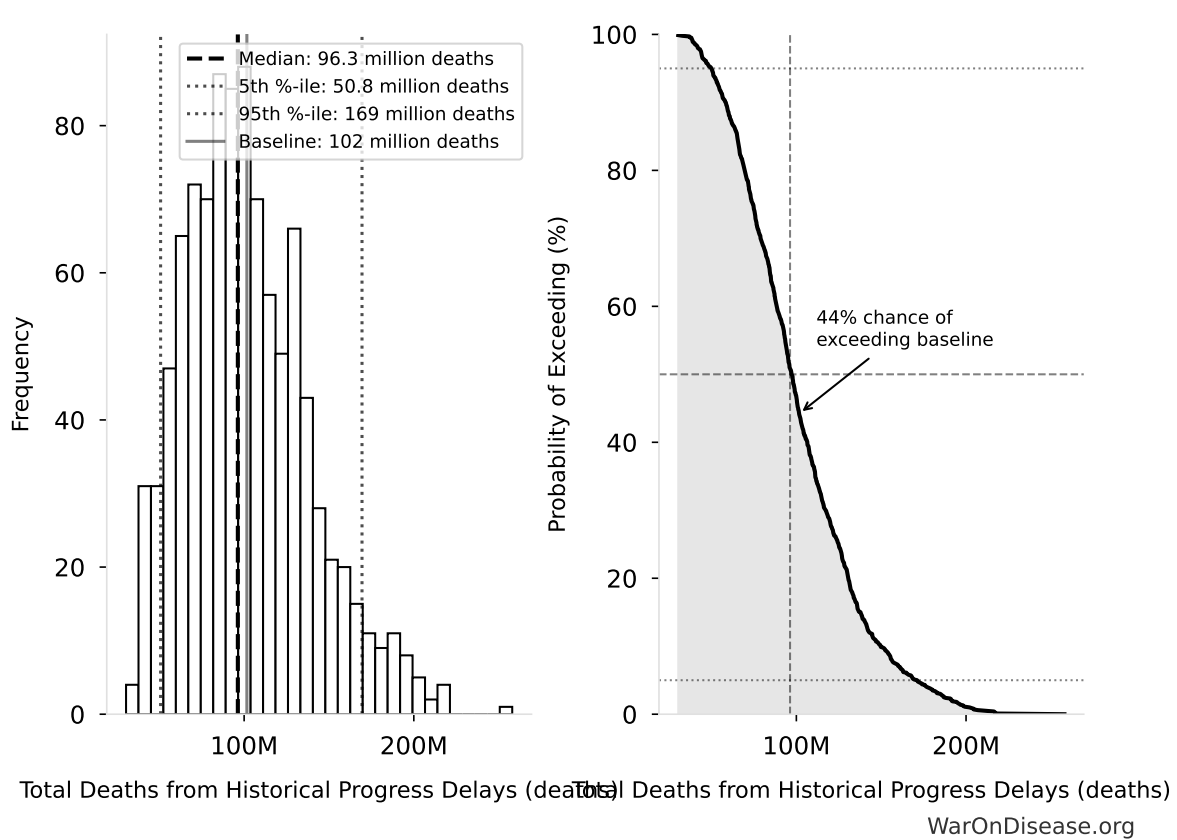
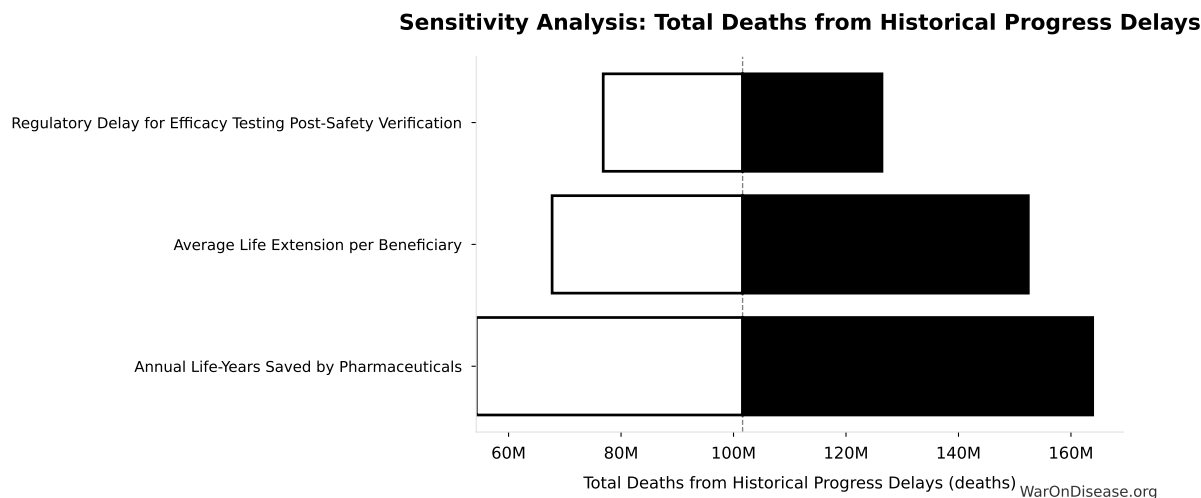


Figure 2: Monte Carlo Distribution: Total Deaths from Historical Progress Delays (10,000 simulations)

Simulation Results Summary: Total Deaths from Historical Progress Delays

Statistic	Value
Baseline (deterministic)	102 million
Mean (expected value)	101 million
Median (50th percentile)	96.3 million
Standard Deviation	36.3 million
90% Range (5th-95th percentile)	[50.8 million, 169 million]

The histogram shows 1,000 of the 10,000 Monte Carlo draws for Total Deaths from Historical Progress Delays; the summary statistics use all 10,000. The exceedance curve (right) shows the probability of the outcome exceeding any given value.



Combined, these represent **8.77 billion Disability-Adjusted Life Years (DALYs)** when adjusted for morbidity. All estimates include Monte Carlo confidence intervals.

Valuing these lost years at a conservative global Value of a Statistical Life Year (VSLY) of \$150,000 (90% CI: \$100,384-\$198,679)/DALY (the standard normative valuation used in WHO and health economics cost-effectiveness analyses), we find a cumulative economic deadweight loss of approximately **\$1.32 quadrillion (90% CI: \$676 trillion-\$2.14 quadrillion)** (2024 USD). The study concludes that the societal cost of **Type II Regulatory Errors** (delayed access to effective therapies) exceeds the averted cost of **Type I Regulatory Errors** (market access for ineffective therapies) by a factor of **3,389 (90% CI: 1,811-5,734)**.

3 Scale

9/11: 2,977 dead. We spent \$8 trillion in response.

Holocaust: 6 million dead.

Efficacy lag: 102 million dead. That's 34,132 9/11s (90% CI: 17,055 9/11s-56,926 9/11s), or 17 Holocausts.

We paid \$4.84 trillion (90% CI: \$3.75 trillion-\$6.05 trillion) (lower bound - Phase 2/3 costs only) to cause 34,132 9/11s (90% CI: 17,055 9/11s-56,926 9/11s).

Monte Carlo Analysis: Cumulative Efficacy Testing Cost (1962-2024)

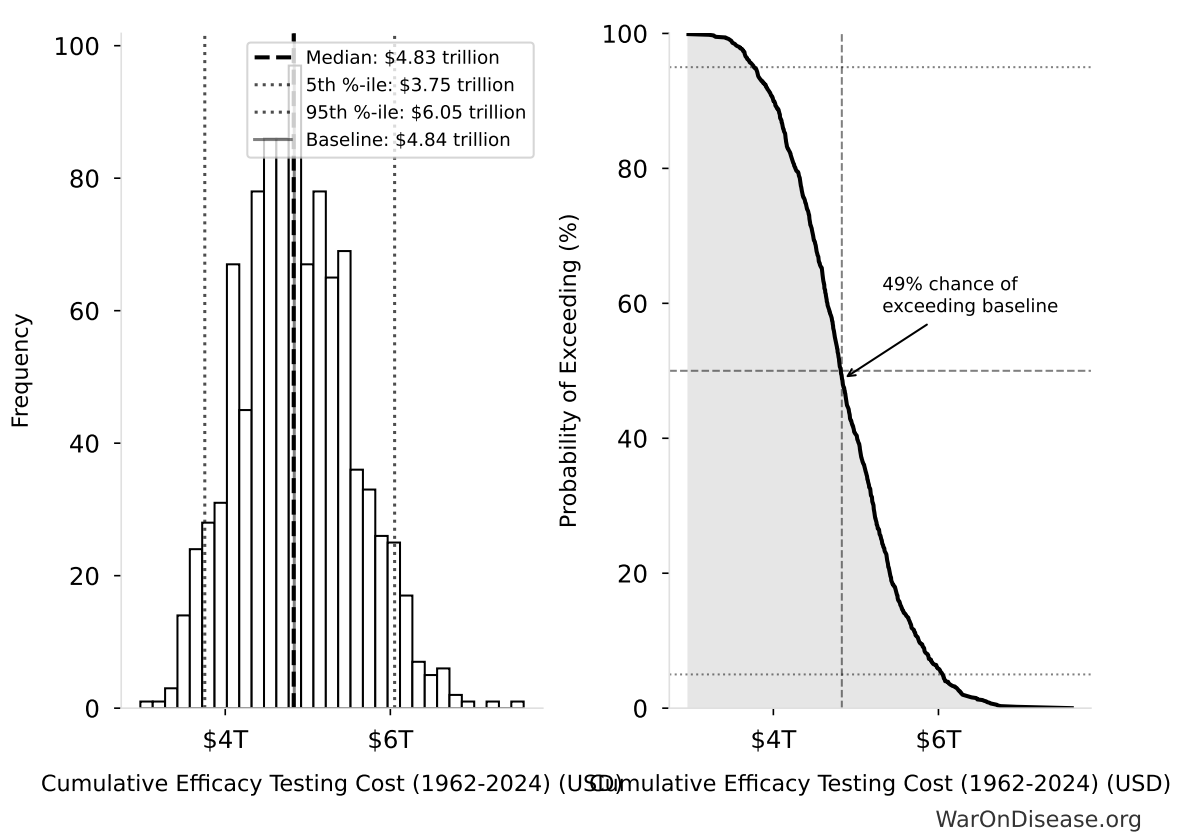


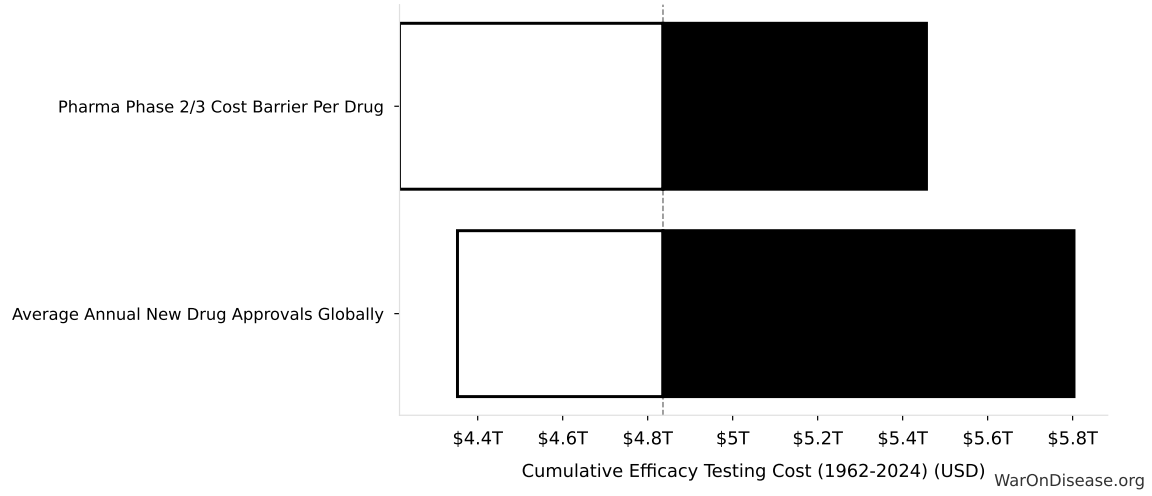
Figure 3: Monte Carlo Distribution: Cumulative Efficacy Testing Cost (1962-2024) (10,000 simulations)

Simulation Results Summary: Cumulative Efficacy Testing Cost (1962-2024)

Statistic	Value
Baseline (deterministic)	\$4.84 trillion
Mean (expected value)	\$4.86 trillion
Median (50th percentile)	\$4.83 trillion
Standard Deviation	\$701 billion
90% Range (5th-95th percentile)	[\$3.75 trillion, \$6.05 trillion]

The histogram shows 1,000 of the 10,000 Monte Carlo draws for Cumulative Efficacy Testing Cost (1962-2024); the summary statistics use all 10,000. The exceedance curve (right) shows the probability of the outcome exceeding any given value.

Sensitivity Analysis: Cumulative Efficacy Testing Cost (1962-2024)



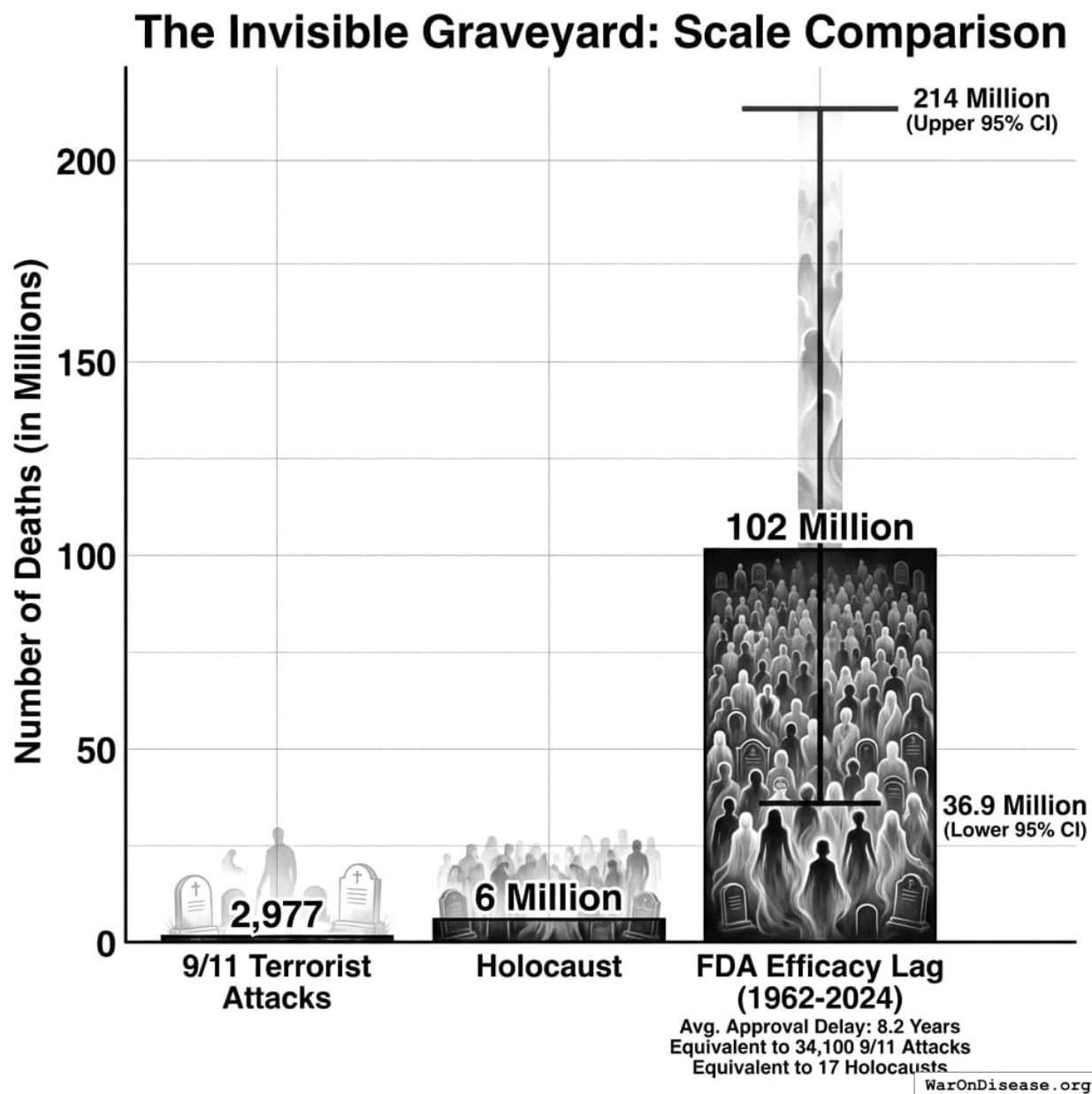


Figure 4: The FDA has killed more people than the Holocaust, but they did it by accident while trying to help, which is somehow more disturbing.

That's \$1.56 billion (90% CI: \$1.23 billion-\$1.89 billion) per drug for Phase 2/3 efficacy trials, paid by patients through higher drug prices. Before 1962, the AMA's 144 thousand physicians tracked patient outcomes and JAMA published the results. We replaced that with tiny trials on handpicked patients.

Without mandatory pre-market trials, the market wouldn't be blind. Knowing whether drugs work is one of the highest consumer demands imaginable. Organizations like Consumer Reports, JAMA, and independent research institutes would compete to provide rigorous, large-scale efficacy data - with no pharma conflicts of interest, across real-world populations, with ongoing monitoring instead

of a pre-approval snapshot.

These are underestimates. They only count delays to drugs that got developed. The \$2.6 billion (95% CI: \$1.5 billion-\$4 billion) approval cost killed other drugs before they started. We can't count deaths prevented by cures that don't exist.

$$\begin{aligned}
 & N_{9/11,equiv} \\
 &= \frac{Deaths_{lag,total}}{N_{9/11}} \\
 &= \frac{102M}{2,980} \\
 &= 34,100
 \end{aligned}$$

where:

$$\begin{aligned}
 & Deaths_{lag,total} \\
 &= Lives_{saved,annual} \times T_{lag} \\
 &= 12.4M \times 8.2 \\
 &= 102M
 \end{aligned}$$

where:

$$\begin{aligned}
 & Lives_{saved,annual} \\
 &= \frac{LY_{saved,annual}}{T_{ext}} \\
 &= \frac{149M}{12} \\
 &= 12.4M
 \end{aligned}$$

Monte Carlo Analysis: Efficacy Lag Deaths (9/11 Equivalents)

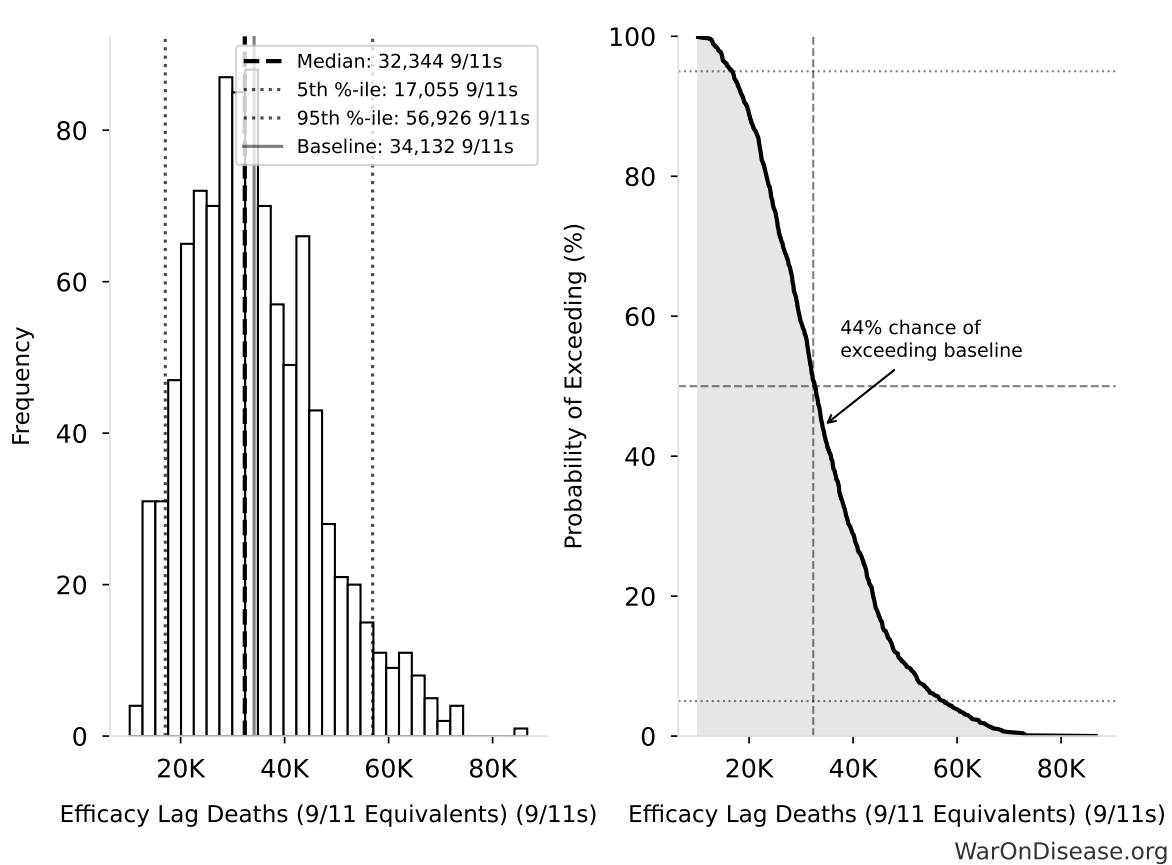
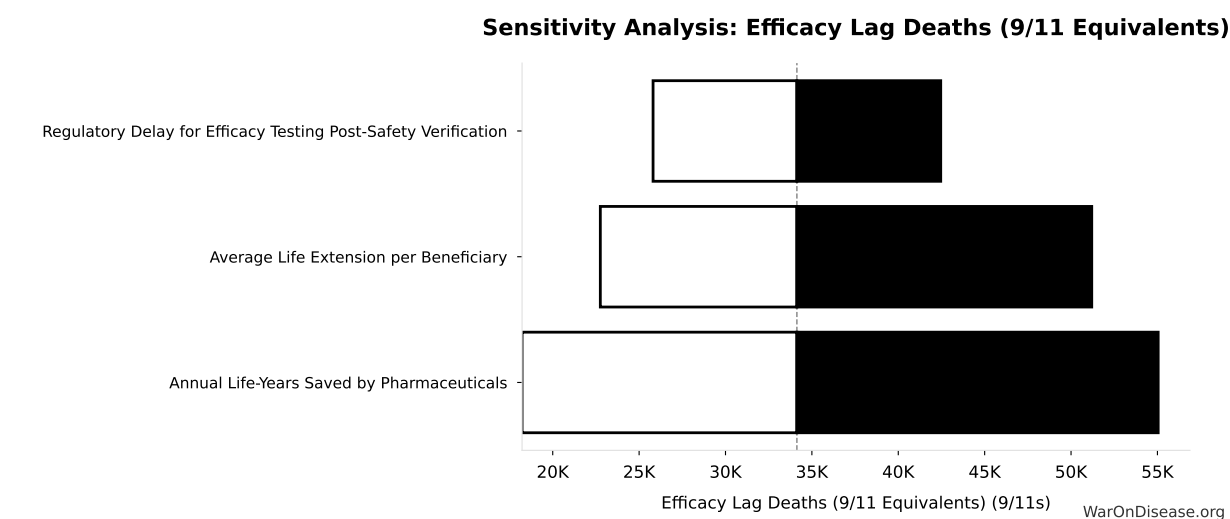


Figure 5: Monte Carlo Distribution: Efficacy Lag Deaths (9/11 Equivalents) (10,000 simulations)

Simulation Results Summary: Efficacy Lag Deaths (9/11 Equivalents)

Statistic	Value
Baseline (deterministic)	34,132
Mean (expected value)	34,033
Median (50th percentile)	32,344
Standard Deviation	12,202
90% Range (5th-95th percentile)	[17,055, 56,926]

The histogram shows 1,000 of the 10,000 Monte Carlo draws for Efficacy Lag Deaths (9/11 Equivalents); the summary statistics use all 10,000. The exceedance curve (right) shows the probability of the outcome exceeding any given value.



Sensitivity Indices for Efficacy Lag Deaths (9/11 Equivalents)

Regression-based sensitivity showing which inputs explain the most variance in the output.

