Separating Progress from Hype:
Flaws, Fragility & Formulas in Scientific Evidence
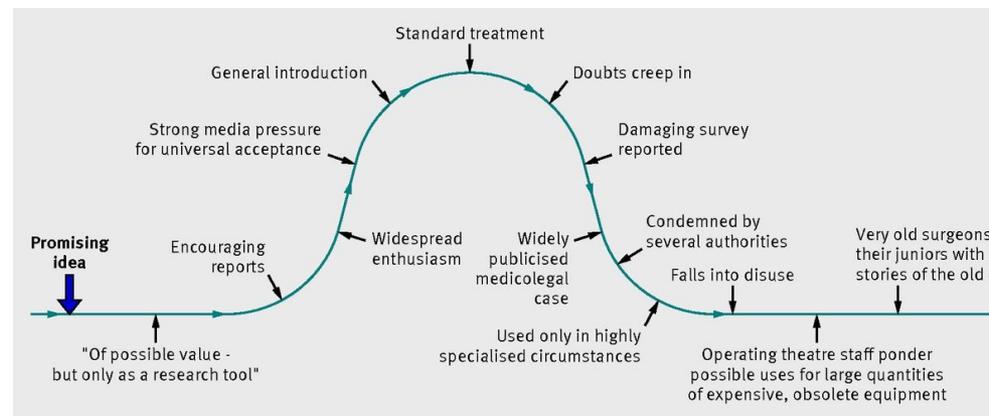
Burton W. Lee, MD
Professor of Medicine, University of Pittsburgh
President, Global Critical Care Collaborations
burton.w.lee@pitt.edu

PROGRESS
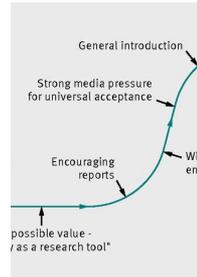
Amini. BMC Public Health 2021;21:401.
Cardiovascular Disease.

Mortality Rate 1990 to 2016
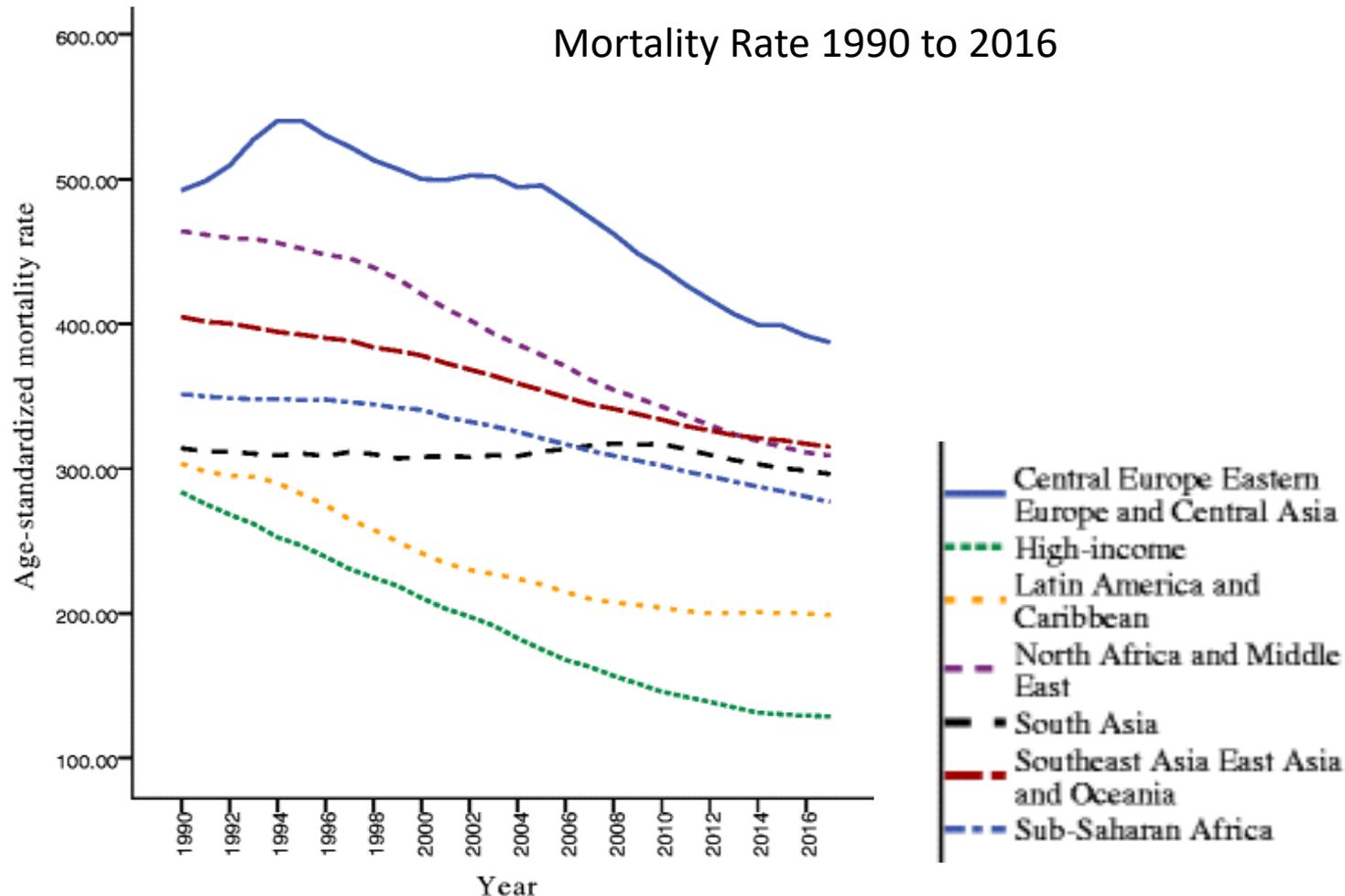
PROGRESS
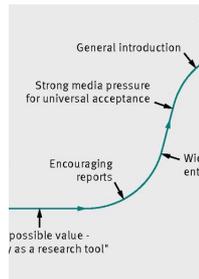
Roser. World HIV Mortality
https://ourworldindata.org/hiv-aids

