The therapeutic validation

of

L o n g C o v i d.

Keynote address for the National Academies of Sciences, Engineering, and Medicine.

Jeremy Samuel Faust MD MS, June 23, 2023

Disclosures

- ***MedPage Today.***
- ***Annals of Emergency Medicine.***
- ***Inside Medicine (Substack).***

What I do every day in the emergency department.

No diagnosis, no treatment. ☹

Right diagnosis, right treatment. 😊

Wrong diagnosis, wrong treatment.

Matters. ☹

Does not matter. 🤷‍♂️

Scenario #1

“Doc, your patient has a hemoglobin of 5.6, their heart rate is 120, and the blood pressure is 80/50.”

“Do you want to transfuse them with packed red blood cells?”

A. Yes. Heck yes.
B. No. Heck no.
C. Depends, what is the cause of their anemia?

1. Iron-Deficiency Anemia
2. Vitamin-Deficiency Anemia
3. Aplastic Anemia
4. Hemolytic Anemia
5. Sickle Cell Anemia
6. Thalassemia
7. Pernicious Anemia
8. Fanconi Anemia
9. Diamond-Blackfan Anemia
10. Autoimmune Hemolytic Anemia

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6. Thala[illegible]
7. Pe[illegible]Ai[illegible]
8. [illegible] Anemia[illegible]
9. [illegible]ond-Blackfan [illegible]ia
10. Autoimmune Hemolytic Anemia

Scenario #2

“Doc, your patient has a fever of 102.6, their heart rate is 130, and the blood pressure is 80/50.”

“Do you want to take our their appendix?”

A. Yes. Heck yes.
B. No. Heck no.
C. Depends, what is the cause of their sepsis?

1. Pneumonia
2. Abdominal Infections
3. Kidney Infections (Pyelonephritis)
4. Bloodstream Infections (Bacteremia)
5. Skin Infections (Cellulitis)
6. Urinary Tract Infections
7. Gallbladder Infections (Cholecystitis)
8. Meningitis
9. Surgical Site Infections
10. Influenza (and other viral infections)

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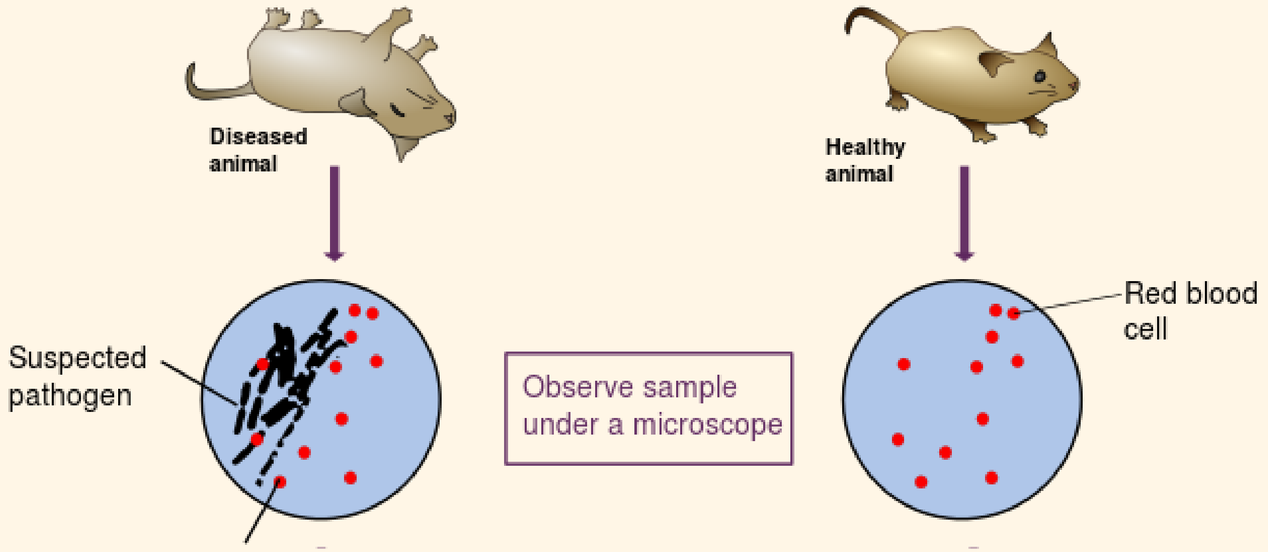
What is a disease?