Input Parameter	Sensitivity Coefficient	Interpretation
Total Deaths from Historical Progress Delays (deaths)	1.0000	Strong driver

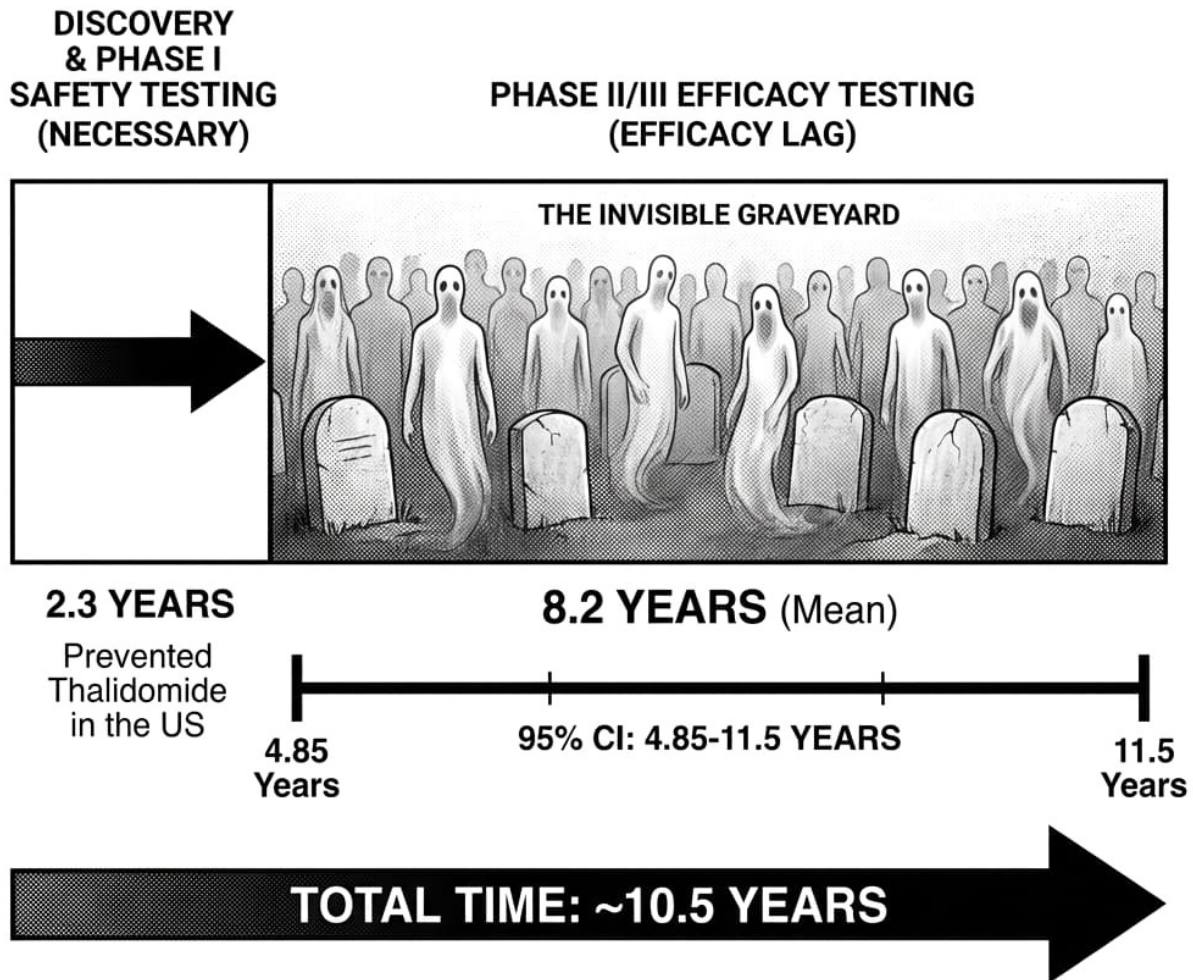
Interpretation: Standardized coefficients show the change in output (in SD units) per 1 SD change in input. Values near ± 1 indicate strong influence; values exceeding ± 1 may occur with correlated inputs.

4 Introduction

The modern pharmaceutical regulatory model relies on a binary licensure model: a drug is either “safe and effective” (approved) or “unsafe/ineffective” (prohibited). While Phase I trials typically establish safety within 2.3 years, the requirement to prove statistical efficacy (Phase II/III) extends the pre-market timeline by an additional **8.2 years (90% CI: 4.84 years-11.5 years)** on average.

This study evaluates the **Bifurcated Regulatory Model (BRM)**, defined as “Safety-First / Efficacy-Later”, to measure the “Invisible Graveyard”: the population that dies during the regulatory latency period between safety verification and final approval.

The Efficacy Lag: Where Patients Die Waiting



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Figure 6: Phase I makes sure the drug won't kill you. Phases II and III make sure you die before you can take it.

5 Literature Review: The Drug Lag Debate

5.1 Foundational Economic Analysis

The regulatory cost of FDA efficacy requirements was first rigorously quantified by Peltzman¹⁰, who estimated that the 1962 Kefauver-Harris Amendments reduced the flow of new drugs by 50-60%. His analysis concluded that the costs of reduced pharmaceutical innovation substantially exceeded any benefits from keeping ineffective drugs off the market, resulting in net welfare losses to society.

FOUNDATIONAL ECONOMIC ANALYSIS: FDA EFFICACY REGULATORY COSTS & DRUG LAG

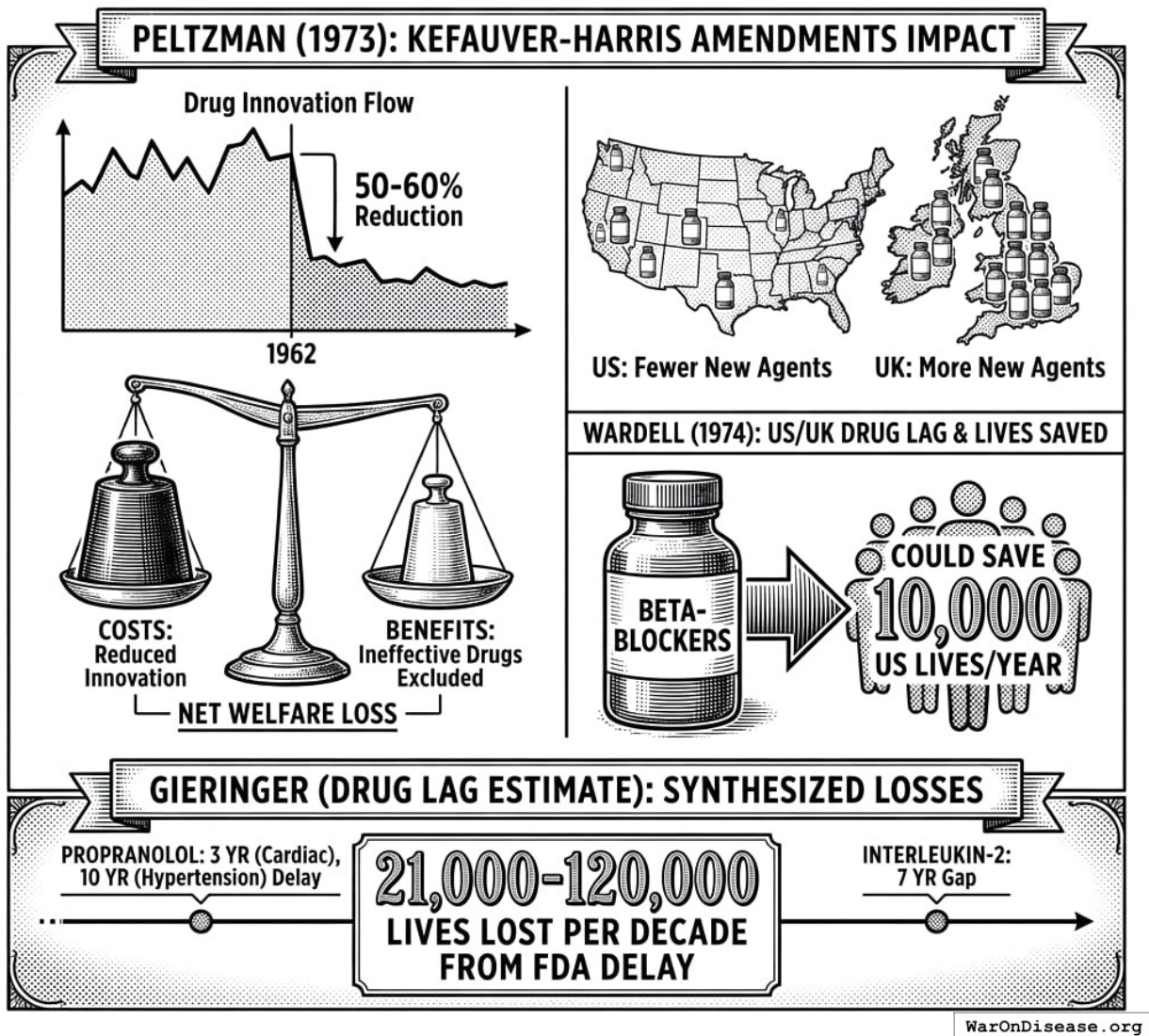


Figure 7: Safety regulations cut drug production in half. They saved us from dangerous medicines by ensuring half of us would die without any medicine at all.

Wardell¹¹ documented the emerging “drug lag” between US and UK drug approvals, finding that the UK had access to significantly more new therapeutic agents. His estimate that beta-blockers alone could save 10,000 American lives annually if approved became a landmark finding in regulatory economics.

Gieringer¹² synthesized these estimates, calculating 21,000-120,000 lives lost per decade from FDA delay. His work documented specific drug delays: propranolol (approved in the US 3 years after Europe for cardiac use, 10 years later for hypertension), interleukin-2 (7-year gap), and numerous other therapeutics.

5.2 The Current Debate

Contemporary research continues to find significant regulatory costs. The Tufts Center for the Study of Drug Development documents development timelines of 10.5 years (95% CI: 6 years-12 years) and costs of \$2.6 billion (95% CI: \$1.5 billion-\$4 billion) per approved drug. BIO's clinical development success rates show only 10% of drugs entering Phase I ultimately reach patients.

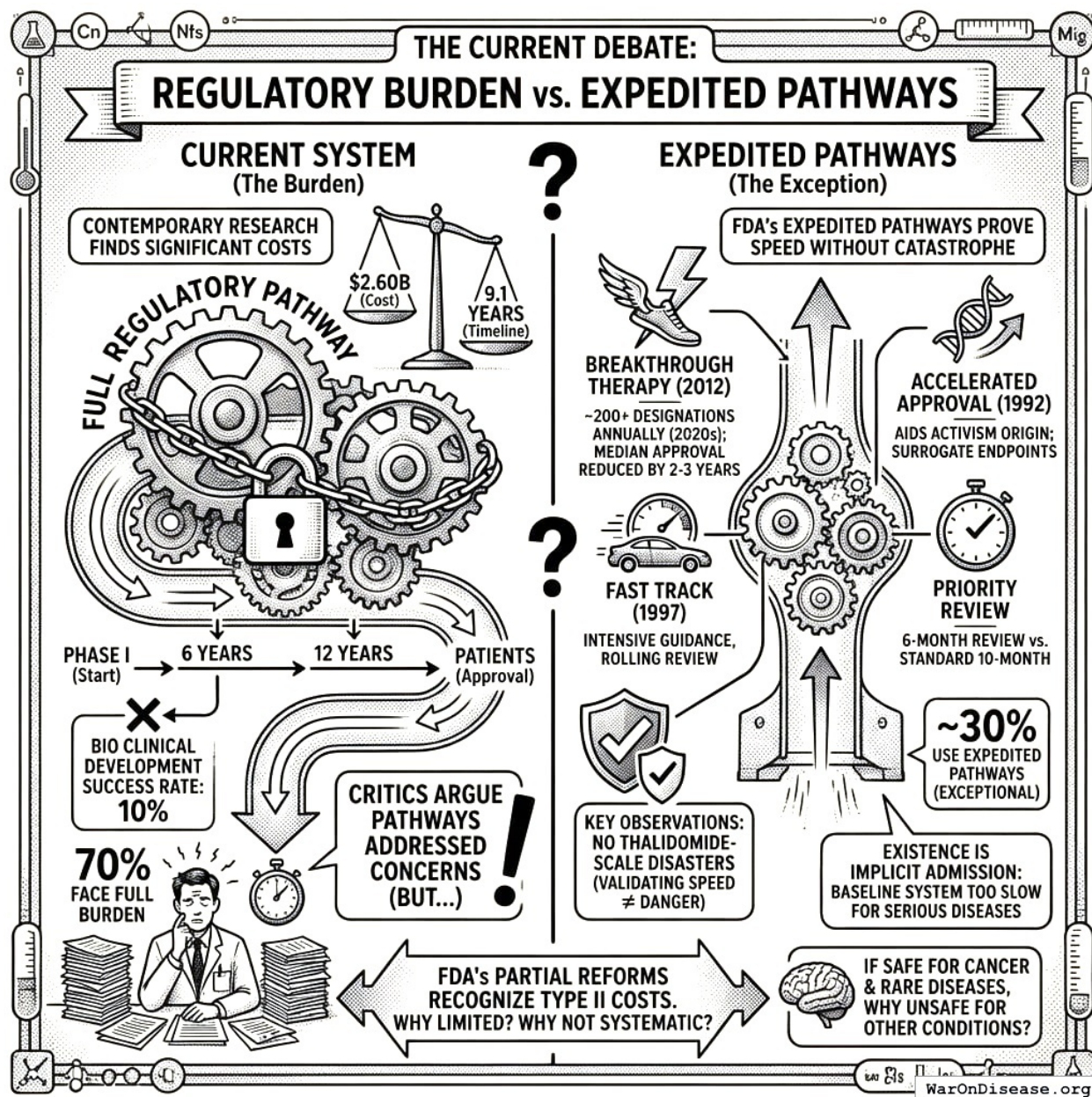


Figure 8: The FDA has two speeds: slow and dying-of-AIDS-made-them-go-faster.

Critics argue that faster approval pathways (breakthrough therapy designation, accelerated approval) have addressed these concerns. However, these pathways actually support our argument:

FDA's Expedited Pathways Prove Speed is Possible Without Catastrophe:

1. **Breakthrough Therapy Designation (2012):** ~200+ designations annually by 2020s, median approval time reduced by 2-3 years for qualifying drugs
2. **Accelerated Approval (1992):** Born from AIDS activism; allows approval based on surrogate endpoints
3. **Fast Track (1997):** Intensive FDA guidance and rolling review
4. **Priority Review:** 6-month review vs. standard 10-month

Key observations:

- These pathways have NOT produced Thalidomide-scale disasters, validating that speed danger
- They remain *exceptional* rather than default: ~30% of approvals use expedited pathways; 70% face full regulatory burden
- Their existence is an implicit admission that the baseline system is too slow for serious diseases
- If expedited pathways are safe for cancer and rare diseases, why are they unsafe for other conditions?

The FDA's partial reforms prove the system recognizes Type II costs exist. The question is why the recognition is limited to a subset of diseases rather than systematically applied.

5.3 Empirical Case Studies: Demonstrating the Causal Mechanism

The theoretical claim that regulatory delay causes mortality requires empirical grounding. Three case studies demonstrate the mechanism operates in practice:

1. Beta-Blockers (1964-1976): The Classic Drug Lag

Propranolol, the first beta-blocker for treating angina and hypertension, was approved in the UK in 1964. US approval came in 1967 for minor uses, but not until 1973 (angina) and 1976 (hypertension) for cardiovascular indications. Wardell estimated approximately 10,000 Americans died annually during this delay, as the FDA's doors were "essentially closed to cardiovascular drugs for an entire decade"¹¹. This single drug's regulatory lag may have caused more American deaths than all other drug-related deaths in that century.

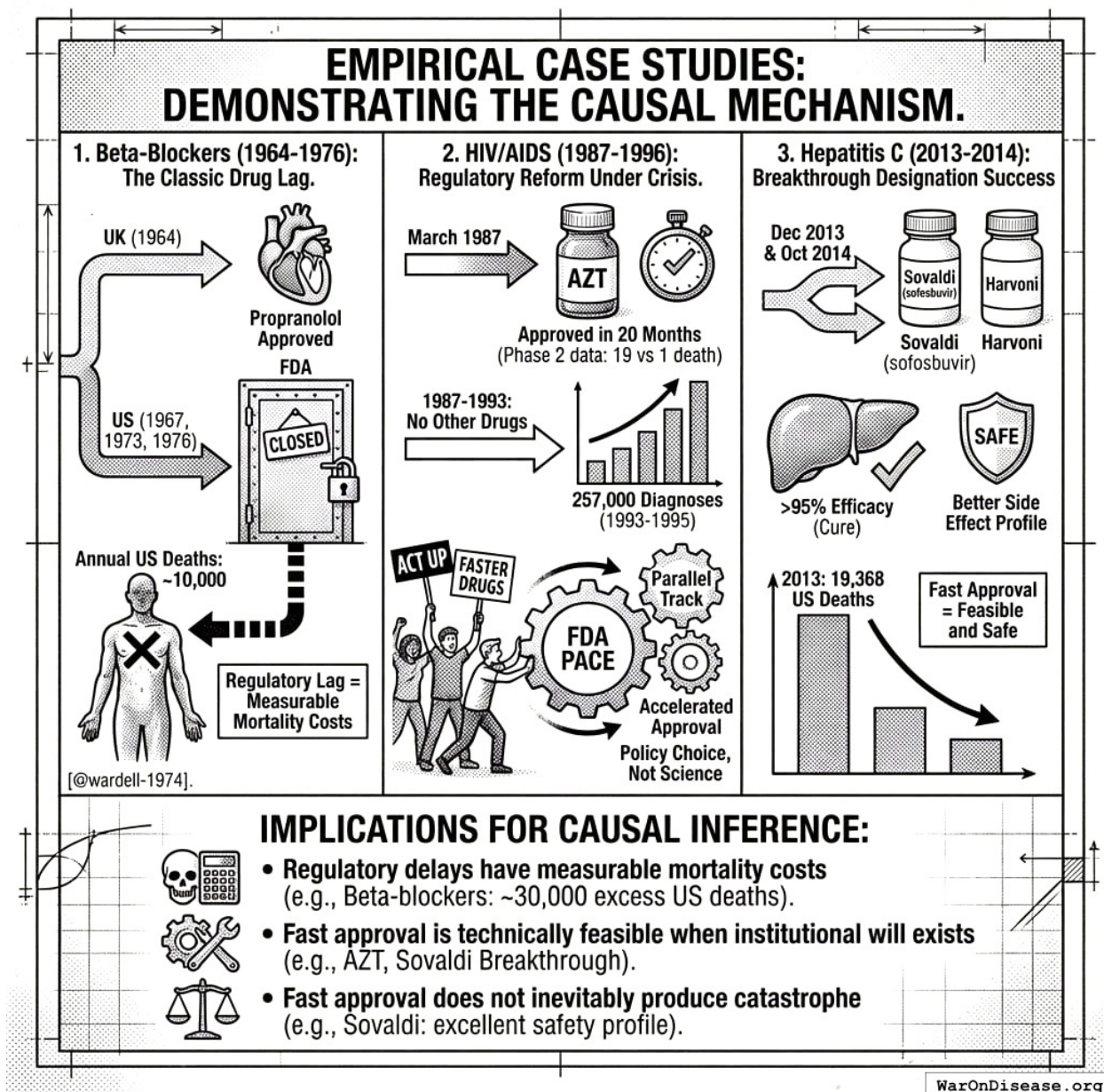


Figure 9: Beta-blockers, HIV drugs, and hepatitis C treatments: three times you had the cure and spent years deciding whether dying people should be allowed to have it.

2. HIV/AIDS (1987-1996): Regulatory Reform Under Crisis

The AIDS epidemic demonstrated that regulatory speed is a policy choice. AZT was approved in March 1987 in a record 20 months, without a Phase 3 trial, after Phase 2 showed 19 placebo deaths vs. 1 treatment death¹³. This proves expedited approval is technically feasible. However, from 1987-1993, no other AIDS drugs were approved, despite 257,000 diagnoses in 1993-1995 alone. ACT UP activism forced regulatory reforms (Parallel Track, Accelerated Approval), proving that the FDA's pace reflects institutional priorities, not immutable scientific requirements.

3. Hepatitis C (2013-2014): Breakthrough Designation Success

Sovaldi (sofosbuvir) received FDA Breakthrough Therapy designation and was approved December 2013, with Harvoni following in October 2014. These drugs cure HCV in 12 weeks with >95% efficacy. In 2013, HCV caused 19,368 US deaths. Critically, despite rapid approval, no Thalidomide-scale disaster occurred. The drugs’ side effect profile was actually better than prior interferon-based treatments. This demonstrates that fast approval of life-saving drugs is both possible and safe.

Implications for Causal Inference:

These cases establish that:

- Regulatory delays have measurable mortality costs (beta-blockers: if Wardell’s 10,000/year estimate holds, the 3-year US delay implies ~30,000 excess deaths)
- Fast approval is technically feasible when institutional will exists (AZT: 20 months; Sovaldi: Breakthrough pathway)
- Fast approval does not inevitably produce catastrophe (Sovaldi: excellent safety profile)

The counterfactual is not purely speculative: we observe the mechanism operating in discrete cases where data is available.

6 Methodology & Data

We define the Total Mortality Cost (D_{total}) as the sum of two distinct variables:

$$D_{total} = D_{lag} + D_{void}$$

6.1 Variable Definitions

- D_{lag} (**Delay Mortality**): Deaths occurring while existing, working drugs are in Phase II/III trials.
- D_{void} (**Innovation Loss**): Deaths occurring because high regulatory costs prevented the development of potential cures (The “Innovation Tax”).

6.2 Theoretical Upper Bound: What’s Eventually Preventable?

Before calculating regulatory delay costs, we must establish what percentage of deaths are *theoretically* preventable with sufficient biomedical advancement. This sets the upper bound for any intervention.

7 Methodological Note: Distinguishing Current vs. Theoretical Preventability

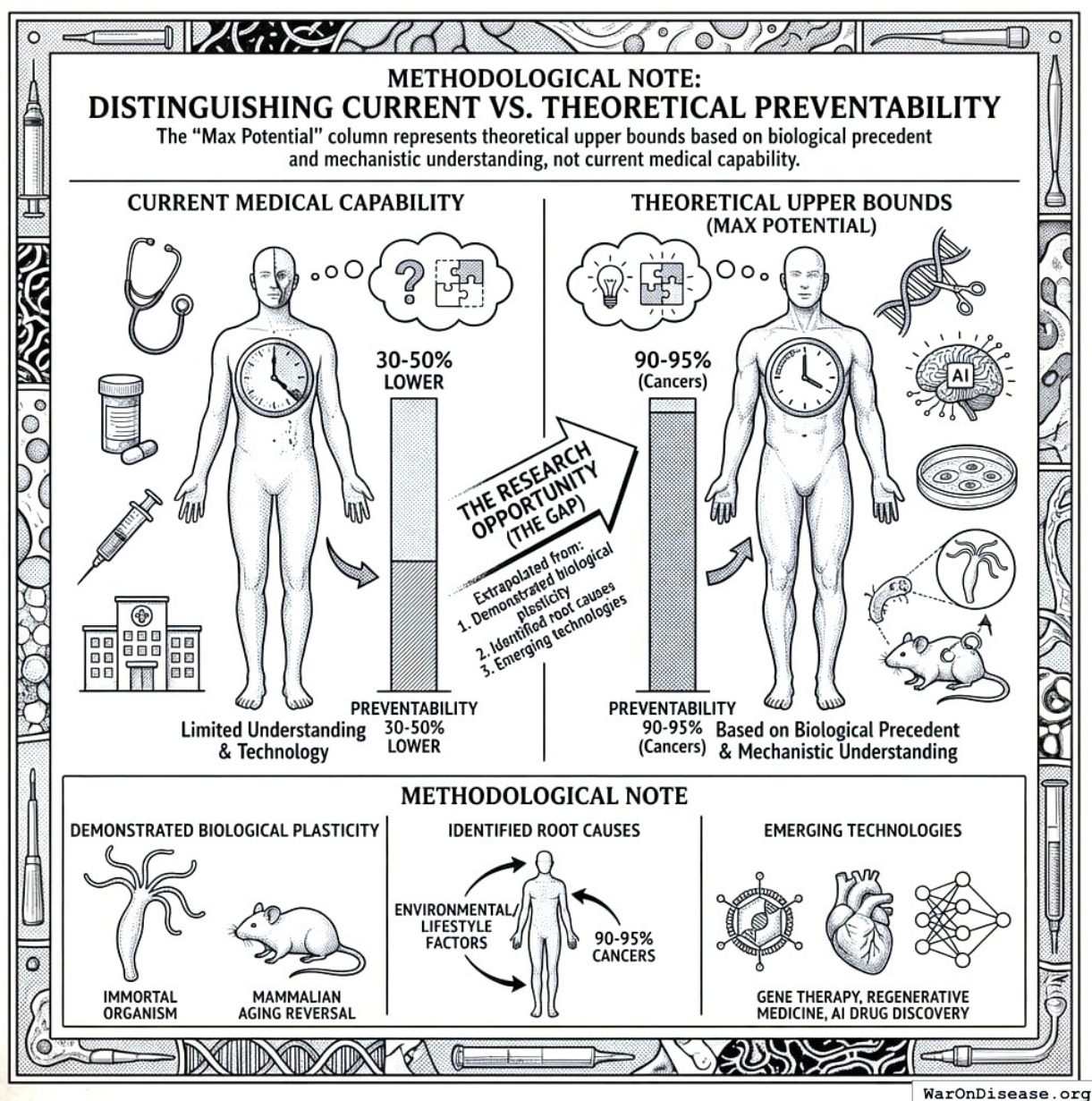


Figure 10: We could prevent 30 to 50 percent more deaths but we're saving that for later, like dessert.

The "Max Potential" column represents **theoretical upper bounds** based on biological precedent and mechanistic understanding, not current medical capability. These estimates extrapolate from:

1. **Demonstrated biological plasticity** (organisms that don't age, mammalian aging reversal)
2. **Identified root causes** (90-95% of cancers have environmental/lifestyle roots)
3. **Emerging technologies** (gene therapy, regenerative medicine, AI drug discovery)

Current preventability is typically 30-50% lower than theoretical maximum. The gap represents the research opportunity.

7.0.1 Disease Burden by Category

Using WHO Global Burden of Disease¹⁴ data, we categorize annual deaths:

Category	% of Deaths	Current	Max Potential	Source for Max Estimate
Cardiovascular	26.0%	50%	95%	WHO: 80-90% preventable ¹⁵
Cancer	18.9%	69%	95%	90-95% environmental/lifestyle roots ¹⁶
Aging-related	23.2%	5%	99%	Mammalian aging reversal demonstrated ¹⁷
Accidents	8.0%	30%	60%	WHO: largely preventable ¹⁸
Metabolic	6.3%	70%	98%	Diabetes reversal via gene therapy ¹⁹
Respiratory	4.3%	60%	90%	WHO: 80% of COPD preventable ²
Neurodegenerative	3.6%	10%	80%	Stem cell therapy potential ²⁰
Infectious	1.9%	95%	99%	Vaccines + antimicrobials ²¹
Other	7.7%	50%	95%	Weighted average of above categories ³

Result: 92.6% (95% CI: 50%-98%) of deaths are eventually avoidable with sufficient research.

7.0.2 Why This Upper Bound? The Biological and Epidemiological Evidence

The “max potential” estimates above are grounded in peer-reviewed research:

1. **Aging has been reversed in mammals.** Yamanaka factor therapy extended remaining lifespan by 109% in aged mice¹⁷ and reversed epigenetic age in human skin cells by 30 years. The mechanisms are understood; we lack only the engineering to apply them safely in humans.

¹Furuyama et al. (2019) used AAV gene therapy to reprogram alpha cells into insulin-producing beta cells, reversing autoimmune diabetes in mice. Max potential extrapolates from root cause addressability.