Share of deaths from HIV/AIDS, 1990 to 2019

Sub Saharan Africa

Death rate from HIV/AIDS
The number of deaths from HIV/AIDS per 100,000 people.

USA 1990 to 2019
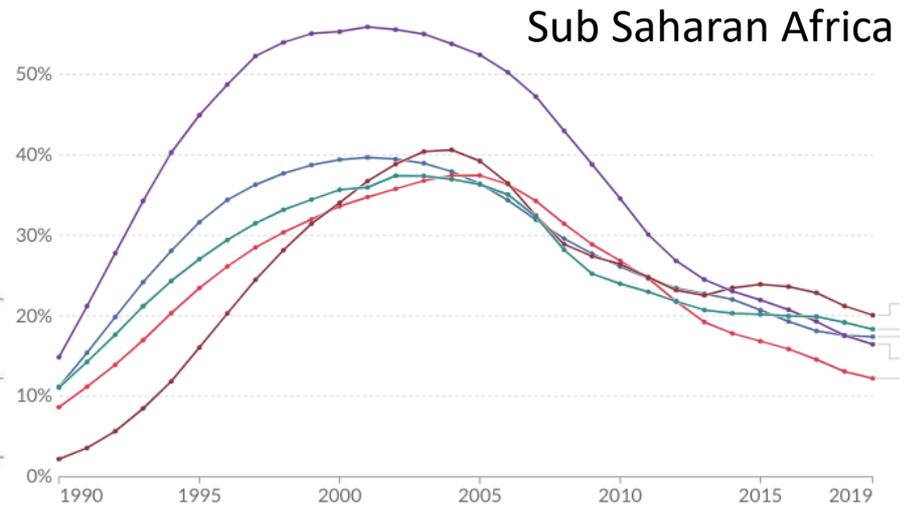
HYPE - PERIPETEIA (Medical Reversals)

Ioannidis. JAMA 2005; 294:218-28.
34 HIGHLY CITED (>1000 Citations)
  Confirmed?   20 (59%)

Prasad. JAMA 2012; 307:37-8.
35 NEJM STUDIES - Retesting Established Clinical Practice
  Replicated?   16 (46%)

Begley. Nature 2012; 483:531-3.
53 LANDMARK STUDIES
  Replicated?   6 (11%)

McKibbon. BMC Medicine 2004; 2:33.