Koch's Postulates:

① The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.



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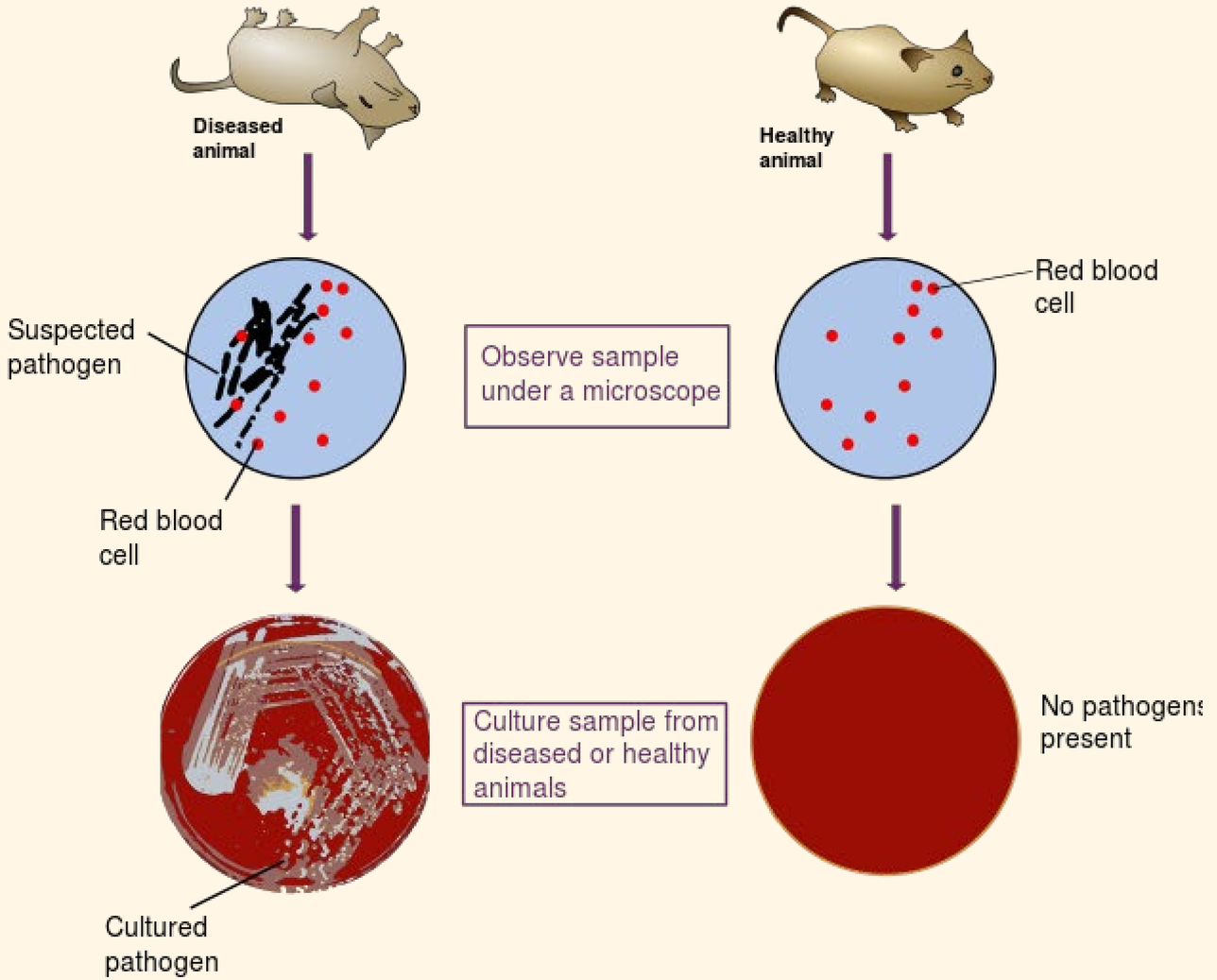