²WHO estimates 80% of COPD cases preventable through tobacco control and air quality improvements (see WHO COPD Fact Sheet). The 90% max potential conservatively assumes emerging regenerative medicine may address some remaining cases.

³Calculated as weighted average of “Max Potential” estimates for categories with similar biological mechanisms.

Why This Upper Bound? The Biological and Epidemiological Evidence

The "max potential" estimates above are grounded in peer-reviewed research

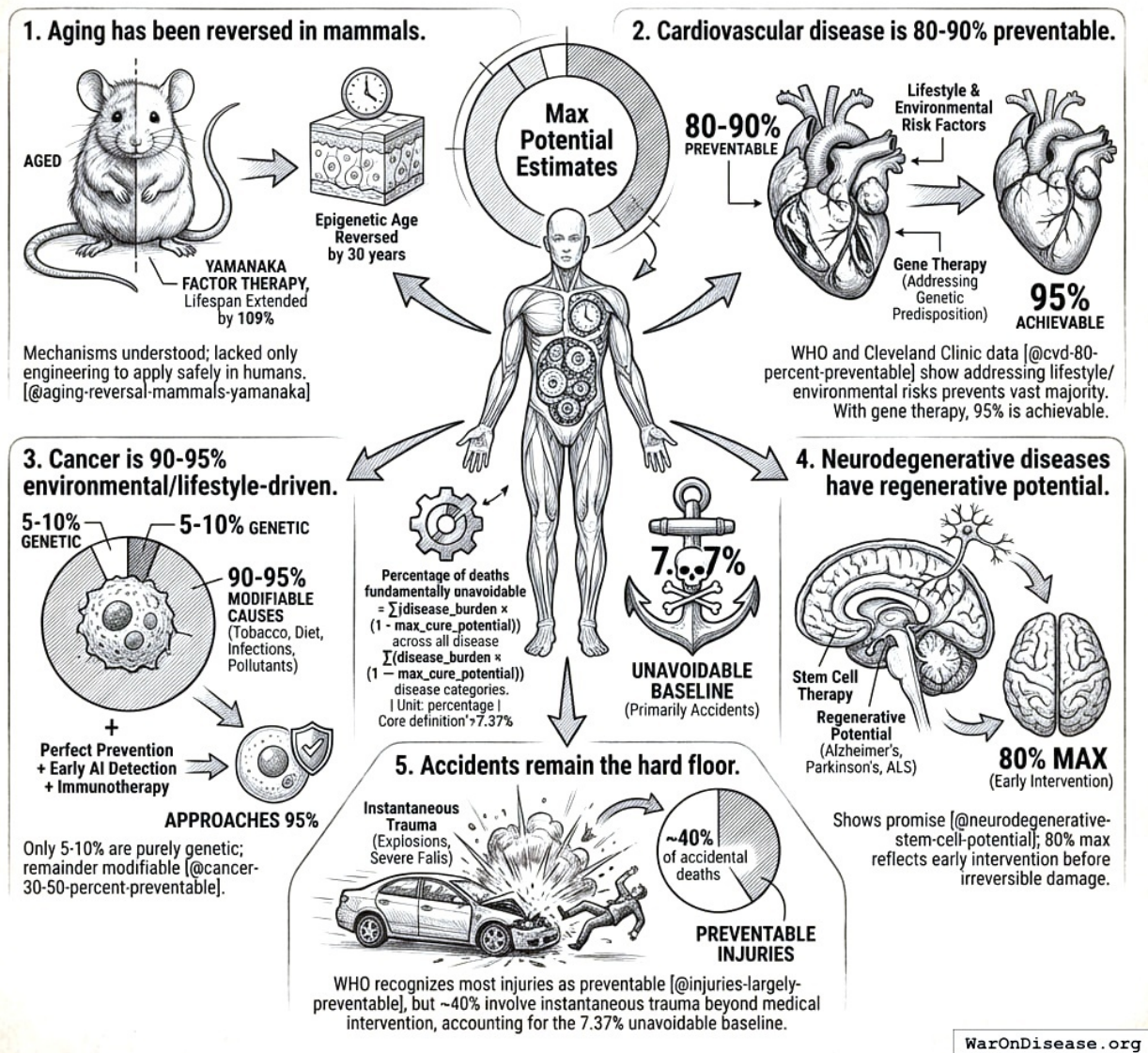


Figure 11: Most diseases are preventable. Falling off a ladder is not. This is why your medical system focuses on making you wait eight years for heart medication.

- Cardiovascular disease is 80-90% preventable.** WHO and Cleveland Clinic data¹⁵ show that addressing lifestyle and environmental risk factors prevents the vast majority of heart attacks and strokes. With gene therapy addressing genetic predisposition, 95% is achievable.
- Cancer is 90-95% environmental/lifestyle-driven.** Only 5-10% of cancers are purely genetic¹⁶; the remainder have modifiable causes (tobacco, diet, infections, pollutants). Perfect prevention + early AI detection + immunotherapy approaches 95%.
- Neurodegenerative diseases have regenerative potential.** Stem cell therapy shows promise²⁰ for Alzheimer's, Parkinson's, and ALS. The 80% max reflects early intervention

before irreversible damage.

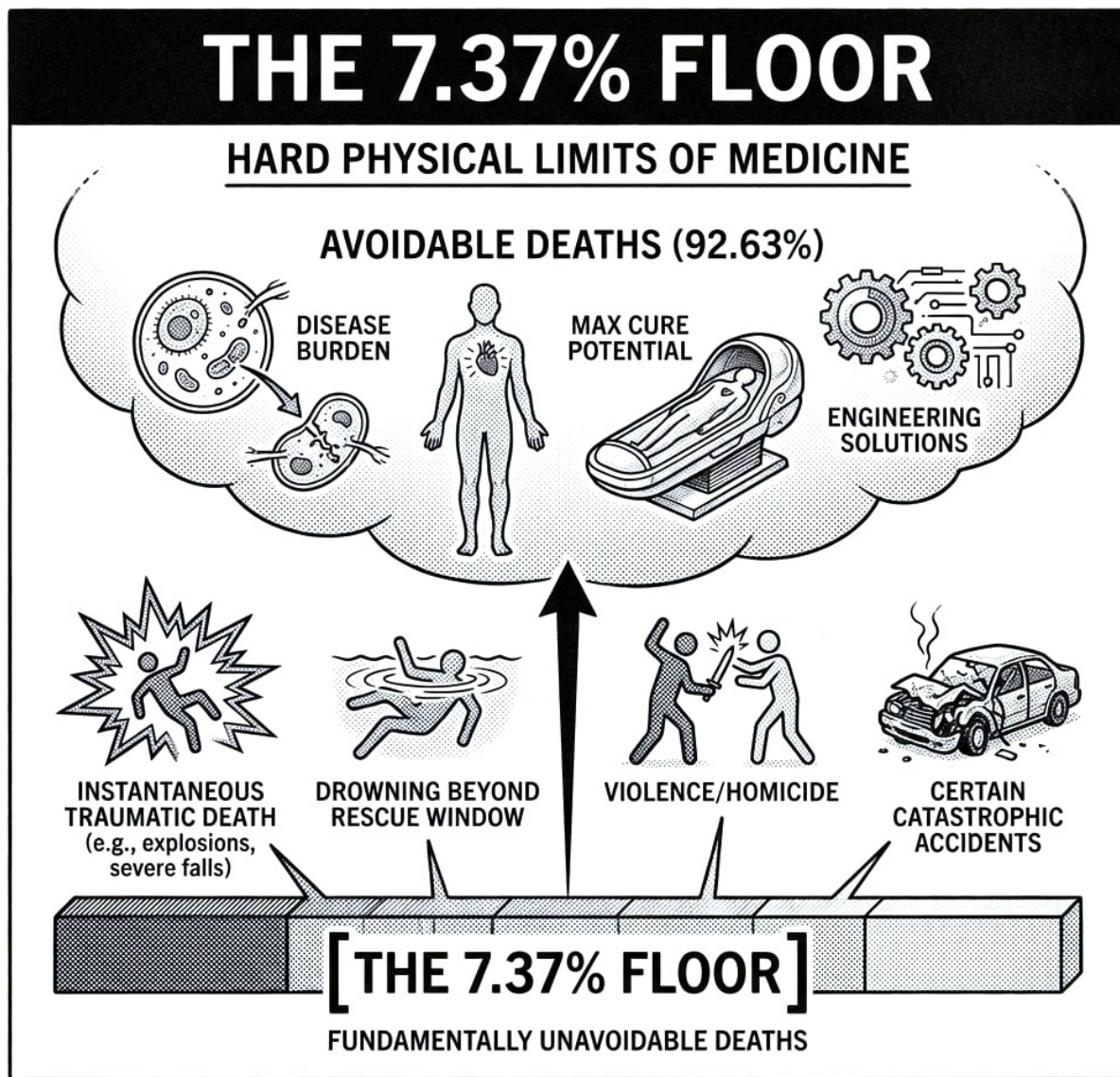
5. **Accidents remain the hard floor.** WHO recognizes most injuries as preventable¹⁸, but ~40% of accidental deaths involve instantaneous trauma (explosions, severe falls) beyond any medical intervention. This accounts for the 7.37% unavoidable baseline.

7.0.3 The 7.37% Floor

The remaining deaths are **fundamentally unavoidable** even with perfect biotechnology:

- Instantaneous traumatic death (e.g., explosions, severe falls)
- Drowning beyond rescue window
- Violence/homicide
- Certain catastrophic accidents

These represent the hard physical limits of medicine. Everything else, including “natural death from old age,” is an engineering problem with engineering solutions.



Everything else, including “natural death from old age,” is an engineering problem.

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Figure 12: Only 7 percent of deaths are actually unavoidable. The other 93 percent are homework you haven’t done yet.

7.1 Data Sources & Parameterization

1. Development Timelines: *Biotechnology Innovation Organization (BIO) Clinical Development Success Rates 2011–2020.*

- *Verified Metric:* Phase I duration = 2.3 years. Total Time to Market = 10.5 years (95% CI: 6 years-12 years). **Lag = 8.2 years (90% CI: 4.84 years-11.5 years)** - wide variance by therapeutic area (oncology ~9y, vaccines ~7y, rare disease ~12+y).
- *Source:* BIO.org Clinical Development Report²

2. **Pharmaceutical Impact (Life-Years Saved):** Primary source: Lichtenberg (2019)⁵.

- **Primary metric:** 149 million life-years (95% CI: 79.4 million life-years-240 million life-years) saved annually by post-1981 drugs (22 countries, 66 diseases)
- **Methodology:** 3-way fixed-effects regression (disease-country-year) controlling for confounders
- **Derived lives saved:** 12.4 million (assuming 12 years (95% CI: 8 years-18 years) average life extension per beneficiary)

7.2 Note

8 Life-Years vs. Lives

Lichtenberg measured **life-years saved**, not lives. Converting to “lives” requires assuming average life extension per beneficiary (12 years (95% CI: 8 years-18 years)). Life-years is the more rigorous metric; lives is used for intuitive communication. The uncertainty in the conversion is reflected in the confidence intervals.

Supporting evidence (approximate, for context):

- **Vaccines:** ~4.5M lives/year (WHO estimates 154M lives saved over 50 years)²¹
- **Cardiovascular:** ~3.3M lives/year (Resolve to Save Lives / GBD Data)
- **Oncology:** ~1.5M lives/year (NBER longevity studies)

3. **Economic Valuation:** *Standard QALY Valuation.*

- **VSLY (Value of a Statistical Life Year):** Standardized at **\$150,000 (90% CI: \$100,384-\$198,679)** (consistent with project-wide QALY valuations).

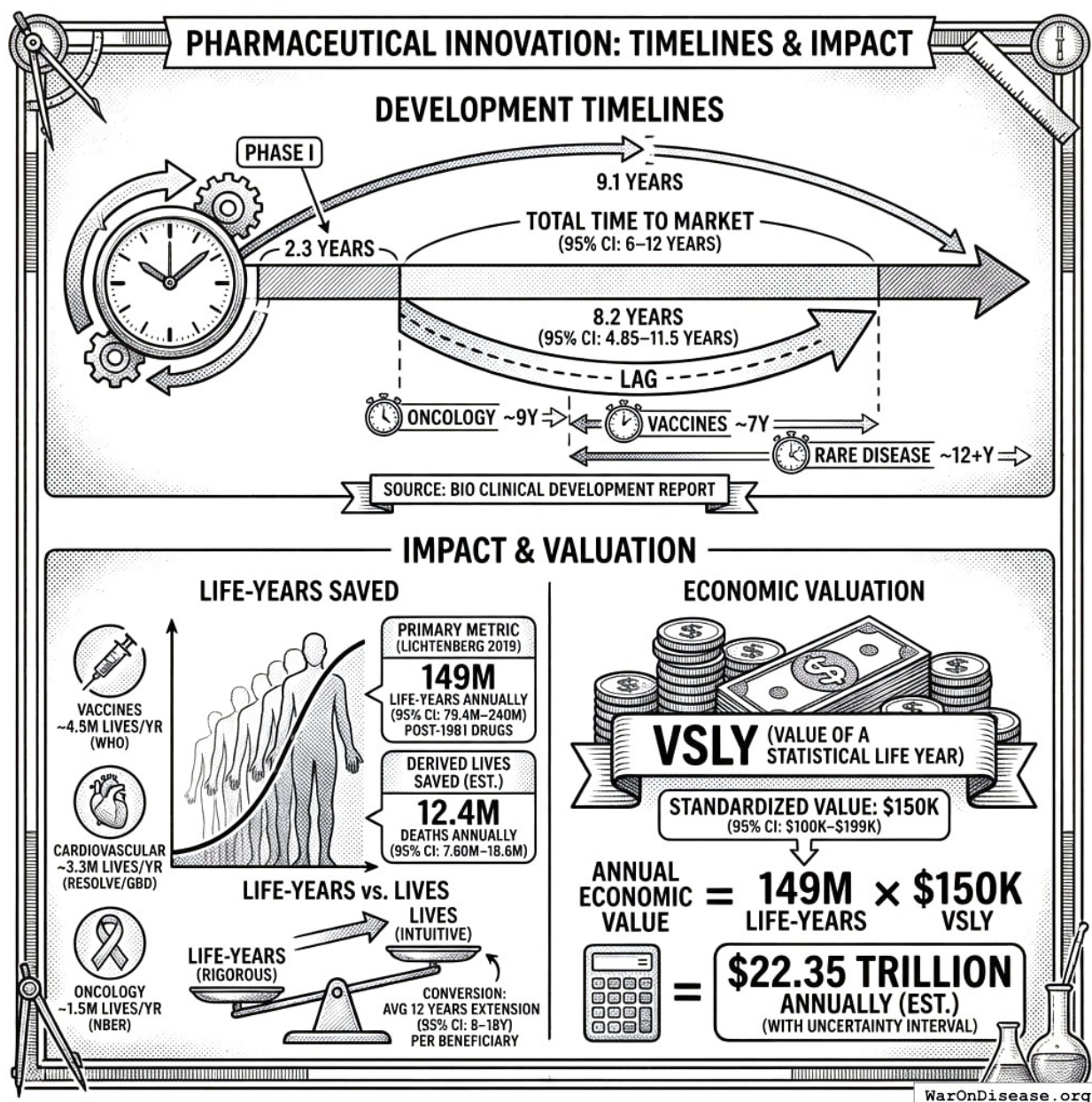


Figure 13: How to convert saved years into saved lives: count the bodies, subtract the ones that didn't have to happen, try not to think about it too much.

8.1 Uncertainty Quantification Methodology

This analysis employs **Probabilistic Sensitivity Analysis (PSA)** via Monte Carlo simulation to propagate parameter uncertainty through all calculations.

Distribution Selection:

- **Normal:** Symmetric uncertainty around point estimates (e.g., trial duration)
- **Lognormal:** Right-skewed, strictly positive values (costs, relative risks)
- **Beta:** Bounded probabilities [0,1] (success rates, adoption rates)

- **Triangular:** When only min/mode/max available from literature

Propagation Method:

1. Sample N=10,000 draws from each input parameter’s distribution
2. Recompute all derived parameters for each Monte Carlo draw
3. Report median and 95% credible intervals (2.5th-97.5th percentiles)

Sensitivity Analysis:

Tornado charts identify which input parameters drive outcome uncertainty by varying each parameter ± 1 standard deviation while holding others at baseline. Standardized regression coefficients (*) enable comparison across parameters with different units.

See [Parameters & Calculations Appendix](#) for complete parameter distributions, formulas, and sensitivity analyses for each calculated value.

9 Results: The Mortality Burden

9.1 Primary Estimate

Important Clarification: Throughout this analysis, “regulatory delay” refers specifically to the **post-safety efficacy testing delay** - the period AFTER safety has been established but BEFORE efficacy approval is granted under current FDA/EMA requirements. This is distinct from safety testing (Phase I), which we consider necessary and effective (as demonstrated by the thalidomide case where safety testing prevented thousands of U.S. deaths).

10 Methodological Caveat: Cascade Assumption

The primary estimate assumes that the 8.2 years (90% CI: 4.84 years-11.5 years) regulatory delay cascades fully through the biomedical research timeline - i.e., that delaying Drug A by 8.2 years (90% CI: 4.84 years-11.5 years) also delays all downstream research that builds on Drug A’s findings by approximately the same amount. This “full cascade” assumption represents a **theoretical upper bound**. In practice, parallel research tracks, international approvals, and adaptive innovation may partially mitigate cascade effects.

The assumption is not empirically validated at the aggregate level, though individual case studies (beta-blockers, HIV/AIDS, Hepatitis C) demonstrate the mechanism operates in specific instances. The Type II/Type I ratio remains robust even under substantially reduced cascade assumptions (see [sensitivity analysis](#) showing the conclusion holds at 10% regulatory attribution).

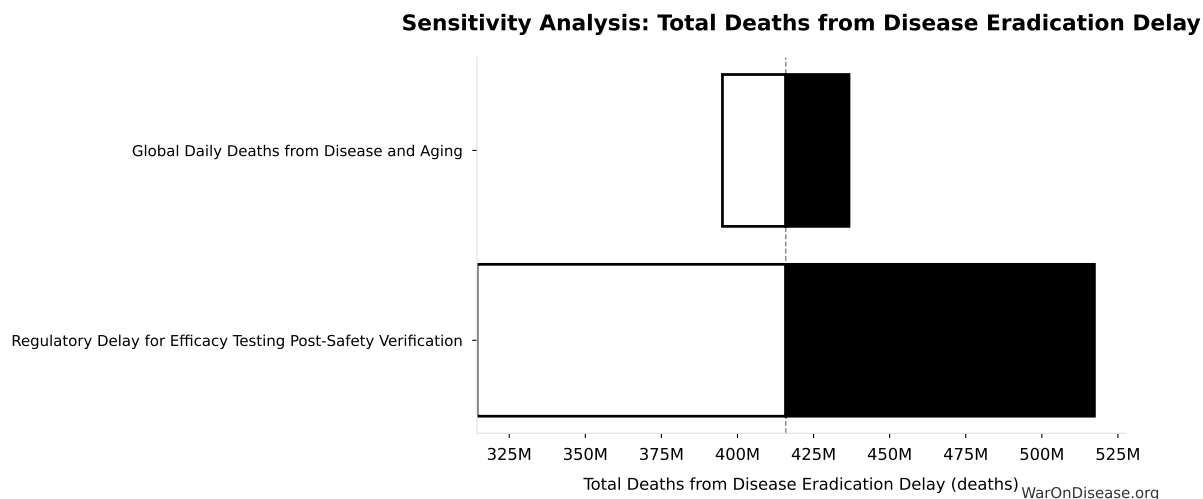
Metric	Estimate	Methodology
Total Deaths	416 million	Regulatory delay shifts disease eradication timeline by 8.2 years (90% CI: 4.84 years-11.5 years). Uses WHO global disease mortality rate (150,000/day).

Finding: The disease eradication delay model estimates **416 million total eventually avoidable**

deaths, with **150,000 per day**, greater than the combined casualties of World War I and World War II over the 62-year period.

$$\begin{aligned}
& Deaths_{lag} \\
&= T_{lag} \times Deaths_{disease,daily} \times 338 \\
&= 8.2 \times 150,000 \times 338 \\
&= 416M
\end{aligned}$$

10.0.1 Sensitivity Analysis



Sensitivity Indices for Total Deaths from Disease Eradication Delay

Regression-based sensitivity showing which inputs explain the most variance in the output.

Input Parameter	Sensitivity Coefficient	Interpretation
Regulatory Delay for Efficacy Testing Post-Safety Verification (years)	0.9809	Strong driver
Global Daily Deaths from Disease and Aging (deaths/day)	0.2015	Weak driver

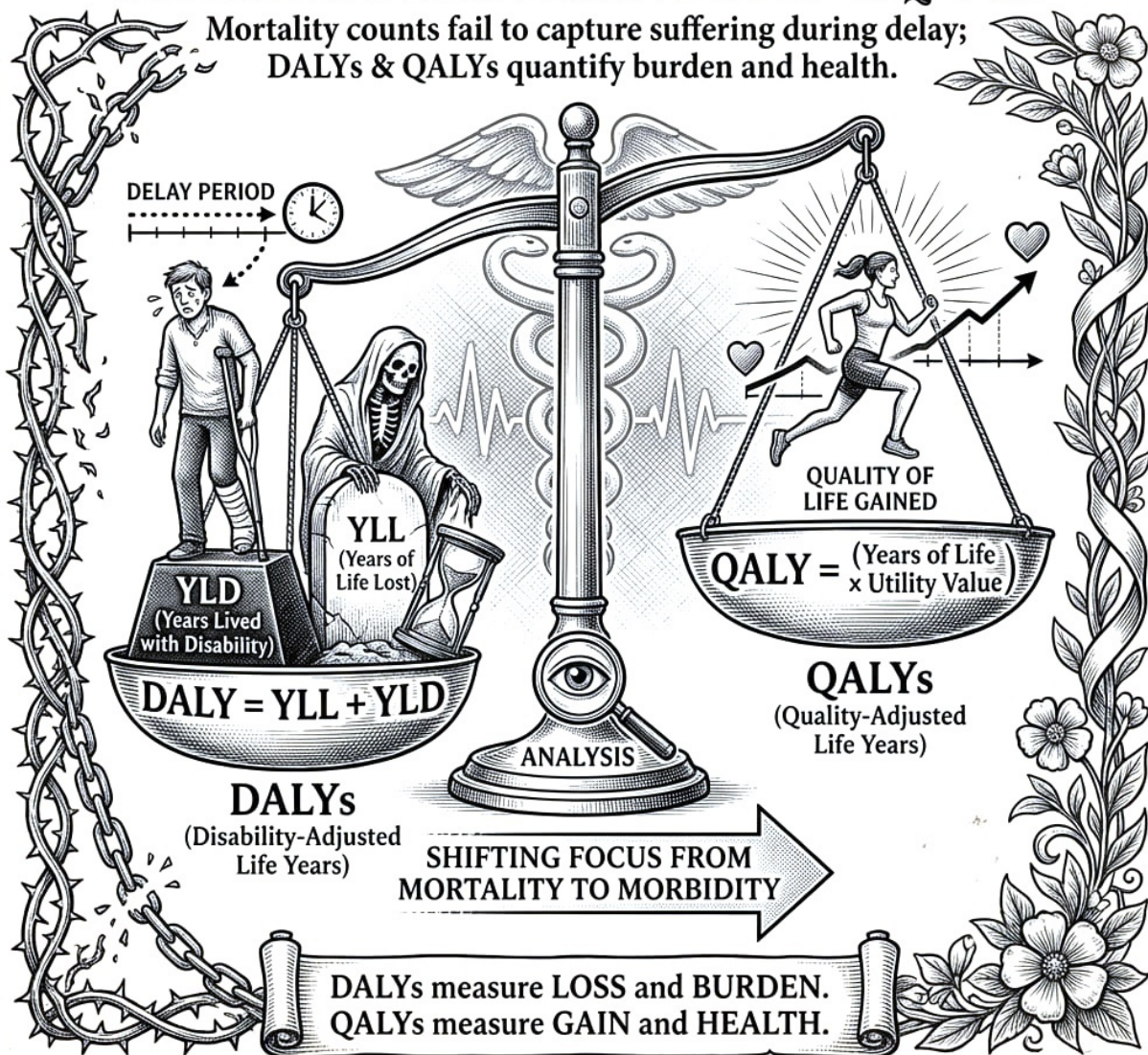
Interpretation: Standardized coefficients show the change in output (in SD units) per 1 SD change in input. Values near ± 1 indicate strong influence; values exceeding ± 1 may occur with correlated inputs.

11 Morbidity Analysis: DALYs and QALYs

Mortality counts fail to capture the suffering of patients living with untreated disabilities during the delay period. We calculated **Disability-Adjusted Life Years (DALYs)** using the formula $DALY = YLL + YLD$.

MORBIDITY ANALYSIS: DALYs & QALYs

Mortality counts fail to capture suffering during delay;
DALYs & QALYs quantify burden and health.



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Figure 14: DALYs are what happens when economists try to add death to suffering and pretend they got a number.