Quality – human; important outcome; appropriate methods & statistics.
Relevance –important to clinical practice (by clinicians with expertise in methodology and specific content).

	#	Pass
All Articles in 2000	60,352	4132

	#	Int Med Stringent	NNR	Int Med Less Stringent	NNR
NEJM	1530	25 (1.6%)	61	67	23
JAMA	1930	25 (1.3%)	77	53	36
Lancet	3858	22 (0.6%)	175	62	62

Of the HQCR articles of internal medicine at its subspecialties, 56% were published in:
NEJM, JAMA, Lancet.

PROGRESS & **PERIPETEIA**
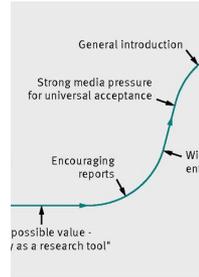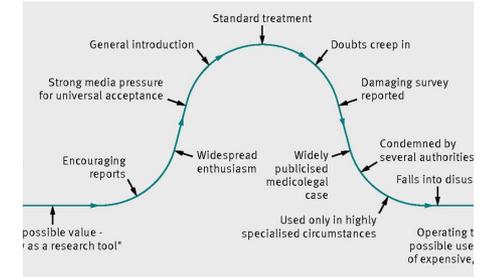
Early Promising Finding – True PROGRESS or Mere PERIPETIEA?

Flaws ➡ Rigorous Methods

Fragility ➡ Hospital Mortality

Therapy	Control	P
1000	1000	
30 (3.0%)	50 (5.0%)	0.03

Therapy	Control	
30 (3.0%)	48 (4.8%)	0.055
Fragility Index	2	Is Loss of F/U < FI?

General introduction

Strong media pressure for universal acceptance

Encouraging reports

possible value - as a research tool"

Standard treatment

General introduction

Doubts creep in

Strong media pressure for universal acceptance

Damaging survey reported

Encouraging reports

Widespread enthusiasm

Widely publicised medicolegal case

Condemned by several authorities

Falls into disus

Used only in highly specialised circumstances

Operating t possible use of expensive,

possible value - as a research tool"

Median Fragility Index   2 (IQR 1 – 3.5)

% with Fragility Index ≤ 1   40% (Ridgeon)

Flaws
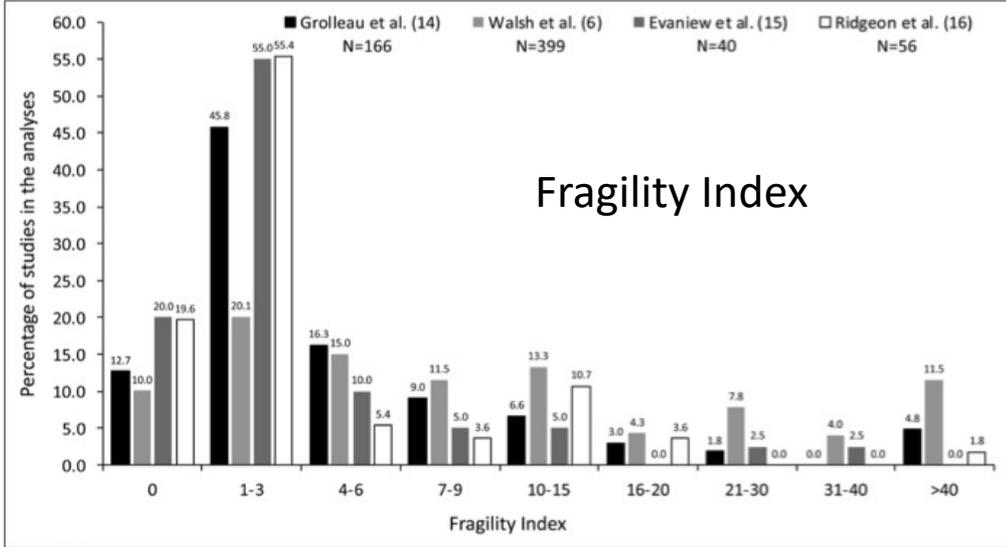
Lobo. CCM 2019; 47: 486-8. Summary of 4 SRs

Fragility

Figure 1. Fragility index of randomized controlled trials analyzed in four systematic reviews (6, 14–16).