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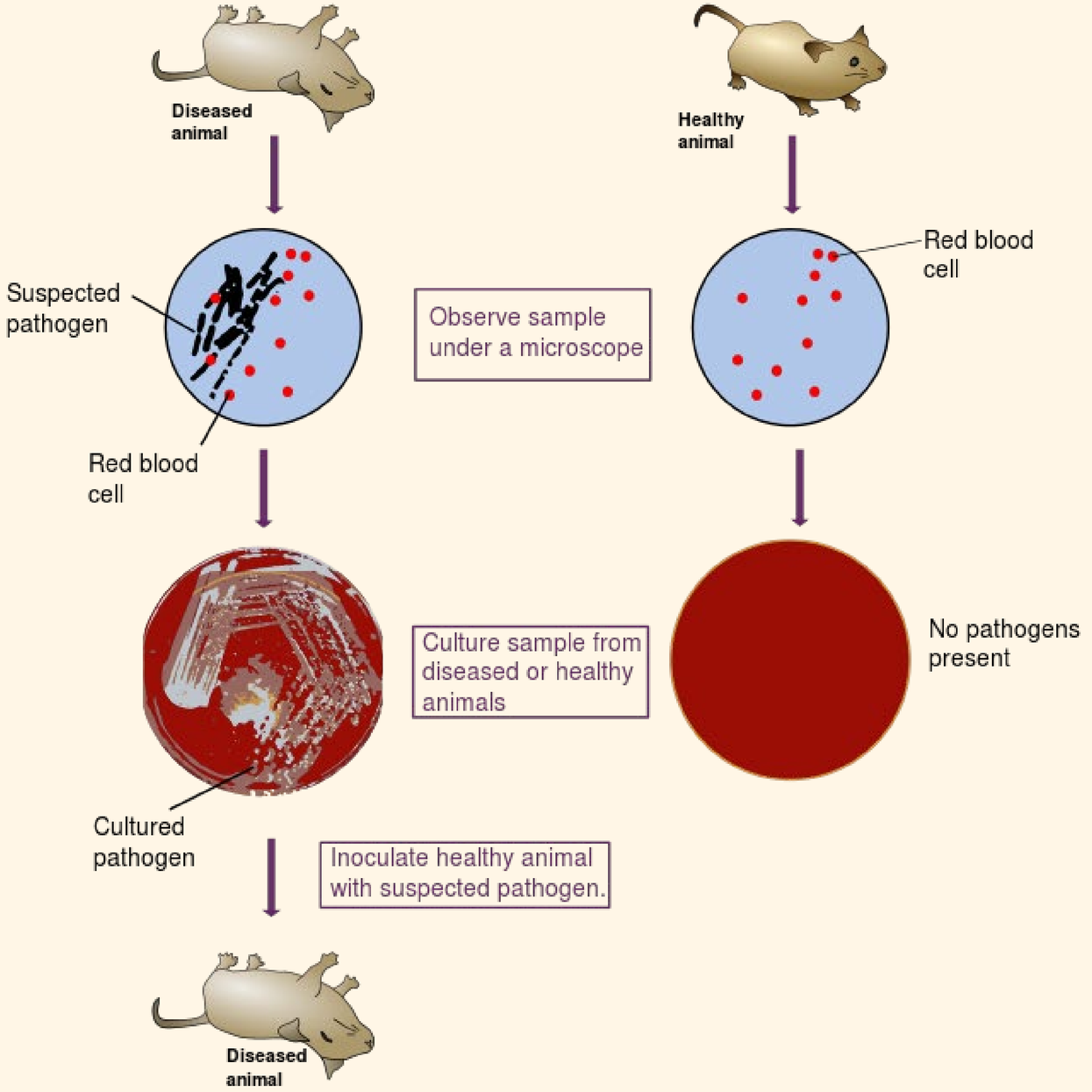