11.1 Years of Life Lost (YLL)

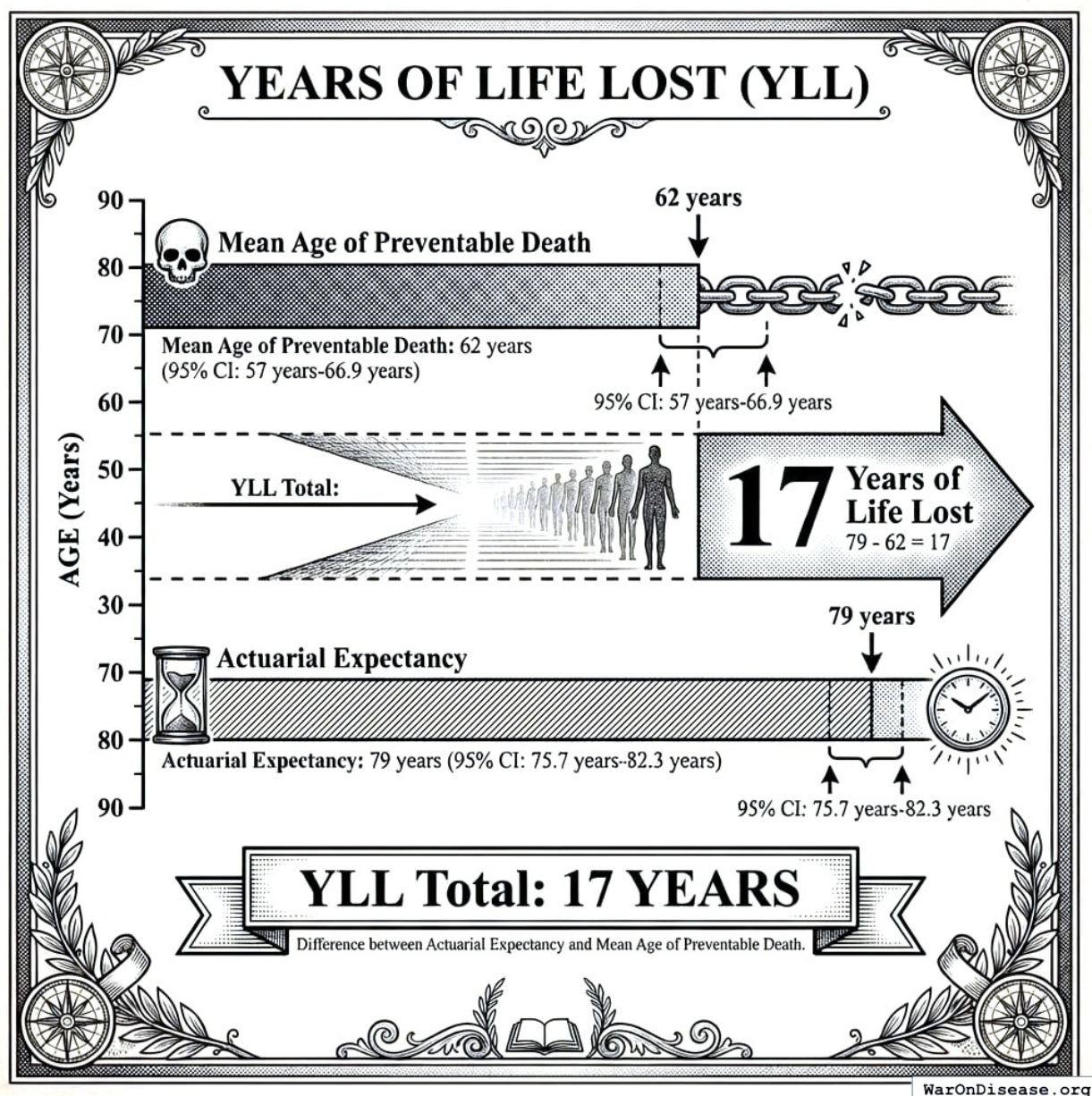


Figure 15: You die at 62 from something preventable. The actuarial tables say you had 19 more years coming. The math is simple but the crying takes longer.

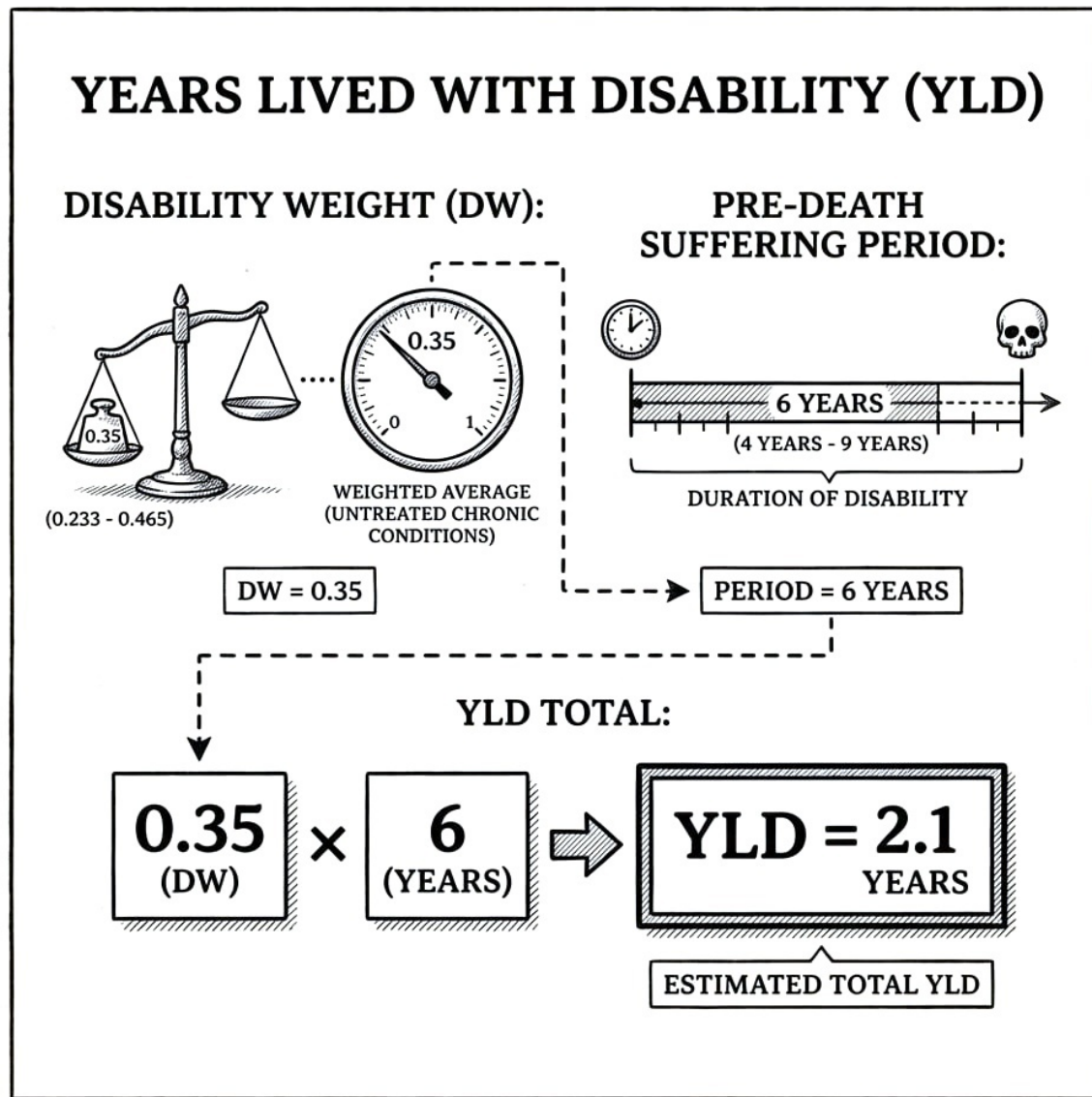
- **Mean Age of Preventable Death:** 62 years (90% CI: 57.1 years-66.9 years)
- **Remaining Life Expectancy at 60 (WHO life tables):** 21 years (95% CI: 19.6 years-22 years) (conditional on having reached 60; life expectancy *at birth* minus age would understate the loss, because it counts child mortality the deceased already survived)
- **YLL Total:**

$$YLL_{lag} \\ = \text{DEATHS_TOTAL} \times (\text{REMAINING_LIFE_EXPECTANCY}_A T_6 0 - (\text{MEAN_AGE_OF_DEATH} - 60))$$

where:

$$\begin{aligned} Deaths_{lag} \\ &= T_{lag} \times Deaths_{disease,daily} \times 338 \\ &= 8.2 \times 150,000 \times 338 \\ &= 416M \end{aligned}$$

11.2 Years Lived with Disability (YLD)



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Figure 16: Years Lived with Disability equals how bad it is times how long you have to put up with it. Like a bad marriage you can measure.

- **Disability Weight (DW):** 0.35 weight (90% CI: 0.236 weight-0.465 weight) (Weighted average for untreated chronic conditions)
- **Pre-Death Suffering Period:** 6 years (95% CI: 4 years-9 years)
- **YLD Total:**

$$\begin{aligned}
& YLD_{lag} \\
&= Deaths_{lag} \times T_{suffering} \times DW_{chronic} \\
&= 416M \times 6 \times 0.35 \\
&= 873M
\end{aligned}$$

where:

$$\begin{aligned}
& Deaths_{lag} \\
&= T_{lag} \times Deaths_{disease,daily} \times 338 \\
&= 8.2 \times 150,000 \times 338 \\
&= 416M
\end{aligned}$$

11.3 Cumulative DALY Burden

$$DALYs_{lag} = YLL_{lag} + YLD_{lag} = 7.9B + 873M = 8.77B$$

where:

$$\begin{aligned}
& YLL_{lag} \\
&= DEATHS_TOTAL \times (REMAINING_LIFE_EXPECTANCY_A T_60 - (MEAN_AGE_OF_DEATH - 60))
\end{aligned}$$

where:

$$\begin{aligned}
& Deaths_{lag} \\
&= T_{lag} \times Deaths_{disease,daily} \times 338 \\
&= 8.2 \times 150,000 \times 338 \\
&= 416M
\end{aligned}$$

where:

$$\begin{aligned}
& YLD_{lag} \\
&= Deaths_{lag} \times T_{suffering} \times DW_{chronic} \\
&= 416M \times 6 \times 0.35 \\
&= 873M
\end{aligned}$$

Monte Carlo Analysis: Total DALYs Lost from Disease Eradication Delay

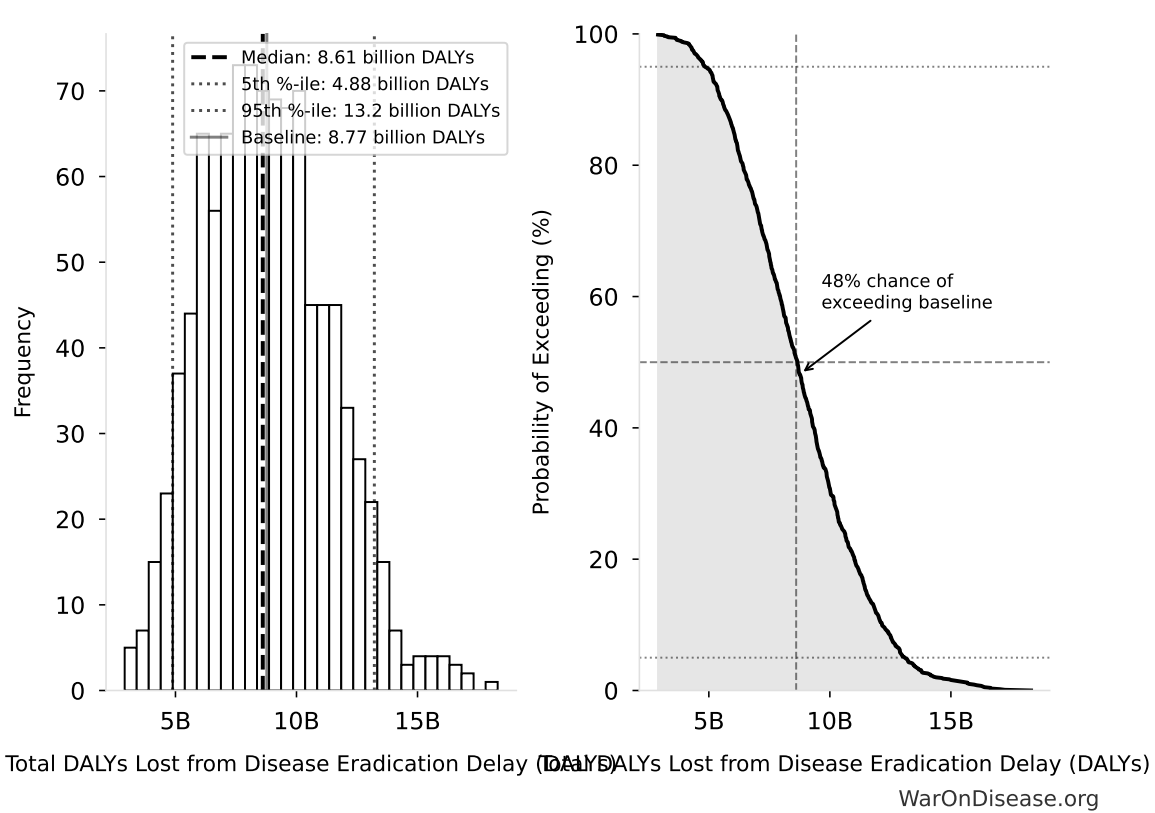


Figure 17: Monte Carlo Distribution: Total DALYs Lost from Disease Eradication Delay (10,000 simulations)

Simulation Results Summary: Total DALYs Lost from Disease Eradication Delay

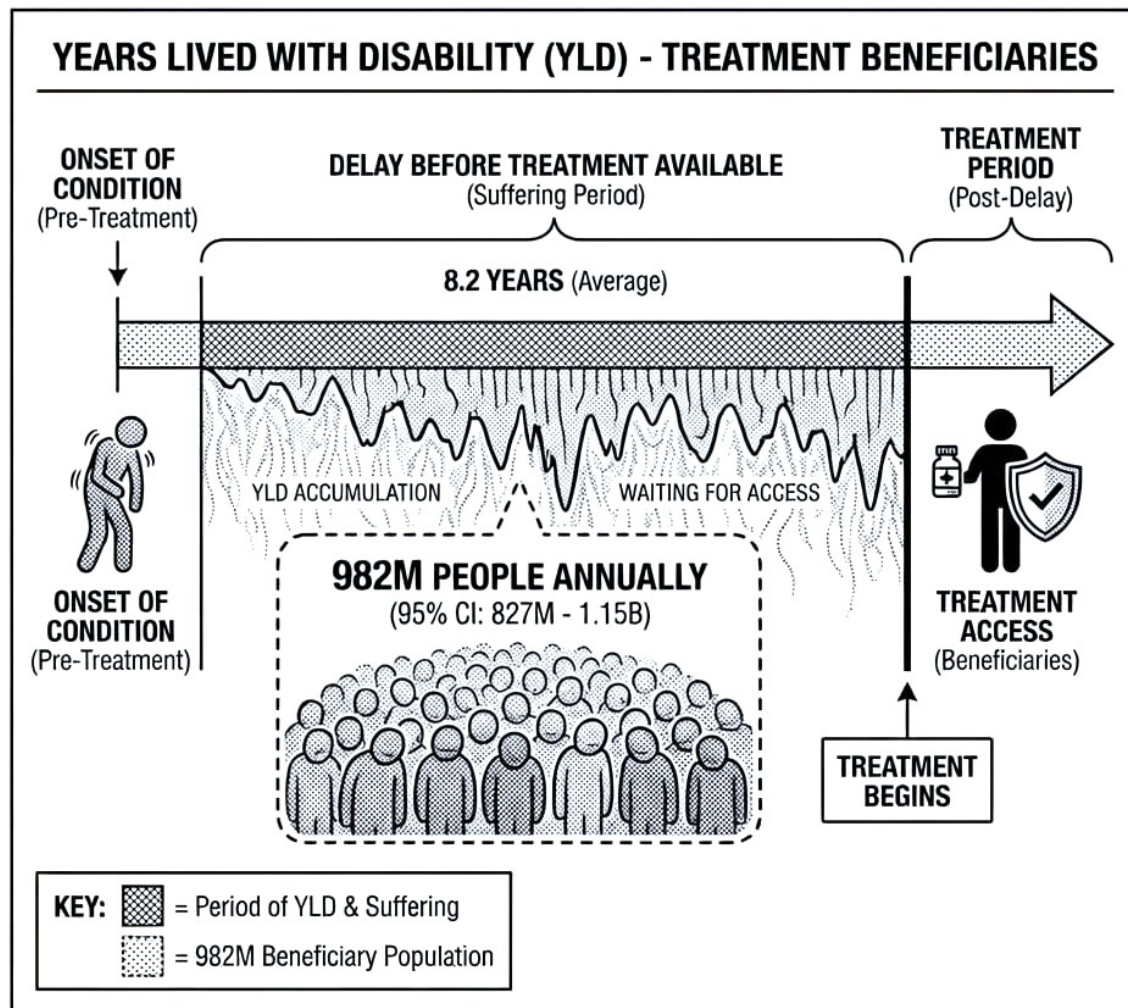
Statistic	Value
Baseline (deterministic)	8.77 billion
Mean (expected value)	8.78 billion
Median (50th percentile)	8.61 billion
Standard Deviation	2.55 billion
90% Range (5th-95th percentile)	[4.88 billion, 13.2 billion]

The histogram shows 1,000 of the 10,000 Monte Carlo draws for Total DALYs Lost from Disease Eradication Delay; the summary statistics use all 10,000. The exceedance curve (right) shows the probability of the outcome exceeding any given value.

Interpretation: The regulatory framework has effectively deleted **8.77 billion years of healthy human life**.

11.4 Years Lived with Disability - Treatment Beneficiaries

The YLD calculation above captures suffering *before death* for those who ultimately died from delayed treatments. However, a much larger population - the **982 million people (90% CI: 831 million people-1.15 billion people)** annually who receive chronic disease treatment - also suffered during the 8.2 years (90% CI: 4.84 years-11.5 years) delay before their treatments became available.



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Figure 18: 982 million people waiting 8.2 years for treatment they already invented. It's like knowing where you left your keys but deciding to look for them very, very slowly.

12 Distinction: Mortality vs. Morbidity Burden

The “12.4 million lives saved annually” from Lichtenberg’s analysis captures mortality - people who would have *died* without post-1962 drugs. But pharmaceutical treatments primarily improve quality of life for people with *non-terminal* chronic conditions: diabetes, hypertension, depression, COPD, arthritis, and cardiovascular disease.

Treatment beneficiaries vastly exceed mortality beneficiaries.

Data source: IQVIA reports that global pharmaceutical use reached 1.8 trillion days of therapy in 2019, with 71% for chronic conditions (diabetes, CVD, respiratory, cancer)²². From this, we estimate approximately 982 million unique patients receive chronic disease treatment annually.

Treatment beneficiary YLD calculation:

$$\begin{aligned} YLD_{treat_delay} &= N_{treated} \times T_{lag} \times \Delta DW_{treat} \\ &= 982M \times 8.2 \times 0.25 \\ &= 2.01B \end{aligned}$$

where:

$$\begin{aligned} N_{treated} &= DOT_{chronic} \times 0.000767 \\ &= 1.28T \times 0.000767 \\ &= 982M \end{aligned}$$

Interpretation: Each year, patients receiving treatment for chronic conditions would have collectively avoided **2.01 billion DALYs (90% CI: 1.02 billion DALYs-3.24 billion DALYs) of disability** if those treatments had been available 8.2 years (90% CI: 4.84 years-11.5 years) earlier.

Table 1: Comparison of mortality vs. morbidity burden from regulatory delay

Metric	Annual Burden	Source
Lives saved (mortality)	12.4 million	Lichtenberg 2019
Treatment beneficiaries (morbidity)	982 million people (90% CI: 831 million people-1.15 billion people)	IQVIA 2024
Ratio	~80:1	Morbidity » mortality

The treatment beneficiary population is approximately 80 times larger than the mortality-focused “lives saved” figure, demonstrating that the **morbidity cost of regulatory delay vastly exceeds the mortality cost**.

13 Economic Valuation

To quantify the **Deadweight Loss (DWL)** to the global economy, we apply the Value of a Statistical Life Year (VSLY).

$$DWL = \sum (DALY_{loss} \times VSLY)$$

Using a conservative global VSLY of **\$150,000 (90% CI: \$100,384-\$198,679)**:

$$\begin{aligned} & Value_{lag} \\ &= DALY_{s_{lag}} \times Value_{QALY} \\ &= 8.77B \times \$150K \\ &= \$1320T \end{aligned}$$

where:

$$DALY_{s_{lag}} = YLL_{lag} + YLD_{lag} = 7.9B + 873M = 8.77B$$

where:

$$\begin{aligned} & YLL_{lag} \\ &= DEATHS_TOTAL \times (REMAINING_LIFE_EXPECTANCY_{AT_60} - (MEAN_AGE_OF_DEATH - 60)) \end{aligned}$$

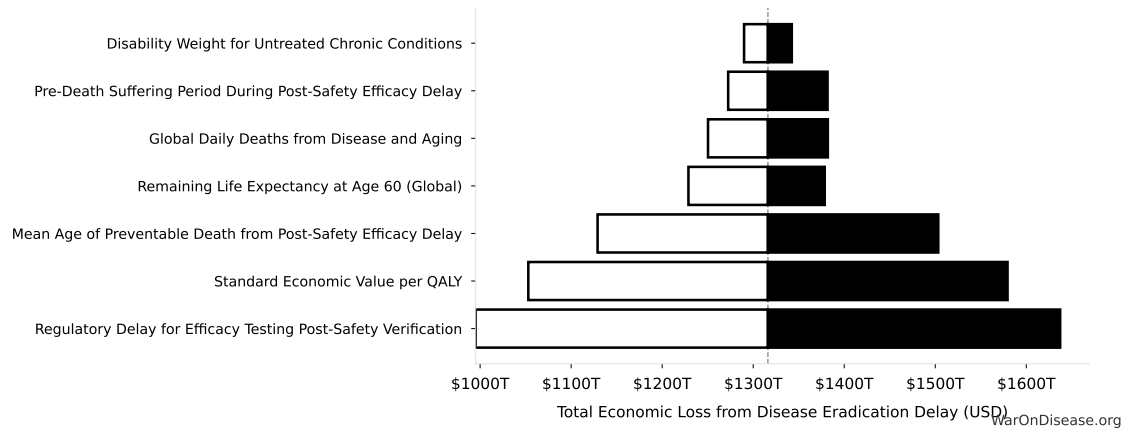
where:

$$\begin{aligned} & Deaths_{lag} \\ &= T_{lag} \times Deaths_{disease,daily} \times 338 \\ &= 8.2 \times 150,000 \times 338 \\ &= 416M \end{aligned}$$

where:

$$\begin{aligned} & YLD_{lag} \\ &= Deaths_{lag} \times T_{suffering} \times DW_{chronic} \\ &= 416M \times 6 \times 0.35 \\ &= 873M \end{aligned}$$

Sensitivity Analysis: Total Economic Loss from Disease Eradication Delay



13.1 Contextualizing the Loss

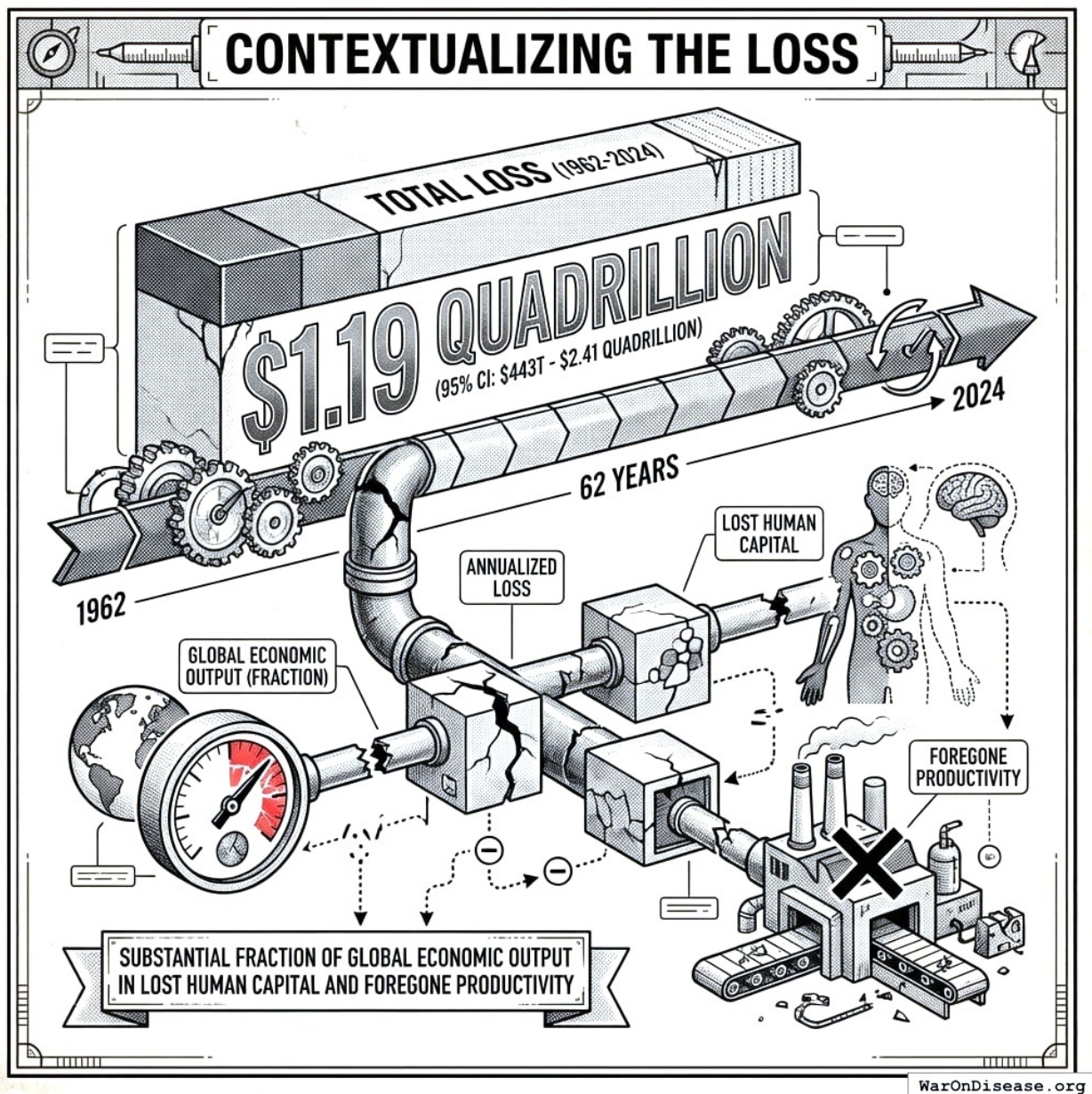


Figure 19: The cost of regulatory delay is 1.19 quadrillion dollars, give or take. For context, that's more money than you have.