THE FRAGILITY

Papazian. NEJM 2010; 363: 1107-16.

ClinCalc.com

Fragility Index Calculator
Calculates the number of patients required to lose statistical significance

ClinCalc.com » Statistics » Fragility Index Calculator

Study Data

Control Group		Experimental Group	
Number WITH primary endpoint	66	Number WITH primary endpoint	56
Number WITHOUT primary endpoint	96	Number WITHOUT primary endpoint	121
Total number of control patients	162	Total number of experimental patients	177

⇄ Enter number of patients without primary endpoint instead

Reset   Calculate

RESULTS

Fragility Index
0

CONCLUSIONS

In patients with severe ARDS, early administration of a neuromuscular agent improved the adjusted 90-day survival and increased the time off the v without increasing muscle weakness.

90-Day Mortality	NMB	Control
	177	162
	56 (31.6%)	66 (40.7%)

NHLBI. ROSE Trial. NEJM 2019; 380: 1997-2008.

CONCLUSIONS

Among patients with moderate-to-severe ARDS who were treated with a strategy involving a high PEEP, there was no significant difference in mortality at 90 days between patients who received an early and continuous cisatracurium infusion and those who were treated with a usual-care approach with lighter sedation targets.

PROGRESS
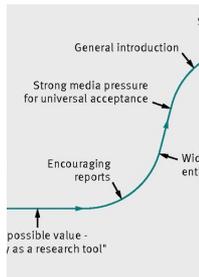
& PERIPETEIA
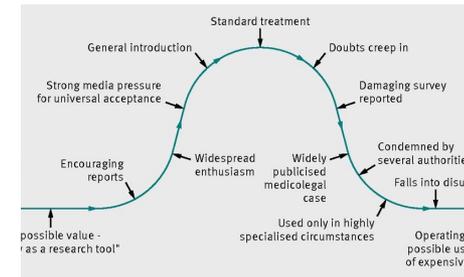
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812   FEBRUARY 4, 2021   VOL. 384   NO. 5

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

Baden. NEJM 2020; 383: 2603-15.

Median Fragility Index	2 (IQR 1 – 3.5)
% with Fragility Index ≤ 1	40%

Lobo. CCM 2019; 47: 486-8. Summary of 4 SRs
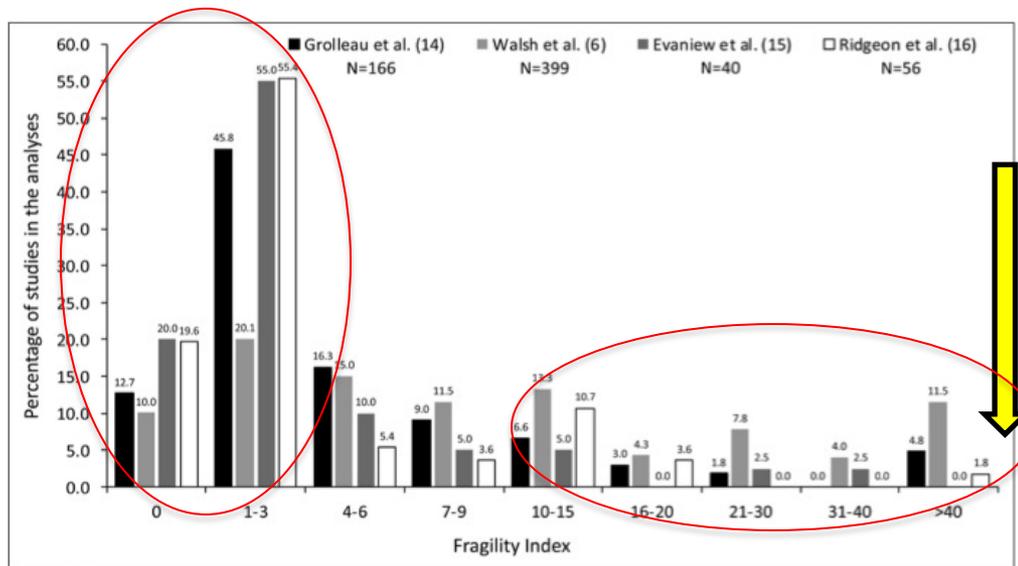
COVID-19 Infection