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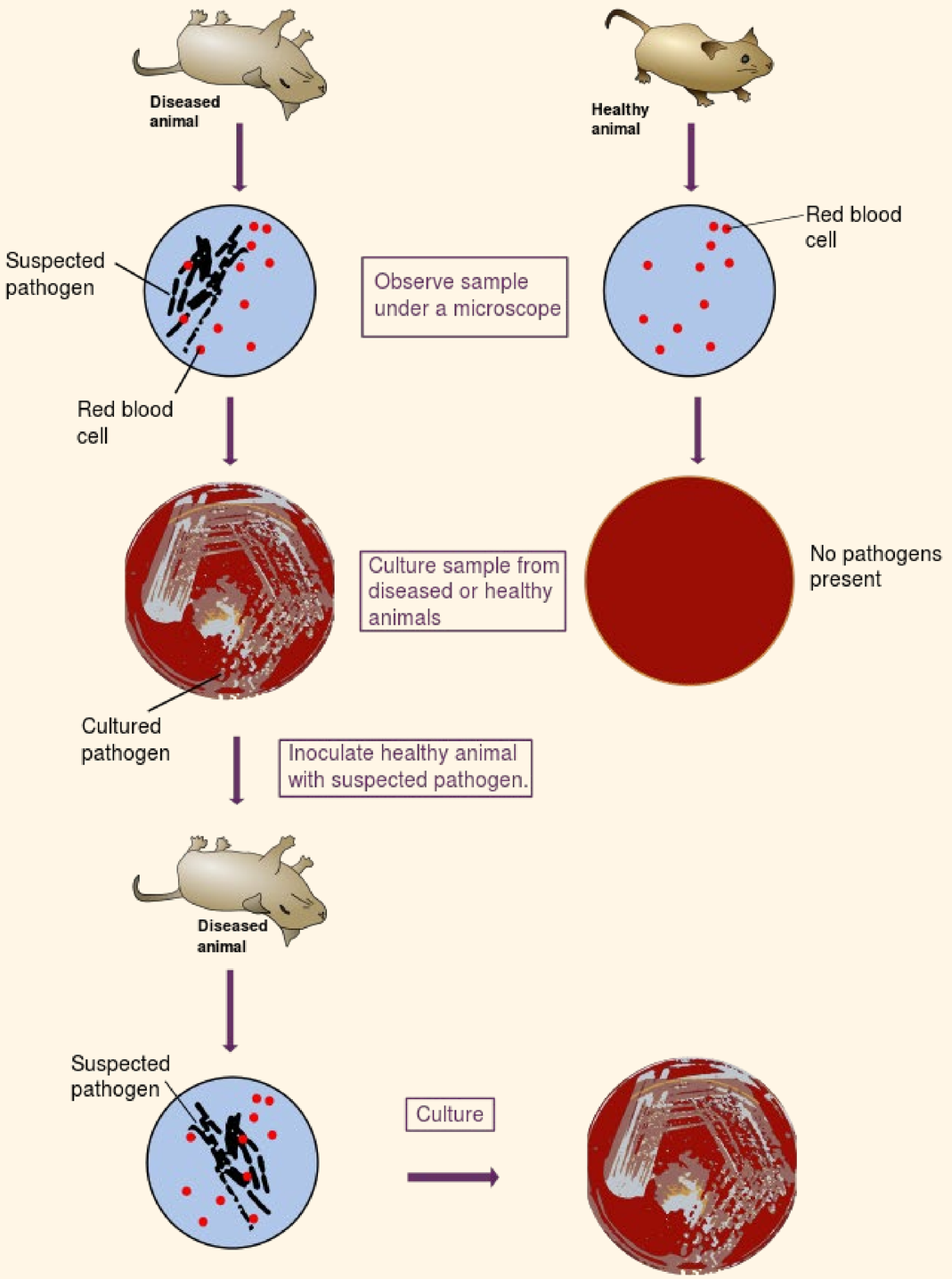
④ The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.



What if we *invert* Koch's postulates?

Koch:
1. Isolate, identify pathogen.
2. Use it to cause disease.

Inverted construct:
1. Identify cohort with illness.
2. Effectively treat disease.

What if we *invert* Koch's postulates?

Recruit volunteers who may have a new disease.

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50% placebo
50% drug

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Volunteers who got the drug do better

=Therapeutic Validation

The therapeutic validation principle.

“A treatment can only be effective if there is something to treat.”
“The efficacy of a medical intervention provides evidence that a disease entity has been adequately characterized.”

- **Requirements**:
- High quality data.
  - Prospective
  - Placebo-controlled
  - Blinded
  - Clinical trial (relevant outcomes).

The therapeutic validation principle.

- **Corollaries**:
- Must only help persons with the disease (e.g., nitroglycerin for chest pain versus medications that relieve pain for variety of conditions).

- Inverse is not necessarily true (e.g., AIDS did not become a disease only after effective treatments were found; amyotrophic lateral sclerosis remains a disease without effective treatments).