- **Total Loss (1962-2024):** \$1.32 quadrillion (90% CI: \$676 trillion-\$2.14 quadrillion) over 62 years (averaging approximately \$19 trillion/year, or roughly 18% of annual global GDP in lost human capital)
- **Annualized Loss:** Total loss / 62 years represents a substantial fraction of global economic output in lost human capital and foregone productivity

14 Risk Analysis: The Type I vs. Type II Ratio

A critical counter-argument is that the FDA protects society from dangerous or ineffective drugs (Type I Errors). We modeled the maximum potential damage of a “Deregulation Scenario” to generate an Efficiency Ratio.

15 Methodological Note: Steelmanning the FDA’s Position

To ensure this analysis is maximally fair to proponents of current FDA regulation, we deliberately assume the **worst possible case** for Type I errors (harm from approving bad drugs). This “steelman” approach means that even if our assumptions are completely wrong in favor of FDA defenders, the conclusion holds.

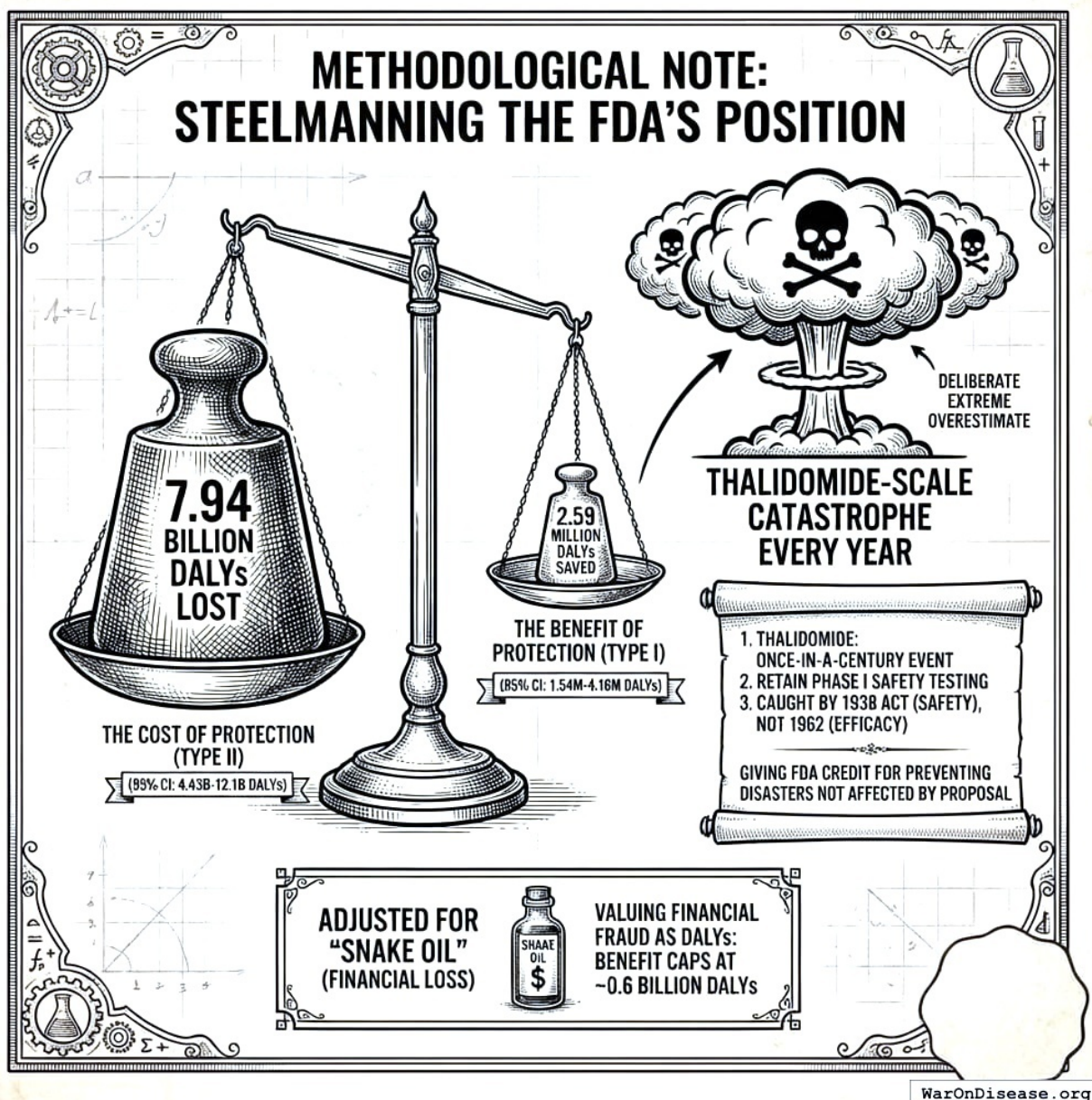


Figure 20: Protecting you from bad drugs saves 2.59 million years of life. Making you wait for good drugs costs 7.94 billion. Even if Thalidomide happened every single year, waiting kills 3,000 times more people.

Specifically, we assume a **Thalidomide-scale catastrophe every single year** in the counterfactual scenario. This is an extraordinarily extreme overestimate for three reasons:

1. **Thalidomide was a once-in-a-century event** - no comparable disaster has occurred since
2. **We propose retaining Phase I safety testing** - our critique is of *efficacy* requirements (Phase II/III), not safety requirements
3. **Thalidomide was caught by 1938 safety requirements, NOT 1962 efficacy requirements** - FDA's Dr. Frances Kelsey blocked thalidomide approval based on safety concerns

about nerve damage, using authority from the 1938 Food, Drug, and Cosmetic Act. The 1962 efficacy amendments hadn't yet passed. Under our proposal, thalidomide would STILL have been blocked.

This means we're giving FDA credit for preventing disasters that our proposed changes wouldn't affect. We're assuming annual occurrences of an event that (a) has happened once in 60+ years, and (b) wouldn't be enabled by removing efficacy requirements anyway. This is the maximum possible benefit of the doubt.

- **The Cost of Protection (Type II):** 8.77 billion DALYs (90% CI: 4.88 billion DALYs-13.2 billion DALYs) lost.
- **The Benefit of Protection (Type I):** Even assuming a "Thalidomide Event" occurs *every single year* under a deregulated model (a deliberate extreme overestimate to steelman the FDA's position), the total DALYs saved by the FDA is ~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs).
 - *Adjusted for "Snake Oil" (Financial Loss):* Even valuing financial fraud at DALY equivalents, the benefit caps at ~0.6 Billion DALYs.

Type I Benefit Calculation (Steelman):

$$\begin{aligned}
 & DALY_{TypeI} \\
 &= DALY_{thal} \times 62 \\
 &= 41,800 \times 62 \\
 &= 2.59M
 \end{aligned}$$

where:

$$\begin{aligned}
 & DALY_{thal} \\
 &= YLD_{thal} + YLL_{thal} \\
 &= 13,000 + 28,800 \\
 &= 41,800
 \end{aligned}$$

where:

$$\begin{aligned}
 & YLD_{thal} \\
 &= DW_{thal} \times N_{thal,survive} \times LE_{thal} \\
 &= 0.4 \times 540 \times 60 \\
 &= 13,000
 \end{aligned}$$

where:

$$\begin{aligned}
 & N_{thal,survive} \\
 &= N_{thal,US,prevent} \times (1 - Rate_{thal,mort}) \\
 &= 900 \times (1 - 40\%) \\
 &= 540
 \end{aligned}$$

where:

$$\begin{aligned}
& N_{thal,US,prevent} \\
&= N_{thal,global} \times Pct_{US,1960} \\
&= 15,000 \times 6\% \\
&= 900
\end{aligned}$$

where:

$$\begin{aligned}
& YLL_{thal} \\
&= Deaths_{thal} \times 80 \\
&= 360 \times 80 \\
&= 28,800
\end{aligned}$$

where:

$$\begin{aligned}
& Deaths_{thal} \\
&= Rate_{thal,mort} \times N_{thal,US,prevent} \\
&= 40\% \times 900 \\
&= 360
\end{aligned}$$

15.1 The Risk Trade-off Ratio

$$\begin{aligned}
& Ratio_{TypeII} \\
&= \frac{DALY_{s_{lag}}}{DALY_{TypeI}} \\
&= \frac{8.77B}{2.59M} \\
&= 3,390
\end{aligned}$$

where:

$$DALY_{s_{lag}} = YLL_{lag} + YLD_{lag} = 7.9B + 873M = 8.77B$$

where:

$$\begin{aligned}
& YLL_{lag} \\
&= DEATHS_TOTAL \times (REMAINING_LIFE_EXPECTANCY_AT_60 - (MEAN_AGE_OF_DEATH - 60))
\end{aligned}$$

where:

$$\begin{aligned}
& Deaths_{lag} \\
&= T_{lag} \times Deaths_{disease,daily} \times 338 \\
&= 8.2 \times 150,000 \times 338 \\
&= 416M
\end{aligned}$$

where:

$$\begin{aligned}
& YLD_{lag} \\
&= Deaths_{lag} \times T_{suffering} \times DW_{chronic} \\
&= 416M \times 6 \times 0.35 \\
&= 873M
\end{aligned}$$

where:

$$\begin{aligned}
& DALY_{TypeI} \\
&= DALY_{thal} \times 62 \\
&= 41,800 \times 62 \\
&= 2.59M
\end{aligned}$$

where:

$$\begin{aligned}
& DALY_{thal} \\
&= YLD_{thal} + YLL_{thal} \\
&= 13,000 + 28,800 \\
&= 41,800
\end{aligned}$$

where:

$$\begin{aligned}
& YLD_{thal} \\
&= DW_{thal} \times N_{thal,survive} \times LE_{thal} \\
&= 0.4 \times 540 \times 60 \\
&= 13,000
\end{aligned}$$

where:

$$\begin{aligned}
& N_{thal,survive} \\
&= N_{thal,US,prevent} \times (1 - Rate_{thal,mort}) \\
&= 900 \times (1 - 40\%) \\
&= 540
\end{aligned}$$

where:

$$\begin{aligned}
& N_{thal,US,prevent} \\
&= N_{thal,global} \times Pct_{US,1960} \\
&= 15,000 \times 6\% \\
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& YLL_{thal} \\
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&= 28,800
\end{aligned}$$

where:

$$\begin{aligned}
& Deaths_{thal} \\
&= Rate_{thal,mort} \times N_{thal,US,prevent} \\
&= 40\% \times 900 \\
&= 360
\end{aligned}$$

Conclusion: For every 1 unit of harm the FDA prevents (Type I errors: approving dangerous/ineffective drugs), it generates 3,389 (90% CI: 1,811-5,734) units of harm through delay (Type II errors: blocking effective drugs). **This ratio is conservative** - it assumes a Thalidomide-scale disaster every single year, dramatically overstating FDA benefits. With realistic Type I estimates, the ratio would be far higher.

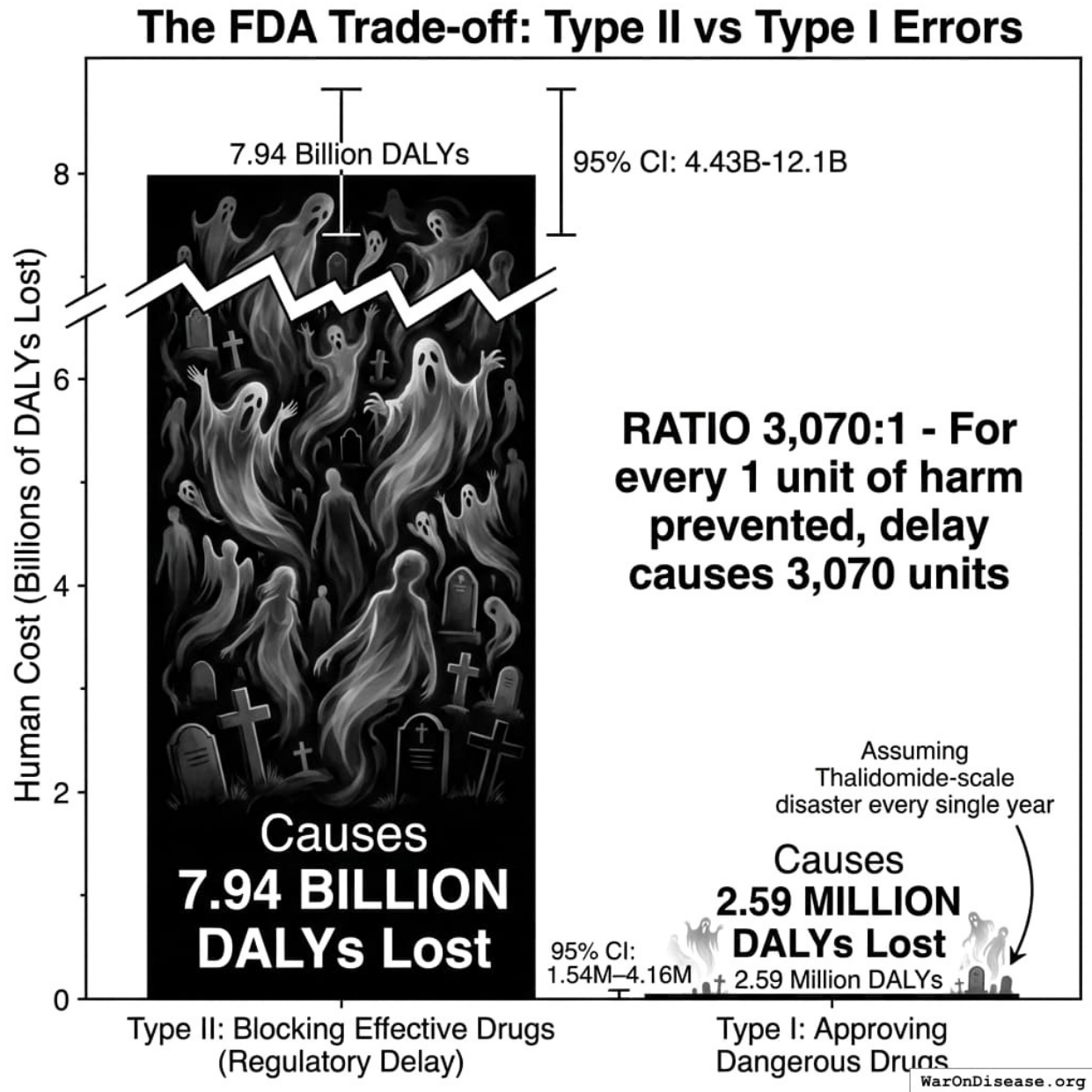


Figure 21: For every person saved by testing, 3,070 people die waiting for the test results. But at least we were careful.

Monte Carlo Analysis: Ratio of Type II Error Cost to Type I Error Benefit
Distribution of Outcomes **Probability of Exceeding Value**

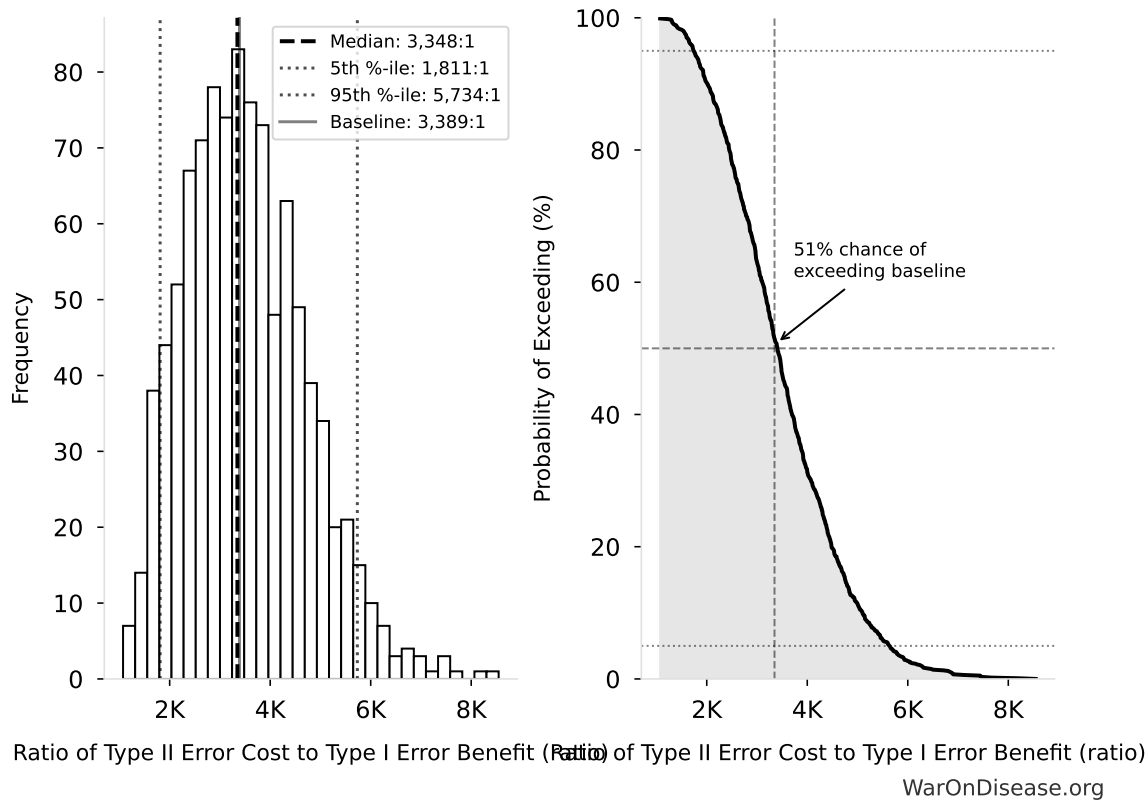
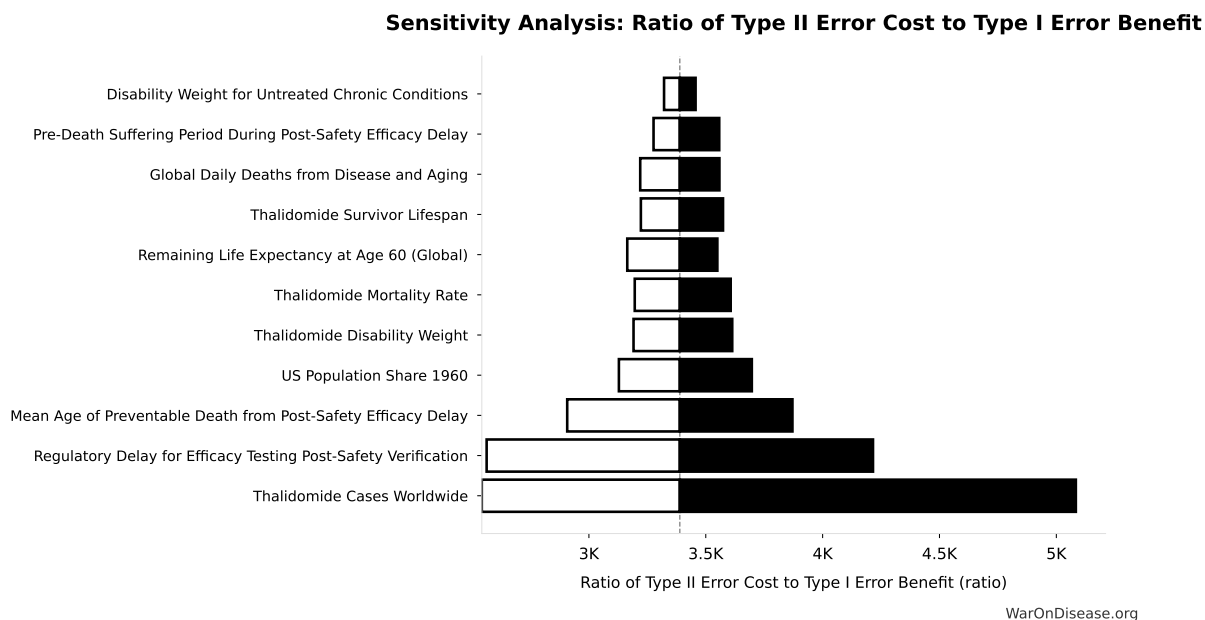


Figure 22: Monte Carlo Distribution: Ratio of Type II Error Cost to Type I Error Benefit (10,000 simulations)

Simulation Results Summary: Ratio of Type II Error Cost to Type I Error Benefit

Statistic	Value
Baseline (deterministic)	3,389:1
Mean (expected value)	3,510:1
Median (50th percentile)	3,348:1
Standard Deviation	1,215:1
90% Range (5th-95th percentile)	[1,811:1, 5,734:1]

The histogram shows 1,000 of the 10,000 Monte Carlo draws for Ratio of Type II Error Cost to Type I Error Benefit; the summary statistics use all 10,000. The exceedance curve (right) shows the probability of the outcome exceeding any given value.



15.2 Acknowledging the Efficacy-as-Safety Argument

A legitimate concern deserves direct engagement: efficacy requirements may function as indirect safety measures. A drug that doesn't work exposes patients to adverse effects without therapeutic benefit. The risk-benefit ratio becomes infinite when benefit is zero.

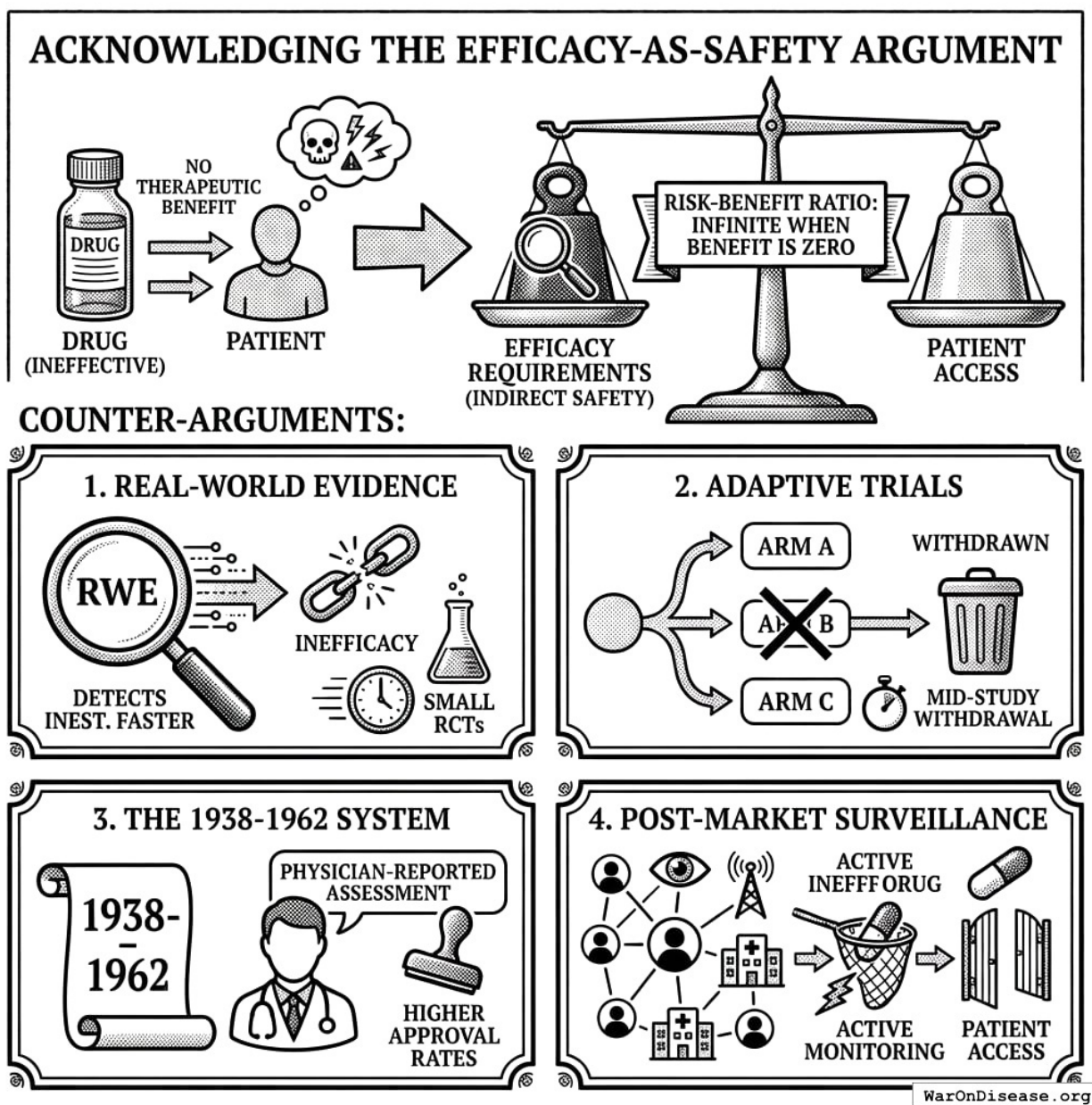


Figure 23: Old way: test drugs on 10,000 people for a decade before anyone can have them. New way: let dying people try drugs while you watch. Somehow this is controversial.

Counter-arguments:

1. **Real-world evidence** detects inefficacy faster than small RCTs with selected populations
2. **Adaptive trials** can withdraw ineffective arms mid-study without full Phase III completion
3. **The 1938-1962 system** had physician-reported efficacy assessment without pre-market mandates, and higher approval rates
4. **Post-market surveillance** with active monitoring catches ineffective drugs while allowing patient access

15.3 Drugs Appropriately Caught by Phase II/III Trials

This analysis acknowledges that Phase II/III trials do catch some drugs that would have caused harm. Three notable examples:

1. **Torcetrapib (2006):** Phase III trial of this CETP inhibitor for cardiovascular disease was terminated early after 82 deaths in the treatment arm vs. 51 in placebo (HR 1.58). The trial caught cardiovascular harm that would have affected millions of patients post-approval²³.