Vaccine	Placebo	P
14134	14073	
11 (0.08%)	185 (1.31%)	0.0000001

Fragility Index	139

Figure 1. Fragility index of randomized controlled trials analyzed in four systematic reviews (6, 14–16).

PROGRESS   **& PERIPETEIA**
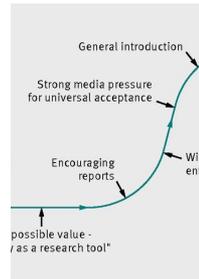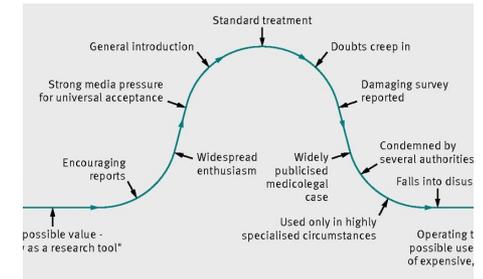
Early Promising Finding – True PROGRESS or Mere PERIPETIEA?

| Flaws | ➡ | Rigorous Methods |
| Fragility | ➡ | Robust Findings |

THE FORMULA

Why Most Published Research Findings Are False Ioannidis. PLoS Medicine 2005; 2(8): e124.

John P. A. Ioannidis

A flawless RCT in patients with ARDS demonstrates that a new drug reduced the 28-day mortality from 46% to 30%. (P < 0.05). Methodology and statistical analysis are flawless. Alpha and beta errors were set at 0.05 and 0.2, respectively.

What is the probability that the drug is truly effective?

For a RCT that is AE ➡ Is the Intervention TE?

$$\text{Odds}_{\text{pretrial}} = \text{TE / TNE} = R$$

$$\text{Odds}_{\text{post-trial}} = 16*\text{Odds}_{\text{pretrial}}$$

$$P[TE|AE] = \frac{16R}{16R + 1}$$

a. About 5%

b. About 20%

c. About 50%.

d. About 80%.

e. About 95%.

Hypothesis Testing Revisited

All Interventions for a Disease

TE TNE

AE (P < 0.05)

ANE (P > 0.05)

(1−β) TE   α TNE

β TE   (1−α) TNE
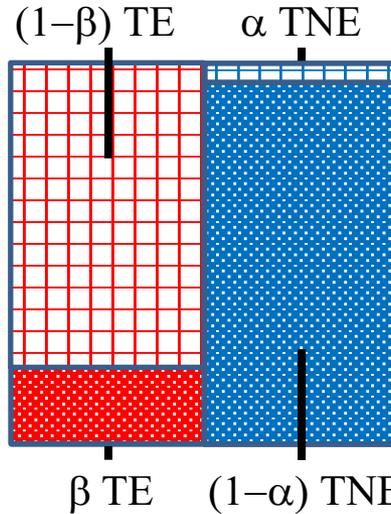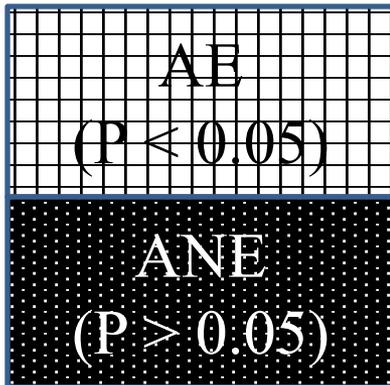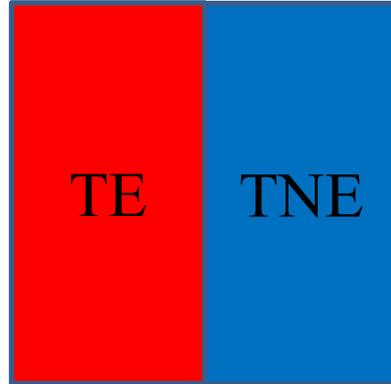
$Odds_{Posttrial} = LR * Odds_{Pretrial}$

What is the H_0?