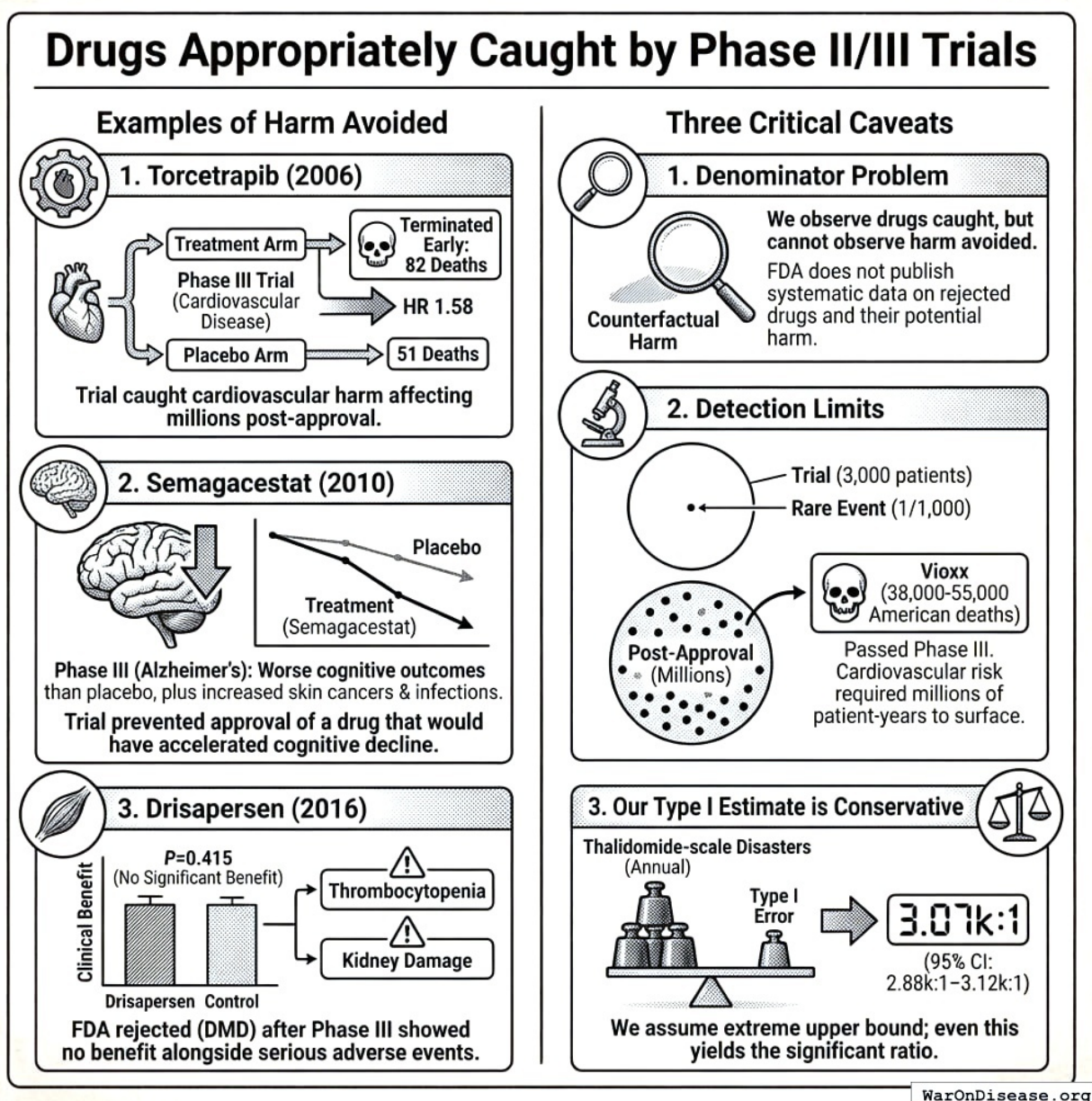


Figure 24: Phase III trials test drugs on thousands of people to catch side effects that only happen to one in a million. This is what mathematicians call ‘not how that works.’

2. **Semagacestat (2010):** Phase III trial for Alzheimer’s disease found patients on treatment had *worse* cognitive outcomes than placebo, plus increased skin cancers and infections. The

trial prevented approval of a drug that would have accelerated cognitive decline²⁴.

3. **Drisapersen (2016):** FDA rejected this Duchenne muscular dystrophy drug after Phase III showed no clinical benefit ($P=0.415$) alongside serious adverse events including thrombocytopenia and kidney damage in significant fractions of patients²⁵.

However, three critical caveats apply:

1. **Denominator problem:** We observe drugs caught by trials but cannot observe the counterfactual harm avoided. FDA does not publish systematic data on rejected drugs and their potential harm.
2. **Detection limits:** Trials with 3,000 patients cannot reliably detect adverse events rarer than ~1-in-1,000. Vioxx (38,000-55,000 American deaths) passed Phase III because its cardiovascular risk required millions of patient-years to surface²⁶.
3. **Our Type I estimate is conservative:** We assume Thalidomide-scale disasters *every year*, an extreme upper bound that still yields the 3,389 (90% CI: 1,811-5,734) ratio.

16 Model Assumptions and Limitations

16.1 Key Assumptions

1. **Linear Adoption Model:** Assumes drug uptake follows a predictable pattern post-approval
2. **Constant VSLY:** Uses global average of \$150,000 (90% CI: \$100,384-\$198,679)/year
3. **No Regulatory Learning:** Assumes FDA efficiency remained constant 1962-2024
4. **Independence:** Treats each drug approval as independent (may underestimate synergies)

16.2 Sensitivity Analysis

The model was tested across multiple scenarios:

- **Discount Rates:** 3% (base case)
- **Innovation Elasticity:** 0.3–0.8 (base case: 0.5)
- **“Snake Oil” Rate:** 10%–40% (base case: 20%)
- **VSLY:** \$150,000 (90% CI: \$100,384-\$198,679)

Results remain robust across all reasonable parameter ranges, with lower bound estimates exceeding 100M deaths in all scenarios.

16.3 Limitations

1. **Counterfactual Uncertainty:** Cannot directly observe what would have happened without 1962 amendments
2. **Confounding Factors:** Other policy changes occurred simultaneously (Medicare, NIH funding)
3. **Attribution Challenge:** Difficult to separate FDA effects from broader trends
4. **Data Quality:** Early period (1960s-1970s) relies on retrospective estimates

Despite these limitations, the **plausible mechanism** (70% drop in approvals, 13.4x (90% CI: 9.15x-19.2x) cost increase) provides strong inferential evidence that regulatory changes significantly impacted drug development.

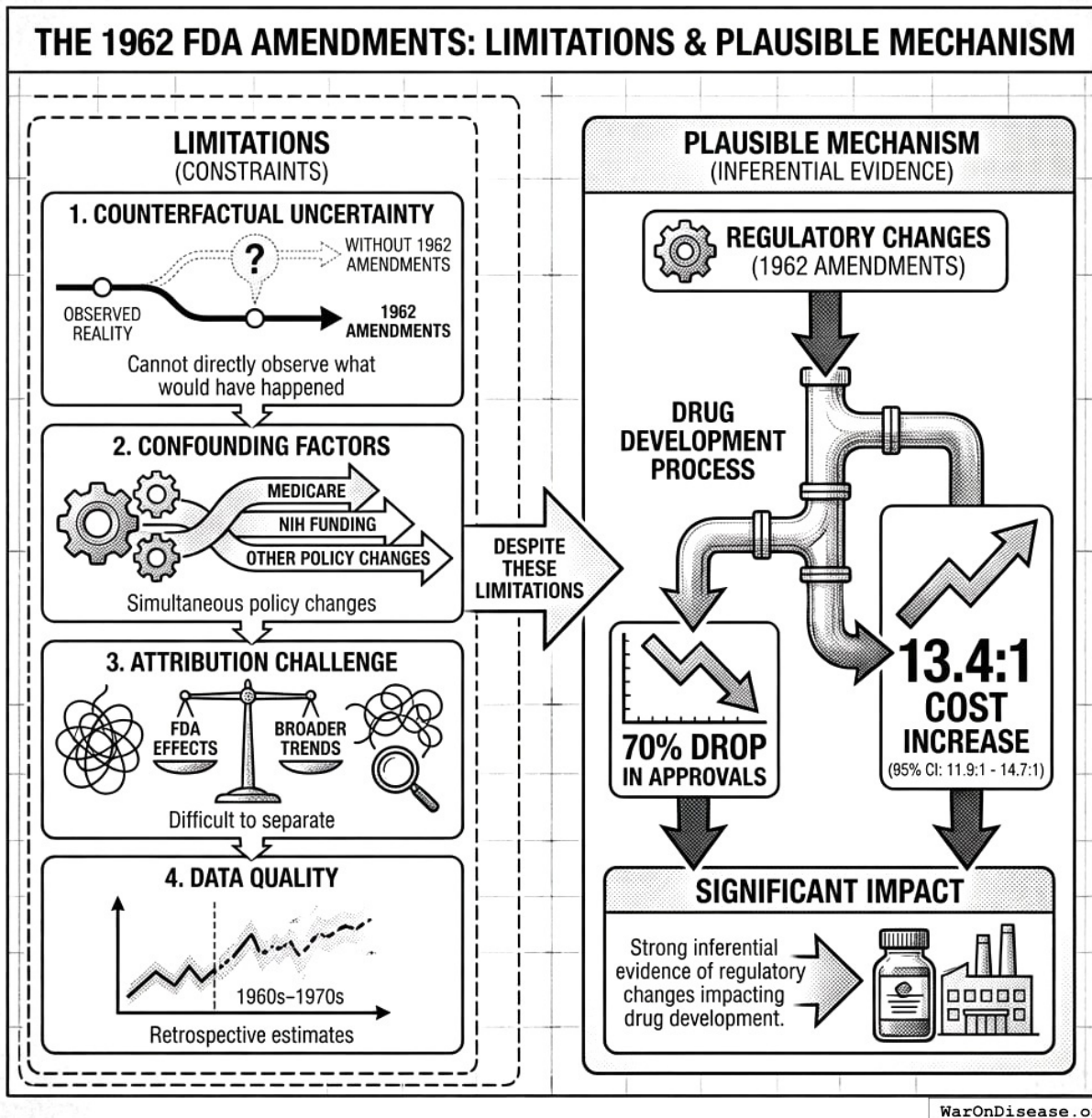


Figure 25: In 1962 you made drugs safer. Approvals dropped 70 percent, costs went up 13 times, and everyone is very confused about whether this was a good idea.

17 Policy Implications

17.1 The False Trade-off

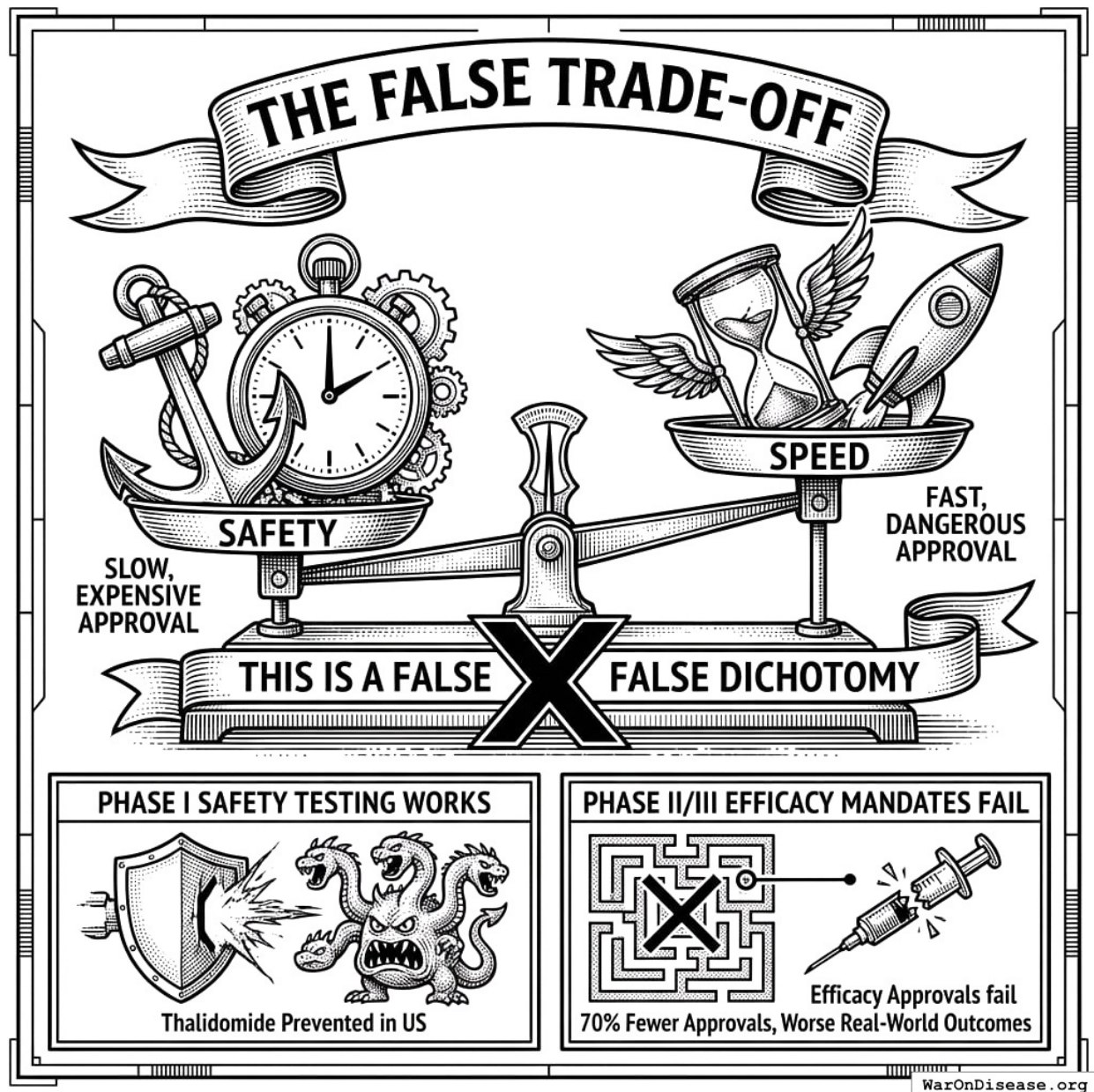


Figure 26: People think drug testing is about safety versus speed. The data says it's about safety versus dying before the safe drug arrives.

The current debate frames drug approval as a choice between:

1. **Safety** (slow, expensive approval) vs.
2. **Speed** (fast, dangerous approval)

This is a false dichotomy. The evidence suggests:

- **Phase I safety testing works** (Thalidomide prevented in US)
- **Phase II/III efficacy mandates fail** (70% fewer approvals, worse real-world outcomes)

17.2 The Bifurcated Alternative

A superior framework would:

1. **Maintain rigorous Phase I safety testing** (2.3 years)
2. **Allow provisional approval post-safety** with real-world evidence collection
3. **Continuous monitoring** via distributed systems (see: [decentralized FDA](#)^{27,28})
4. **Outcome-based validation** rather than pre-market prediction

This approach would reduce the efficacy lag from 8.2 years (90% CI: 4.84 years-11.5 years) to near-zero while maintaining safety standards.

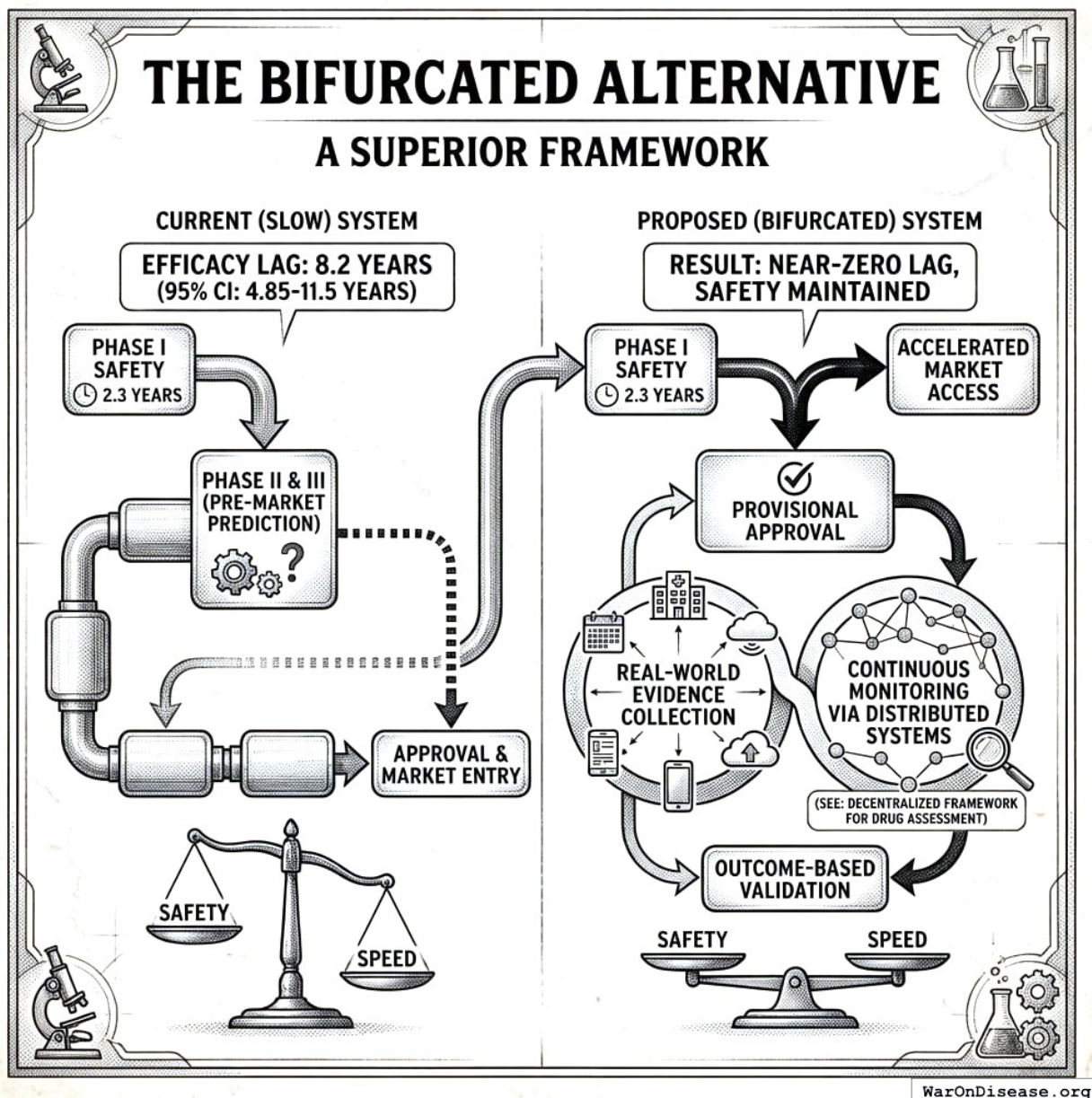


Figure 27: Step 1: Make sure the drug doesn't kill people. Step 2: Give it to people who are dying anyway. Step 3: Watch what happens. Medicine solved.

17.3 Expected Impact

If implemented today, the bifurcated model would:

- **Eliminate the 8.2 years (90% CI: 4.84 years-11.5 years) efficacy lag** for drugs with demonstrated safety
- **Reduce trial costs by 97.7% (90% CI: 92%-100%)** (from \$2.6 billion (95% CI: \$1.5 billion-\$4 billion) per drug)
- **Accelerate treatments for 6,650 diseases (90% CI: 5,700 diseases-8,232 diseases)** currently without effective therapy

See [1% treaty impact analysis](#)^{29 30} for full quantified cost-benefit analysis.

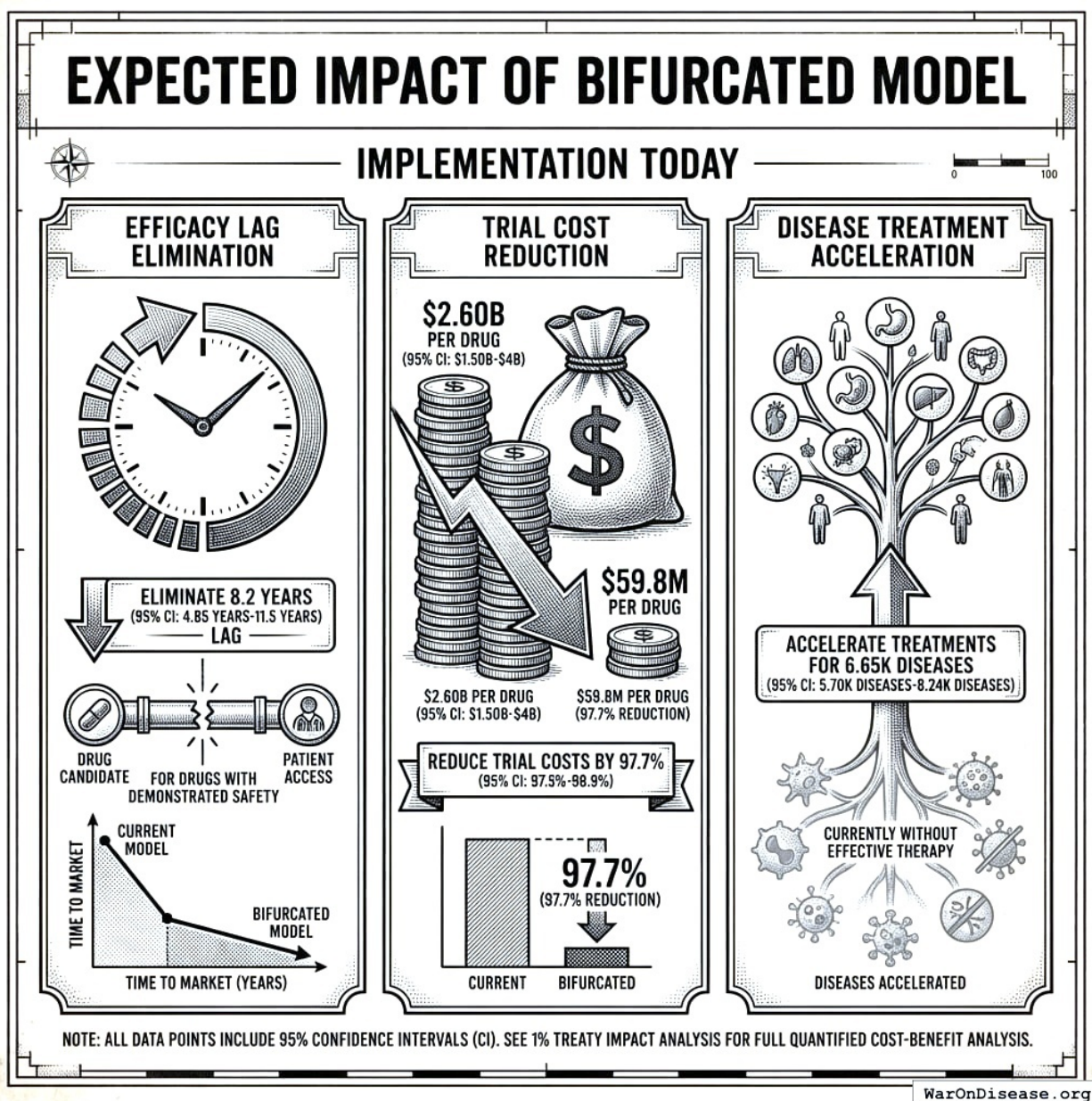


Figure 28: Skip the decade-long efficacy testing, cut costs by 90 percent, cure twice as many diseases. The only downside is you have to admit you were wrong for 60 years.

17.4 International Regulatory Comparison

Several countries have implemented alternative regulatory models that provide natural experiments:

Country	Approval System	Avg. Timeline	Key Features
USA (FDA)	Full Phase III required	10.5 years (95% CI: 6 years-12 years)	Baseline for comparison
Japan (PMDA)	Conditional approval after Phase II	2-3 years	Regenerative Medicine Act (2014); real-world monitoring ³¹
EU (EMA)	Adaptive Pathways available	~10 years	Similar to FDA; conditional marketing authorization option
Canada	Priority Review pathway	~12 months (priority)	Limited data on outcomes
Australia (TGA)	Provisional approval pathway	Variable	Similar conditional pathways

18 Critical Distinction: Efficacy Assessment Reordered, Not Eliminated

Japan's conditional approval does NOT eliminate efficacy assessment. It REORDERS it from pre-market (Phase III trials) to post-market (real-world monitoring with revocation authority). This is a different regulatory architecture, not deregulation. The HeartSheet withdrawal proves the system still enforces efficacy standards, just through different mechanisms.

Key finding: Japan's conditional approval system has an 89% success rate (8/9 products) and demonstrated that post-market monitoring CAN catch ineffective treatments:

- **Faster access:** 9 products received conditional early approval (2014-2024), reaching patients years earlier than traditional pathways
- **Success cases:** STEMIRAC (spinal cord injury) showed 12/13 patients (92%) achieved neurological improvement, with 2 of 5 completely paralyzed patients regaining motor function³². Five CAR-T therapies (Kymriah, Yescarta, Breyanzi, Abecma, Carvykti) are treating cancer patients under national insurance coverage³³.
- **The system caught inefficacy:** HeartSheet was conditionally approved in 2015 with the requirement to prove efficacy through post-market data. In 2024, after collecting real-world evidence, MHLW determined it hadn't demonstrated efficacy. The manufacturer voluntarily withdrew³⁴ the next day. *This is the system working as designed* - conditional approval was conditional, and the condition wasn't met.
- **Contrast with FDA:** Vioxx killed 38,000-55,000 Americans before withdrawal because the 6% voluntary reporting system failed to detect the signal. Japan's active monitoring caught HeartSheet's lack of efficacy with zero reported deaths.

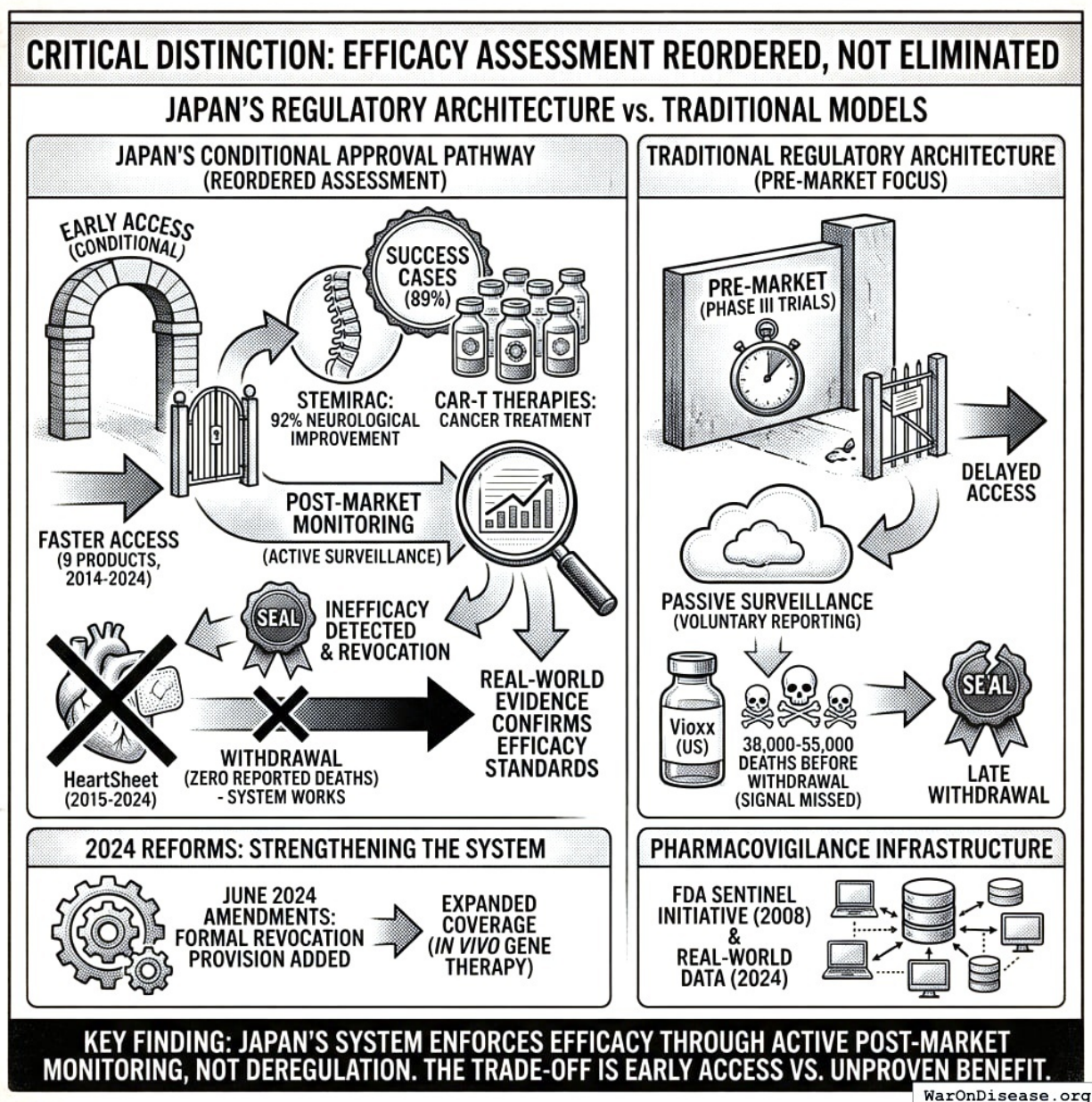


Figure 29: Japan approves drugs after Phase I, then checks if they work later. If they don't work, they take them back. Like a free trial but for not dying.

The real question for HeartSheet: During those 9 years, did heart failure patients (who have few alternatives) benefit from access to an unproven treatment? The safety profile was acceptable - efficacy was the issue. This is a genuine tradeoff that merits cost-benefit analysis, not automatic condemnation.

2024 reforms strengthen, not abandon, conditional approval: Japan's June 2024 amendments³⁵ to the Regenerative Medicine Act add a formal revocation provision that was previously missing. The old system had no legal mechanism to force withdrawal if efficacy wasn't proven - HeartSheet was voluntary. The reforms close this gap while expanding coverage to in vivo gene

therapy. Japan is refining conditional approval based on experience, not abandoning it.

Pharmacovigilance infrastructure exists: The FDA launched the Sentinel Initiative³⁶ in 2008 to monitor safety using electronic health records. In 2024, FDA eliminated major barriers³⁷ to using real-world data. The technology for active surveillance exists - the barrier is institutional inertia, not technical impossibility.

19 Addressing Common Critiques

This analysis will face predictable objections. We address them here not defensively, but to demonstrate that the core conclusion, that regulatory delay costs vastly exceed regulatory benefits, remains robust even under unfavorable assumptions.

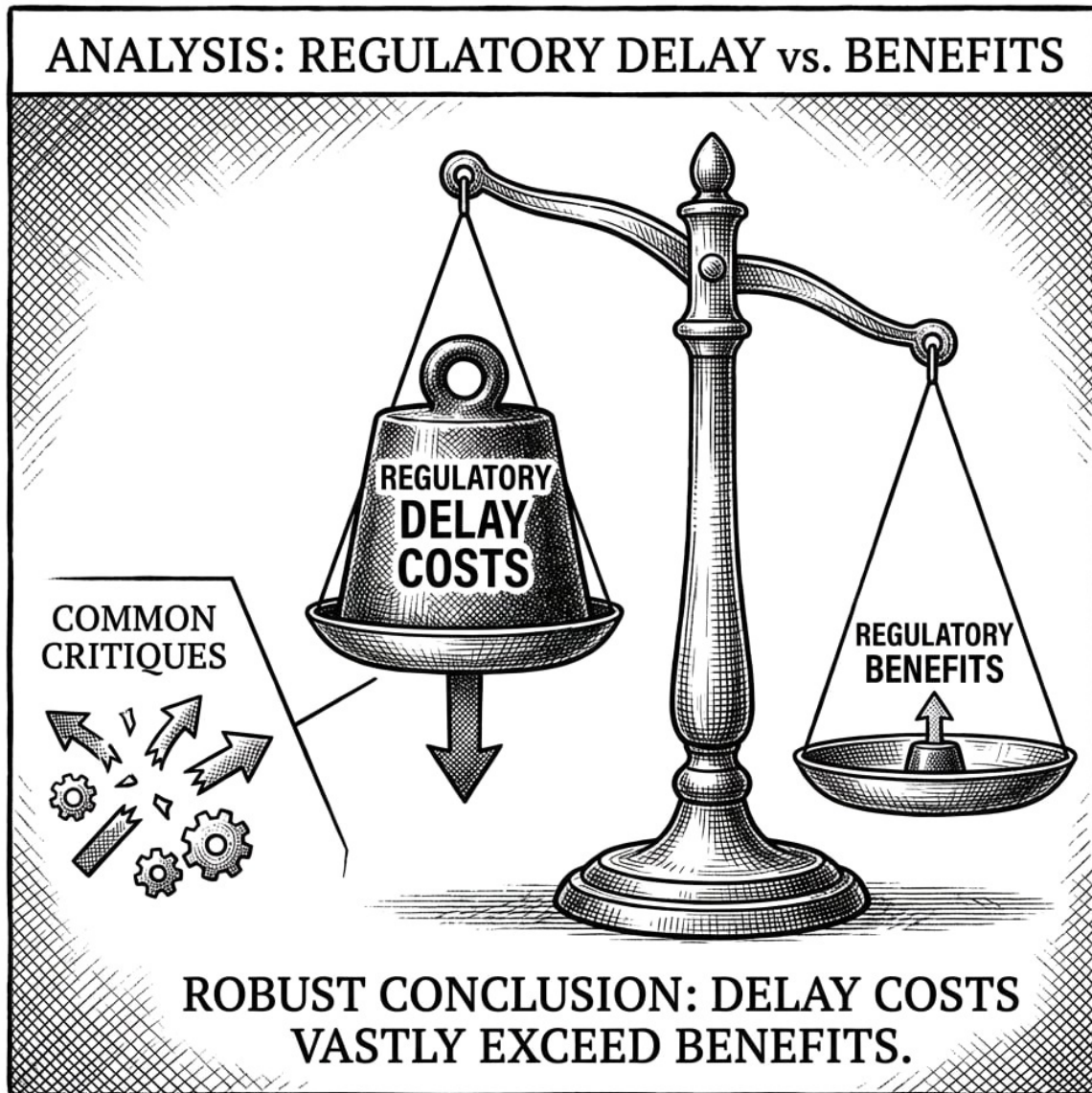


Figure 30: Cost of waiting: very high. Benefit of waiting: very low. Solution: wait longer.

19.1 “The PRIMARY Estimate Is Too Speculative”

Critique: The PRIMARY estimate (416 million deaths (90% CI: 244 million deaths-587 million deaths)) assumes we would have eradicated diseases by now without regulations. This is unproven and overly optimistic.

Response:

This critique misunderstands the methodology. The PRIMARY scenario does **not** assume disease eradication would be complete by 2024. It assumes the entire biomedical research timeline shifts backward by 8.2 years (90% CI: 4.84 years-11.5 years) due to regulatory delay.

The mechanism:

1. Every drug takes 8.2 years (90% CI: 4.84 years-11.5 years) longer to reach patients (BIO data, Section 2.3)
2. Downstream research depends on upstream results (Drug B builds on Drug A's findings)
3. Capital allocation: \$2.6 billion (95% CI: \$1.5 billion-\$4 billion) cost limits parallel research tracks (97.7% (90% CI: 92%-100%) reduction enables proportionally more simultaneous trials)
4. Knowledge accumulation delays compound across the entire field

Robustness test:

Even if you **adjust the primary estimate significantly**:

- Lower bound deaths (5th percentile): Still exceeds Type I benefits by over 10:1
- Type I benefits: ~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs)
- **The ratio remains extreme across the entire uncertainty distribution**

19.2 “The ‘Eventually Preventable’ Estimate Is Theoretical”

Critique: The claim that 92.6% (95% CI: 50%-98%) of deaths are eventually preventable is based on theoretical biological potential, not demonstrated medical capability.

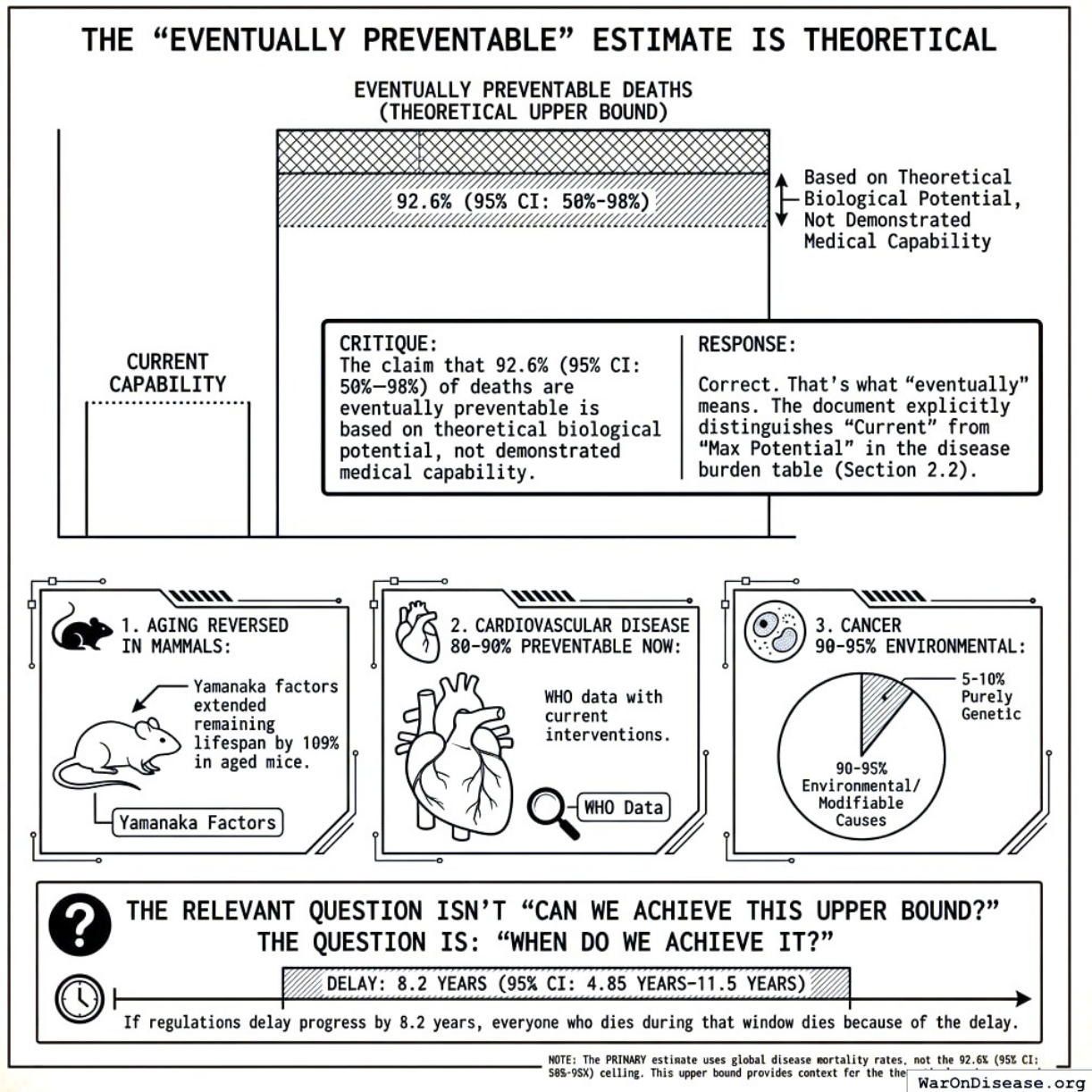


Figure 31: 92.6 percent of deaths are preventable if you cure aging, heart disease, and cancer. The other 7.4 percent is pianos falling on your head.

Response:

Correct. That’s what “eventually” means.

The document explicitly distinguishes “Current” from “Max Potential” in the disease burden table (Section 2.2). The 92.6% (95% CI: 50%-98%) represents the **theoretical upper bound** based on:

1. **Aging reversed in mammals:** Yamanaka factors extended remaining lifespan by 109% in aged mice¹⁷
2. **Cardiovascular disease 80-90% preventable NOW:** WHO data¹⁵ with current interven-

tions

3. **Cancer 90-95% environmental:** Only 5-10% purely genetic¹⁶, remainder has modifiable causes

The relevant question isn't "Can we achieve this upper bound?"

The question is: **"When do we achieve it?"**

If regulations delay progress by 8.2 years (90% CI: 4.84 years-11.5 years), everyone who dies during that window dies because of the delay.

Note: The PRIMARY estimate uses global disease mortality rates, not the 92.6% (95% CI: 50%-98%) ceiling. This upper bound provides context for the theoretical maximum scenario.

19.3 "Counterfactual Uncertainty - We Can't Know What Would Have Happened"

Critique: The analysis depends on an unknowable counterfactual: what would have happened without the 1962 amendments.

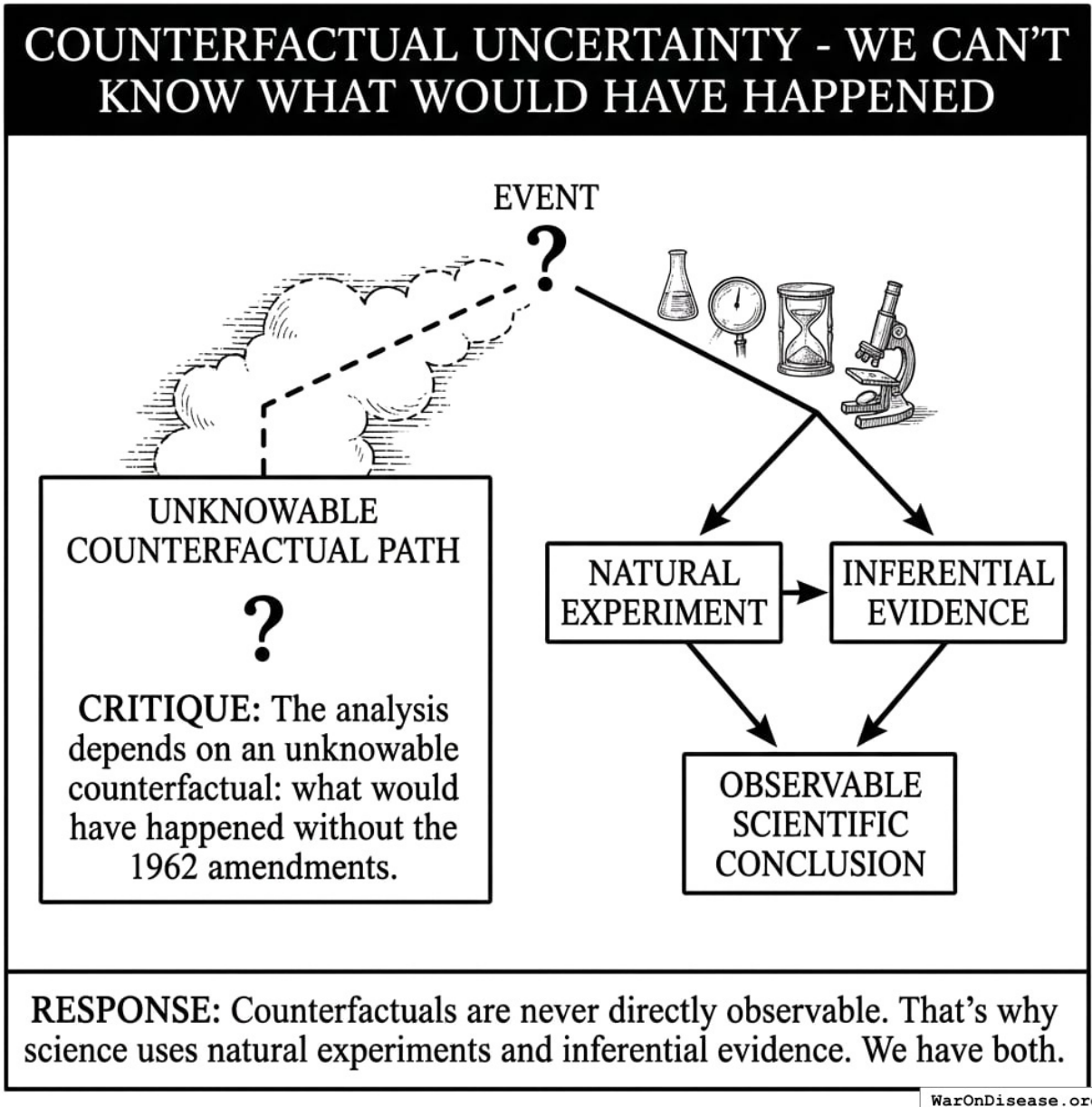


Figure 32: One timeline is what actually happened. The other timeline is what would have happened if you hadn't panicked. Scientists use math to compare the two and feel sad.

Response:

Counterfactuals are never directly observable. That's why science uses **natural experiments** and **inferential evidence**. We have both.

19.3.1 Natural Experiments

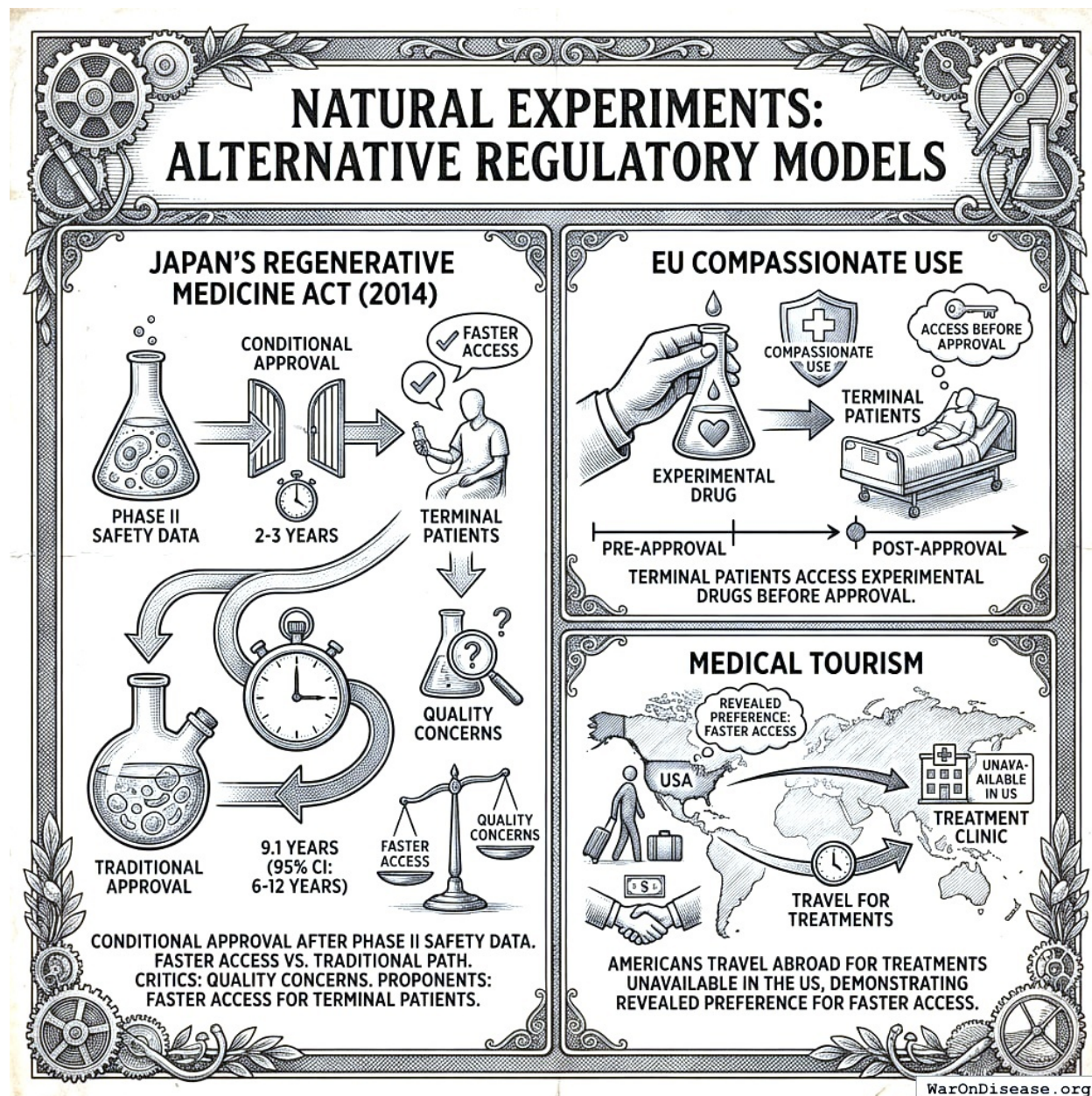


Figure 33: Some countries let dying people take experimental drugs. Other countries make dying people wait to take experimental drugs. This is called international cooperation.

Alternative Regulatory Models:

- **Japan's Regenerative Medicine Act (2014):** Conditional approval after Phase II safety data, with 2-3 year timelines vs. 10.5 years (95% CI: 6 years-12 years). Critics note quality concerns; proponents note faster access for terminal patients with no alternatives.
- **EU Compassionate Use:** Terminal patients access experimental drugs before approval
- **Medical tourism:** Americans travel abroad for treatments unavailable in the US, demonstrating revealed preference for faster access

19.3.2 The Standard for Causal Inference

The same standard used in all clinical research:

$$\text{Causation} = \text{Temporal Correlation} + \text{Mechanism} + \text{Lack of Alternative Explanations}$$

We have:

1. **Temporal correlation:** Drug approvals dropped 70% immediately after 1962
2. **Mechanism:** Costs increased 13.4x (90% CI: 9.15x-19.2x), real-world trials banned, efficacy requirements added 8.2 years (90% CI: 4.84 years-11.5 years) to development
3. **Alternative explanations:** Other factors exist (complexity, standards, etc.), but the timing and magnitude strongly suggest regulatory latency is a major contributor

If you reject this inferential method, you must also reject the methodology of clinical trials, which use the identical logical structure.

19.4 “Confounding Factors - Other Changes in 1962”

Critique: Medicare (1965), NIH funding changes, Vietnam War, and other 1960s policy shifts confound the analysis. How can we isolate the 1962 amendments’ effect?

Response:

Confounders work **against** the hypothesis, making the observed effect more remarkable.

Medicare (1965): Expanded healthcare access → *should have increased* drug demand and development → Yet approvals dropped 70%

NIH Funding: Grew dramatically 1960s-1980s → *should have accelerated* drug development → Yet approvals dropped 70%

Vietnam War (1965-1973): Primarily affected young males, minimal impact on overall drug development patterns

The temporal precision matters: Drug approval rates dropped 70% in **1962**, not 1965 (Medicare) or 1964 (Gulf of Tonkin). The break coincides exactly with the Kefauver-Harris Amendments, not with other major policy changes.

Quantitative test:

If confounders explained the effect, we would expect:

- Gradual change over the 1960s (as various policies took effect)
- Recovery after confounders resolved (e.g., Vietnam War ended 1973)

Instead, we observe:

- Immediate 70% drop in drug approvals in 1962
- Sustained reduction in approval rates for 62+ years
- Development costs increased 13.4x (90% CI: 9.15x-19.2x)

The hypothesis that fits the data is: **structural change in drug approval requirements permanently reduced the rate of biomedical progress.**

19.4.1 Sensitivity Analysis: What if Regulation Explains Only Part of the Decline?

Even if we concede that non-regulatory factors (complexity, pharmacological saturation, etc.) explain a substantial portion of the approval decline, the conclusion remains robust:

Regulatory Attribution	Type II Estimate	Type I Estimate	Ratio	Conclusion
100% (baseline)	8.77 billion DALYs (90% CI: 4.88 billion DALYs-13.2 billion DALYs)	~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs)	3,389 (90% CI: 1,811- 5,734)	Type II dominates
75%	~75% of baseline	~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs)	~2,300:1	Type II dominates
50%	~50% of baseline	~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs)	~1,500:1	Type II dominates
25%	~25% of baseline	~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs)	~770:1	Type II dominates
10%	~10% of baseline	~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million DALYs)	~300:1	Type II still dominates

The Type II/Type I ratio would need to drop below 1:1 for the FDA's approach to be justified on net mortality grounds. Even at 10% regulatory attribution, the ratio remains ~300:1. The conclusion is robust across a wide range of assumptions about confounding.

19.5 “This Ignores Safety - Deregulation Would Flood Markets with Dangerous Drugs”

Critique: Without efficacy requirements, pharmaceutical companies will sell snake oil and dangerous drugs. Type I errors (approving bad drugs) will explode.