What is an α error?

What is the H_A?

What is a β error?

$Odds_{Pretrial} = R = H_A / H_0 = TE / TNE$

RCT is AE (P < 0.05), Is It True?

$$Odds_{Posttrial} = \frac{(1−β)\ TE}{α\ TNE} = 16R$$

$$P[TE|AE] = \frac{16R}{16R + 1}$$

Probability = Odds / (1 + Odds)

Hypothesis Testing Revisited

All Interventions for a Disease
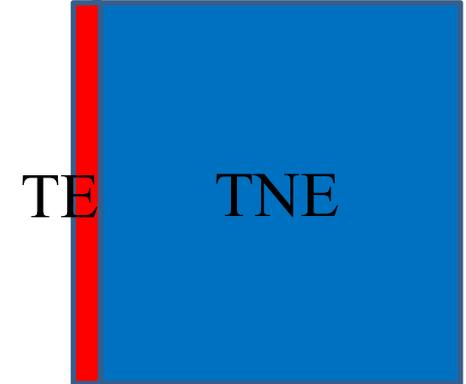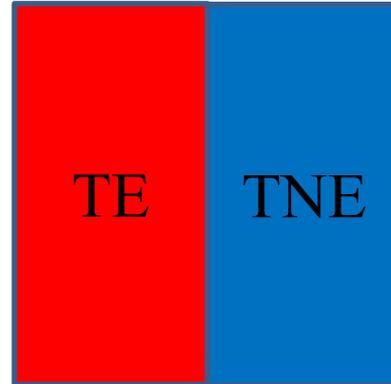
TE   TNE

TE   TNE

A well designed RCT shows the drug to be beneficial for a disease ($P < 0.05$)

$$\text{Odds}_{\text{Pretrial}} = R = \text{TE} / \text{TNE}$$

$1 / 1 = 1$ $1 / 16$

$$\text{Odds}_{\text{Posttrial}} = \text{LR} * \text{Odds}_{\text{Pretrial}}$$

$$\text{Odds}_{\text{Posttrial}} = \frac{(1-\beta)\ \text{TE}}{\alpha\ \text{TNE}} = 16R$$

$16*1 = 16$ $16*(1/16) = 1$

P drug works = Odds / (1 + Odds) $16 / 17 = 94\%$ $1 / 2 = 50\%$

PROGRESS
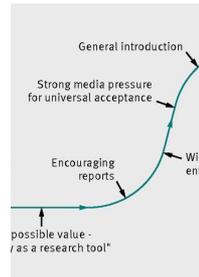
& PERIPETEIA
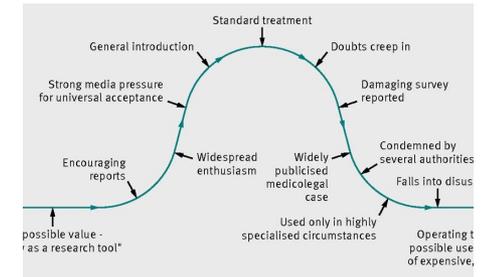
SUMMARY:

Modern medicine has undoubtedly made tremendous PROGRESS in improving health outcomes!

However, HYPE or PERIPETEIA (medical reversals) is also common as many early promising findings are later found to be false.

Early Promising Findings – True PROGRESS or Mere PERIPETIEA?

Fragility ⟹ Robust Findings

Flaws ⟹ Rigorous Methods

Formula ⟹ $Odds_{post\text{-}trial} = LR * R$

Reproducible Findings (SR)

Real World Confirmation