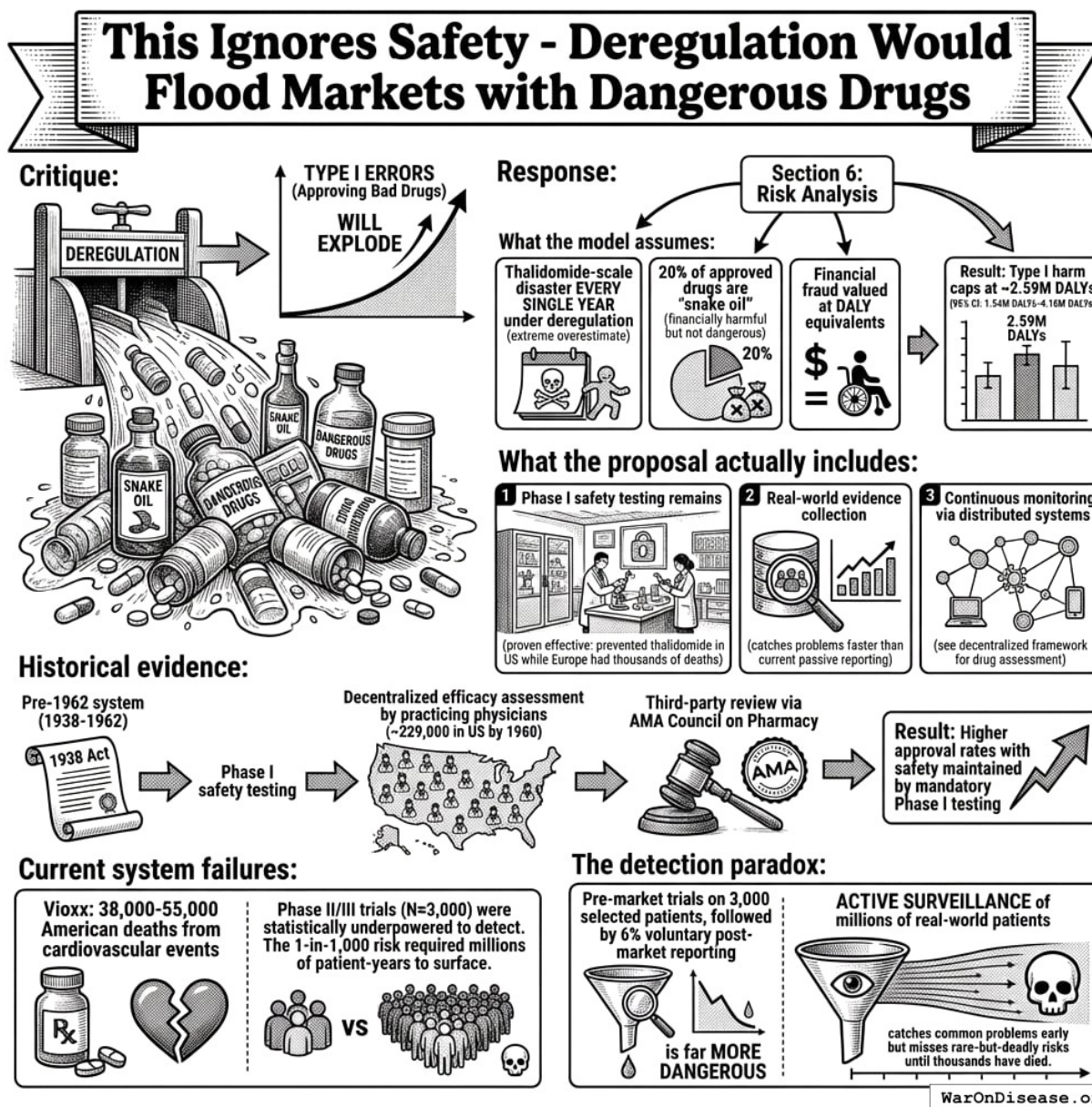


Figure 34: Testing 10,000 people cannot find problems that happen to 1 in a million. But it can delay drugs long enough that a million people never get them at all.

Response:

The analysis explicitly models this in [Section 6: Risk Analysis](#).

What the model assumes:

- Thalidomide-scale disaster **every single year** under deregulation (extreme overestimate)
- 20% of approved drugs are "snake oil" (financially harmful but not dangerous)
- Financial fraud valued at DALY equivalents

Result: Type I harm caps at ~2.59 million DALYs (90% CI: 1.88 million DALYs-3.38 million)

DALYs)

What the proposal actually includes:

1. **Phase I safety testing remains** (proven effective: prevented thalidomide in US while Europe had thousands of deaths)
2. **Real-world evidence collection** (catches problems faster than current passive reporting)
3. **Continuous monitoring** via distributed systems (see [decentralized FDA](#))

Historical evidence:

The pre-1962 system (1938-1962) included:

- Phase I safety testing (mandated by 1938 Food, Drug, and Cosmetic Act)
- Decentralized efficacy assessment by practicing physicians (~229,000 in US by 1960)³⁸⁴
- Third-party review via AMA Council on Pharmacy provided independent evaluation
- **Result:** Higher approval rates with safety maintained by mandatory Phase I testing

Current system failures:

- **Vioxx:** 38,000-55,000 American deaths²⁶ from cardiovascular events that Phase II/III trials (N 3,000) were statistically underpowered to detect. The 1-in-1,000 risk required millions of patient-years to surface.
- **Statistical reality:** Trials with 3,000 patients cannot reliably detect adverse events rarer than ~1-in-1,000

The detection paradox: Pre-market trials on 3,000 selected patients, followed by 6% voluntary post-market reporting, is far **more dangerous** than active surveillance of millions of real-world patients. The current system catches common problems early but misses rare-but-deadly risks until thousands have died.

20 Conclusion

The quantitative evidence demonstrates that the 1962 Kefauver-Harris efficacy requirements have generated catastrophic human costs:

- **416 million eventually avoidable deaths from 8.2 years (90% CI: 4.84 years-11.5 years) timeline shift**
- **8.77 billion DALYs (90% CI: 4.88 billion DALYs-13.2 billion DALYs) lost**
- **\$1.32 quadrillion (90% CI: \$676 trillion-\$2.14 quadrillion) economic destruction** (cumulative DALYs valued at \$150,000 (90% CI: \$100,384-\$198,679)/DALY, standard WHO methodology)
- **3,389 (90% CI: 1,811-5,734) harm ratio** (Type II vs. Type I errors)

The 3,389 (90% CI: 1,811-5,734) ratio demonstrates that these costs dwarf the benefits. The regulatory framework optimizes for bureaucratic risk minimization (avoiding blame for approvals) rather than population health maximization (saving lives).

The path forward is clear: maintain safety testing, eliminate efficacy delay, and deploy distributed real-world evidence systems.

⁴Institute of Medicine data shows 127.4 active physicians per 100,000 population in 1960. At US population of ~180M, this equals approximately 229,000 active physicians.

1. World Health Organization. WHO global health estimates 2024. *World Health Organization* <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates> (2024)
Comprehensive mortality and morbidity data by cause, age, sex, country, and year Global mortality: 55-60 million deaths annually Lives saved by modern medicine (vaccines, cardiovascular drugs, oncology): 12M annually (conservative aggregate) Leading causes of death: Cardiovascular disease (17.9M), Cancer (10.3M), Respiratory disease (4.0M) Note: Baseline data for regulatory mortality analysis. Conservative estimate of pharmaceutical impact based on WHO immunization data (4.5M/year from vaccines) + cardiovascular interventions (3.3M/year) + oncology (1.5M/year) + other therapies. Additional sources: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates>
2. Biotechnology Innovation Organization (BIO). BIO clinical development success rates 2011-2020. *Biotechnology Innovation Organization (BIO)* https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf (2021)
Phase I duration: 2.3 years average Total time to market (Phase I-III + approval): 10.5 years average Phase transition success rates: Phase I→II: 63.2%, Phase II→III: 30.7%, Phase III→Approval: 58.1% Overall probability of approval from Phase I: 12% Note: Largest publicly available study of clinical trial success rates. Efficacy lag = 10.5 - 2.3 = 8.2 years post-safety verification. Additional sources: https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf
3. World Health Organization. [Life expectancy at age 60 \(years\): Global health observatory](#). (2021).
4. Tufts CSDD. Cost of drug development.
Various estimates suggest \$1.0 - \$2.5 billion to bring a new drug from discovery through FDA approval, spread across 10 years. Tufts Center for the Study of Drug Development often cited for \$1.0 - \$2.6 billion/drug. Industry reports (IQVIA, Deloitte) also highlight \$2+ billion figures.
5. Lichtenberg, F. R. [How many life-years have new drugs saved? A three-way fixed-effects analysis of 66 diseases in 27 countries, 2000-2013](#). *International Health* **11**, 403–416 (2019)
Using 3-way fixed-effects methodology (disease-country-year) across 66 diseases in 22 countries, this study estimates that drugs launched after 1981 saved 148.7 million life-years in 2013 alone. The regression coefficients for drug launches 0-11 years prior (beta=-0.031, SE=0.008) and 12+ years prior (beta=-0.057, SE=0.013) on years of life lost are highly significant (p<0.0001). Confidence interval for life-years saved: 79.4M-239.8M (95 percent CI) based on propagated standard errors from Table 2.
6. Nature Reviews Drug Discovery. Drug trial success rate from phase i to approval. *Nature Reviews Drug Discovery: Clinical Success Rates* <https://www.nature.com/articles/nrd.2016.136> (2016)
Overall Phase I to approval: 10-12.8% (conventional wisdom 10%, studies show 12.8%). Recent decline: Average LOA now 6.7% for Phase I (2014-2023 data) Leading pharma companies: 14.3% average LOA (range 8-23%) Varies by therapeutic area: Oncology 3.4%, CNS/cardiovascular lowest at Phase III Phase-specific success: Phase I 47-54%, Phase II 28-34%, Phase III 55-70% Note: 12% figure accurate for historical average. Recent data shows decline to 6.7%, with Phase II as primary attrition point (28% success) Additional sources: <https://www.nature.com/articles/nrd.2016.136> | <https://pmc.ncbi.nlm.nih.gov/articles/PMC6409418/> | <https://academic.oup.com/biostatistics/article/20/2/273/4817524>

7. Kinch, M. S. & Griesenauer, R. H. [Lost medicines: A longer view of the pharmaceutical industry with the potential to reinvigorate discovery](#). *Drug Discovery Today* **24**, 875–880 (2019)
Research identified 1,600+ medicines available in 1962. The 1950s represented industry high-water mark with >30 new products in five of ten years; this rate would not be replicated until late 1990s. More than half (880) of these medicines were lost following implementation of Kefauver-Harris Amendment. The peak of 1962 would not be seen again until early 21st century. By 2016 number of organizations actively involved in R&D at level not seen since 1914.
8. Think by Numbers. Pre-1962 physician-led clinical trials. *Think by Numbers: How Many Lives Does FDA Save?* <https://thinkbynumbers.org/health/how-many-net-lives-does-the-fda-save/> (1966)
Pre-1962: Physicians could report real-world evidence directly 1962 Drug Amendments replaced "premarket notification" with "premarket approval", requiring extensive efficacy testing Impact: New regulatory clampdown reduced new treatment production by 70%; lifespan growth declined from 4 years/decade to 2 years/decade Drug Efficacy Study Implementation (DESI): NAS/NRC evaluated 3,400+ drugs approved 1938-1962 for safety only; reviewed >3,000 products, >16,000 therapeutic claims FDA has had authority to accept real-world evidence since 1962, clarified by 21st Century Cures Act (2016) Note: Specific "144,000 physicians" figure not verified in sources Additional sources: <https://thinkbynumbers.org/health/how-many-net-lives-does-the-fda-save/> | <https://www.fda.gov/drugs/enforcement-activities-fda/drug-efficacy-study-implementation-desi> | <http://www.nasonline.org/about-nas/history/archives/collections/des-1966-1969-1.html>
9. ICER. Value per QALY (standard economic value). *ICER* <https://icer.org/wp-content/uploads/2024/02/Reference-Case-4.3.25.pdf> (2024)
Standard economic value per QALY: \$100,000–\$150,000. This is the US and global standard. willingness-to-pay threshold for interventions that add costs. Dominant interventions (those that save money while improving health) are favorable regardless of this threshold. Additional sources: <https://icer.org/wp-content/uploads/2024/02/Reference-Case-4.3.25.pdf>
10. Peltzman, S. [An evaluation of consumer protection legislation: The 1962 drug amendments](#). *Journal of Political Economy* **81**, 1049–1091 (1973)
Foundational study quantifying the costs of the 1962 Kefauver-Harris Amendments. Peltzman estimated that the efficacy requirements reduced the flow of new drugs by 50-60% and that the costs of reduced innovation substantially exceeded the benefits of keeping ineffective drugs off the market. Concluded that the 1962 amendments resulted in net welfare losses.
11. Wardell, W. M. [Therapeutic implications of the drug lag](#). *Clinical Pharmacology and Therapeutics* **15**, 73–96 (1974)
Documented the "drug lag" between US and UK drug approvals. Found that the UK had access to significantly more new drugs than the US, and that many effective drugs available in Europe were unavailable to American patients. Estimated beta-blockers alone could save 10,000 lives annually if approved in the US. Foundational work demonstrating the mortality cost of regulatory delay.

12. FEE. Patients and doctors vs FDA. *FEE: Patients and Doctors vs FDA* <https://fee.org/articles/patients-and-doctors-vs-the-fda>
Dale Gieringer (1985): 21,000-120,000 lives lost per decade from FDA delay Gieringer: "Loss of life from delay alone in the hundreds of thousands" (not millions) Beta-blockers alone: William Wardell estimated "10,000 lives/year" if allowed; FDA delay 1965-1976 Sam Peltzman: Post-1962 death toll from regulatory delay "easily number in thousands per year Practolol (beta-blocker): "Could save 10,000 lives/year" (Wardell estimate) FDA allowed propranolol 1968 (3 years after Europe); for hypertension/angina not until 1978 Note: "4-10 million" figure not found in sources. Gieringer's estimates: 21K-120K deaths per decade, "hundreds of thousands" total (not millions). Specific drug delays (beta-blockers): 100K deaths estimated Additional sources: <https://fee.org/articles/patients-and-doctors-vs-the-fda> | <https://www.econlib.org/library/Enc/DrugLag.html> | <https://www.fda.gov/oc/2013/08/08/theory-evidence-and-examples-of-fda-harm/>
13. Fischl, M. A. et al. *The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: A double-blind, placebo-controlled trial.* *New England Journal of Medicine* **317**, 185–191 (1987)
Landmark Phase 2 trial of AZT in 282 AIDS patients. 19 placebo recipients died vs. 1 AZT recipient (P < 0.001). Trial stopped early due to overwhelming efficacy. Led to FDA approval in record 107 days.
14. Institute for Health Metrics and Evaluation (IHME). IHME global burden of disease (2.55B DALYs, 2019). *Institute for Health Metrics and Evaluation (IHME)* <https://vizhub.healthdata.org/gbd-compare/> (2020)
Globally, in 2019, the total number of DALYs from all causes was 2.55 billion. Additional sources: <https://vizhub.healthdata.org/gbd-compare/> | <https://www.healthdata.org/research-analysis/about-gbd> | <https://pubmed.ncbi.nlm.nih.gov/33069326/>
15. WHO. 80% of cardiovascular disease is preventable. *WHO: Cardiovascular diseases (CVDs)* [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) (2021)
As many as 80% of all heart attacks and strokes are preventable" through addressing lifestyle risk factors WHO: Most cardiovascular diseases can be prevented by addressing behavioral and environmental risk factors such as tobacco use, unhealthy diet, obesity, physical inactivity, harmful use of alcohol, and air pollution Cleveland Clinic: "90 percent of heart disease is preventable through healthier diet, regular exercise, and not smoking In 2 large cohort studies, a reduction of CVD risk of >80% and diabetes >90% were demonstrated in individuals who followed healthy lifestyle practices Only 5% of individuals follow all lifestyle factors for "ideal" cardiovascular health (American Heart Association) Additional sources: [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) | <https://world-heart-federation.org/what-we-do/prevention/> | <https://newsroom.cleveland-clinic.org/2021/09/29/90-percent-of-heart-disease-is-preventable-through-healthier-diet-regular-exercise-and-not-smoking> | <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC162259/>

16. PMC. 30-50% of cancer is currently preventable; 90-95% has environmental/lifestyle roots. *PMC: Cancer is a Preventable Disease* <https://pmc.ncbi.nlm.nih.gov/articles/PMC2515569/> *IARC/WHO: Environmental and lifestyle factors contribute to about 50% of the global cancer burden; expected to contribute to remaining 50% for which causes currently unknown WHO: 35% of cancer deaths worldwide are due to potentially preventable or modifiable risk factors PMC: "Only 5-10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90-95% have their roots in the environment and lifestyle Breakdown: 25-30% due to tobacco, 30-35% linked to diet, 15-20% due to infections, remainder from radiation, stress, physical activity, pollutants US: 4 out of 10 cancer cases associated with preventable risk factors (tobacco/alcohol use, physical inactivity) Note: Current preventability (35-40%) vs. theoretical max (90-95% if all environmental/lifestyle factors addressed) Additional sources: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2515569/> | <https://www.iarc.who.int/branches-env/> | <https://cancerprogressreport.aacr.org/progress/cpr22-contents/cpr22-preventing-cancer-identifying-risk-factors/>*
17. PMC. Aging reversal demonstrated in mammals using yamanaka factors. *PMC: Chemically Induced Reprogramming to Reverse Aging* <https://pmc.ncbi.nlm.nih.gov/articles/PMC10373966/> (2023)
Harvard/Sinclair: Loss of epigenetic information causes aging; restoring epigenome integrity reverses aging signs in mice OSK therapy (Oct4, Sox2, Klf4): Ectopic induction can restore youthful DNA methylation patterns, transcript profiles, and tissue function without erasing cellular identity Results in mice: Systemically delivered adeno-associated viruses encoding inducible OSK in 124-week-old mice extended median remaining lifespan by 109% over wild-type controls Vision restored in glaucoma mice - first successful reversal (not just halting progression) Cyclic partial reprogramming (2 days on, 5 days off) showed improvements after just 6 weeks including reduced age-related spinal curvature Human cells: Babraham Institute showed cellular reprogramming reverses epigenetic age of human skin cells by 30 years Chemical alternatives: Six chemical cocktails identified that restore youthful genome-wide transcript profile in less than a week without compromising cellular identity Note: Demonstrates biological aging is reversible, not inevitable; safety testing ongoing before human application Additional sources: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10373966/> | <https://www.nature.com/articles/s41467-024-46020-5> | <https://www.liebertpub.com/doi/10.1089/cell.2023.0072> | <https://clinicalepigeneticsjournal.biomedcentral.com/articles/10.1186/s13148-021-01158-7>
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WHO: "Injuries have traditionally been regarded as random, unavoidable 'accidents'. Today both unintentional and intentional injuries are viewed as largely preventable events. 4.4 million injury-related deaths annually: 3.16M unintentional, 1.25M violence-related Injuries are preventable by changing environment, individual behavior, products, social norms, legislation, and governmental/institutional policies When standardized per 100,000 population, death rate is nearly double in low/middle-income vs high-income countries (65 vs 35 per 100,000) 90% of injury-related deaths occur in low- and middle-income countries Note: 60% of accidental deaths theoretically preventable through policy, technology, and behavior change; 40% involve instantaneous trauma beyond medical intervention Additional sources: <https://www.who.int/news-room/fact-sheets/detail/injuries-and-violence> | <https://pmc.ncbi.nlm.nih.gov/articles/PMC2912603/> | <https://www.who.int/publications-detail-redirect/the-injury-chart-book-a-graphical-overview-of-the-global-burden-of-injuries>

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Used AAV-mediated gene therapy to deliver Pdx1 and MafA to mouse pancreas, reprogramming alpha cells into functional insulin-producing beta cells. Reversed autoimmune diabetes in mice, demonstrating gene therapy potential for T1D reversal.
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R3 paradigm: Rejuvenation (restoring cell function), Regeneration (stimulating repair), Replacement (substituting lost cells) Alzheimer's: Stanford study showed stem cell transplants reduced brain abnormalities in mice; Neural Stem Cell Therapy shown to improve cognitive function and reduce amyloid plaques Parkinson's: Clinical trial found Neural Stem Cell Therapy significantly improved motor function and was well-tolerated ALS/Huntington's: MSC (mesenchymal stem cell) therapy effectiveness confirmed; slows ALS progression Challenge: Clinical trials often enroll patients at advanced stages; many preclinically promising drugs ineffective in late-stage human trials Current status: Largely experimental and early clinical trial stages; researchers working to overcome delivery challenges, safety concerns, and targeting widespread neuronal damage Note: 80% theoretical max for neurodegenerative reflects early-stage intervention potential; current treatments limited (10% effective) Additional sources: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7926761/> | <https://med.stanford.edu/news/all-news/2023/09/stem-cell-alzheimers.html> | <https://stemcellres.biomedcentral.com/articles/10.1186/s13287-025-04285-7>
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Every \$1 spent on childhood immunizations results in approximately \$11 in savings. (700% ROI). For low/middle-income countries: \$26.1-\$51.0 ROI using cost-of-illness approach, \$52.2 ROI using value-of-statistical-life approach. US childhood vaccines 1994-2023 saved \$540B in direct costs, \$2.7T in total societal savings. Additional sources: <https://www.americanactionforum.org/research/vaccine-protection-and-productivity-the-economic-value-of-vaccines/> | <https://www.healthaffairs.org/doi/10.1377/hlthaff.2020.00103> | https://immunizationevidence.org/featured_issues/the-value-of-vaccines-investments-in-immunization-yield-high-returns/
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Global days of therapy reached 1.8 trillion in 2019 (234 defined daily doses per person). Diabetes, respiratory, CVD, and cancer account for 71 percent of medicine use. Projected to reach 3.8 trillion DDDs by 2028.
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Phase III trial of gamma-secretase inhibitor semagacestat for Alzheimer's disease was terminated early by Eli Lilly. Patients on treatment showed significantly WORSE cognitive outcomes than placebo, plus increased skin cancers and infections. 1,537 patients randomized. Example of Phase III trial preventing approval of a drug that would have harmed patients.
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Phase III trial of drisapersen for Duchenne muscular dystrophy failed to show clinical benefit (P=0.415). FDA rejected approval in 2016 due to safety concerns including thrombocytopenia in 2% of patients, renal toxicity, and injection site reactions in 79% of patients. BioMarin discontinued development. Example of regulatory system preventing approval of ineffective drug with serious adverse effects.
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Graham testimony (2004): 88,000-139,000 U.S. heart attacks/strokes from Vioxx; up to 55,000 deaths (40% fatality rate) Lancet study estimate: 88,000 Americans had heart attacks from Vioxx; 38,000 died FDA memo (2004): Vioxx contributed to 27,785 heart attacks and sudden cardiac deaths (1999-2003) High-dose Vioxx: Tripled risk of heart attacks and sudden cardiac death Prescriptions: 92.8 million U.S. prescriptions 1999-2003 Withdrawn: September 30, 2004 after APPROVE trial showed cardiovascular risks Note: Vioxx case demonstrates failure of passive post-market surveillance (FAERS) to detect safety signals in time. Voluntary reporting missed cardiovascular risks for years despite millions of prescriptions Additional sources: <https://pmc.ncbi.nlm.nih.gov/articles/PMC534432/> | <https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx> | [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(05\)67712-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)67712-4/fulltext)
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We present the Predictor Impact Score (PIS), a novel composite metric operationalizing Bradford Hill causality criteria for automated signal detection from aggregated N-of-1 observational studies. Combined with pragmatic trial confirmation (based on evidence from 108+ embedded trials), this two-stage framework would generate validated outcome labels at 44.1x lower cost than traditional Phase III trials. This enables continuous, population-scale pharmacovigilance and precision dosing recommendations.
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Only 15 diseases/year get their first treatment each year. With 6.65 thousand diseases lacking effective treatments, the backlog would take 443 years to clear. Integrating pragmatic trials into standard healthcare increases trial capacity 12.3x, cutting that timeline from 443 years to 36 years. The average untreated disease gets a treatment 212 years earlier, saving 10.7 billion deaths at \$0.842 per year of healthy life saved.

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Your governments possess nuclear weapons sufficient to end civilization 122 times but have not cured Alzheimer's once. This treaty asks them to be 1% more rational.
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6.65 thousand diseases have zero FDA-approved treatments; at current trial capacity, exploring them takes 443 years. Redirecting 1% of military spending scales capacity 12.3x, cutting the timeline to 36 years and preventing 10.7 billion deaths. At \$0.00177/DALY, 50.3kx more cost-effective than the best existing interventions. The result holds across every specified adoption pathway.
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Act on Safety of Regenerative Medicine (RM Act) + amended Pharmaceuticals and Medical Devices Act (PMD Act): passed Nov 2013, effective Nov 2014 Conditional and time-limited approval pathway: Obtain approval after exploratory trials demonstrate probable benefit and proven safety 7-year conditional approval period to confirm clinical benefit (e.g., using surrogate endpoints) SAKIGAKE designation (April 2015): Expedited pathway for innovative products targeting serious/life-threatening diseases without effective treatment Benefits: Prioritized consultation, accelerated review, extended re-examination period, premium pricing Examples: Terumo's HeartSheet and Stemirac obtained conditional approval; Stemirac also SAKIGAKE-designated Additional sources: <https://www.fdpi.org/2019/02/global-focus-japans-regenerative-medicine-regulatory-pathways-encouraging-innovation-and-patient-access/> | <https://www.insights.bio/cell-and-gene-therapy-insights/journal/article/310/Experiences-from-Japan-SAKIGAKE-Designation-System-for-Regenerative-Medical-Products> | <https://pmc.ncbi.nlm.nih.gov/articles/PMC6696404/>
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In this investigator-initiated clinical trial (2014-2017), 12 of 13 patients (92%) with cervical spinal cord injury who received MSC transplantation achieved at least one level of improvement on American Spinal Injury Association Impairment Scale. Five of six AIS A patients improved to AIS B (3/6) or AIS C (2/6). No severe side effects. Results led to MHLW conditional approval of STEMIRAC in December 2018.
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Historical physician workforce data: 126.6 active nonfederal M.D. physicians per 100,000 population in 1950; 127.4 in 1960; 137.4 in 1970 (DHHS 1993). At 1960 US population of 180M, this corresponds to approximately 229,000 active physicians.