The therapeutic validation principle at work

Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial

Carolyn T Bramante, John B Buse, David M Liebovitz, Jacinda M Nicklas, Michael A Puskarich, Ken Cohen, Hrishikesh K Belani, Blake J Anderson, Jared D Huling, Christopher J Tignanelli, Jennifer L Thompson, Matthew Pullen, Esteban Lemus Wirtz, Lianne K Siegel, Jennifer L Proper, David J Odde, Nichole R Klatt, Nancy E Sherwood, Sarah M Lindberg, Amy B Karger, Kenneth B Beckman, Spencer M Erickson, Sarah L Fenno, Katrina M Hartman, Michael R Rose, Tanvi Mehta, Barkha Patel, Gwendolyn Griffiths, Neeta S Bhat, Thomas A Murray, David R Boulware**

The therapeutic validation principle at work

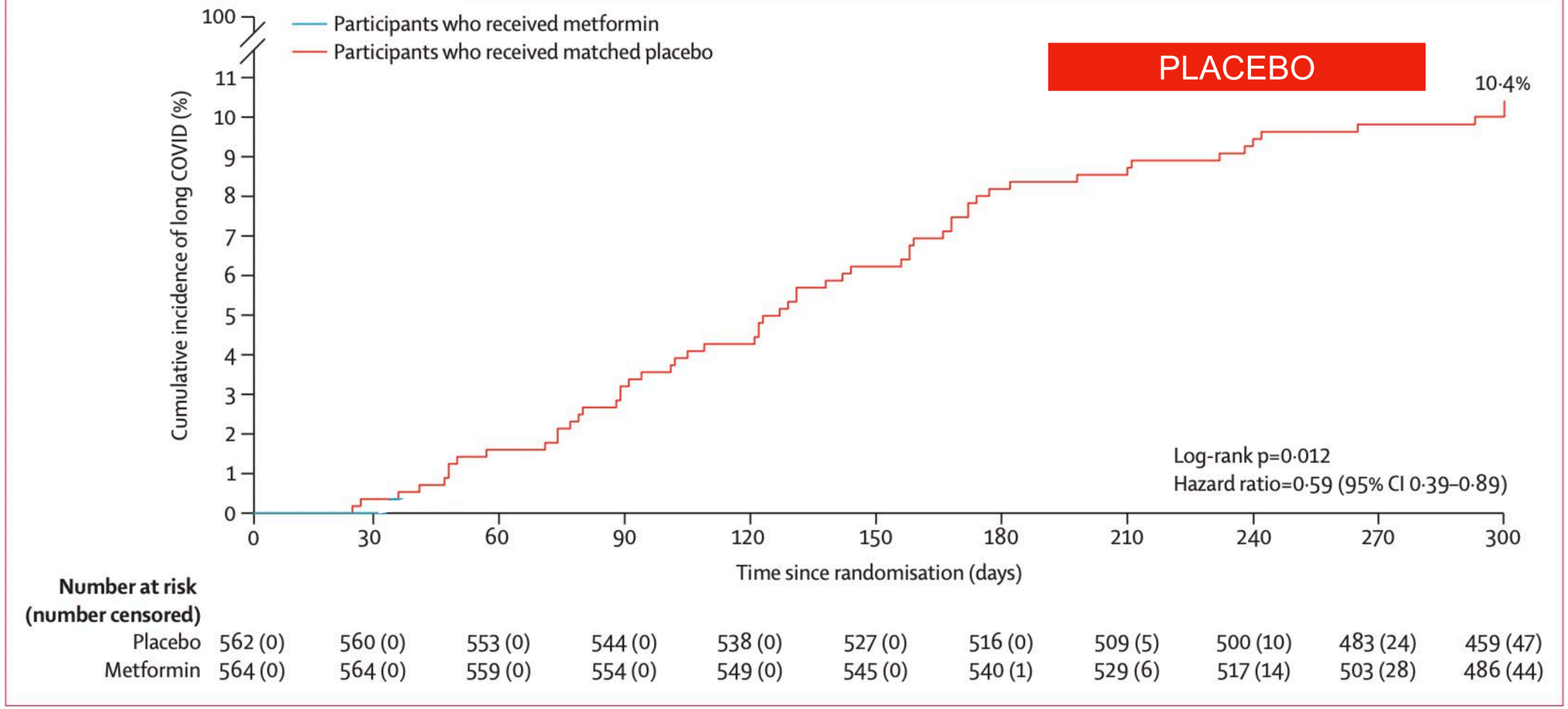
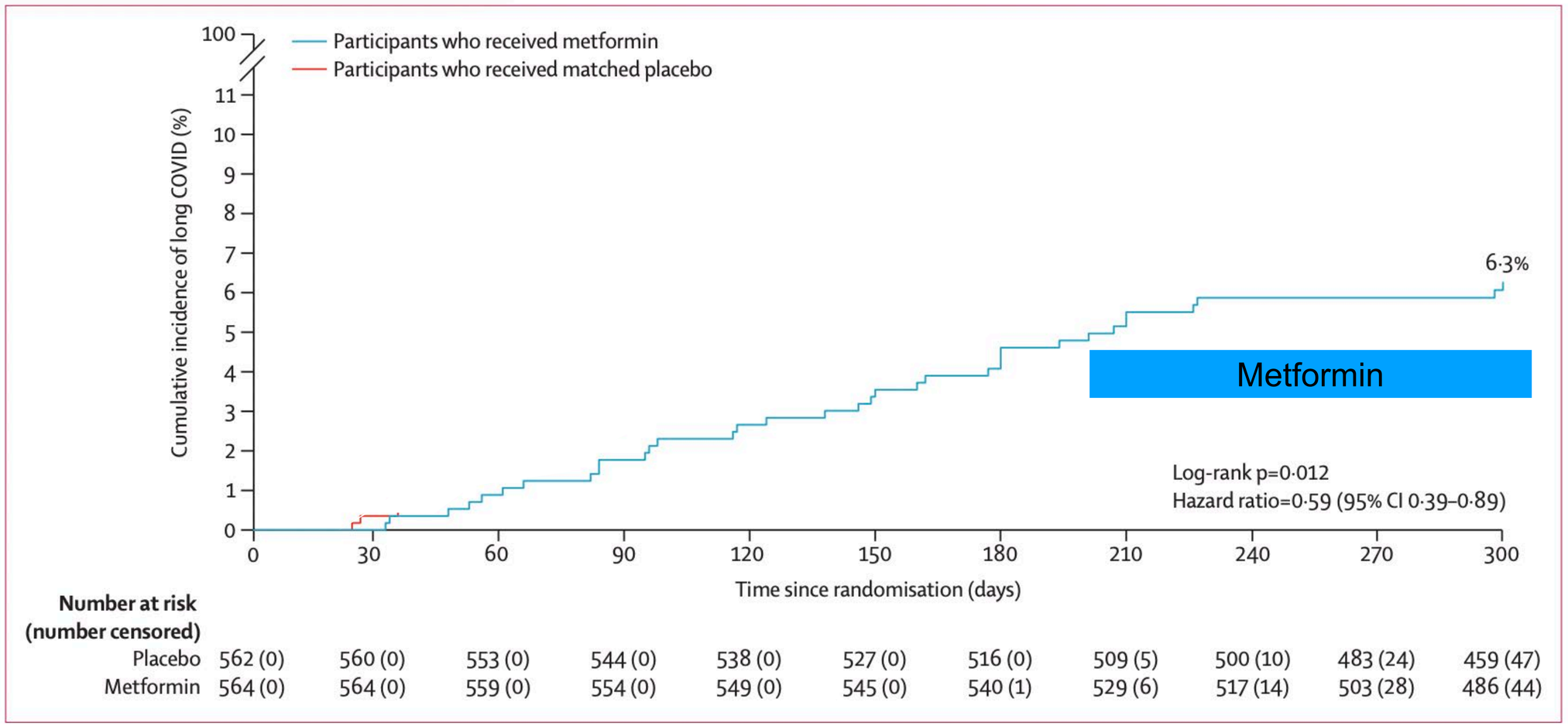


Figure 2: **Cumulative incidence of post-COVID-19 condition (long COVID) diagnoses over 10 months after randomisation**
The absolute risk reduction for metformin compared with matched placebo was 4·1% (95% CI 0·9–7·4).

Bramante et al, Lancet Infectious Diseases, June 2023.

The therapeutic validation principle at work



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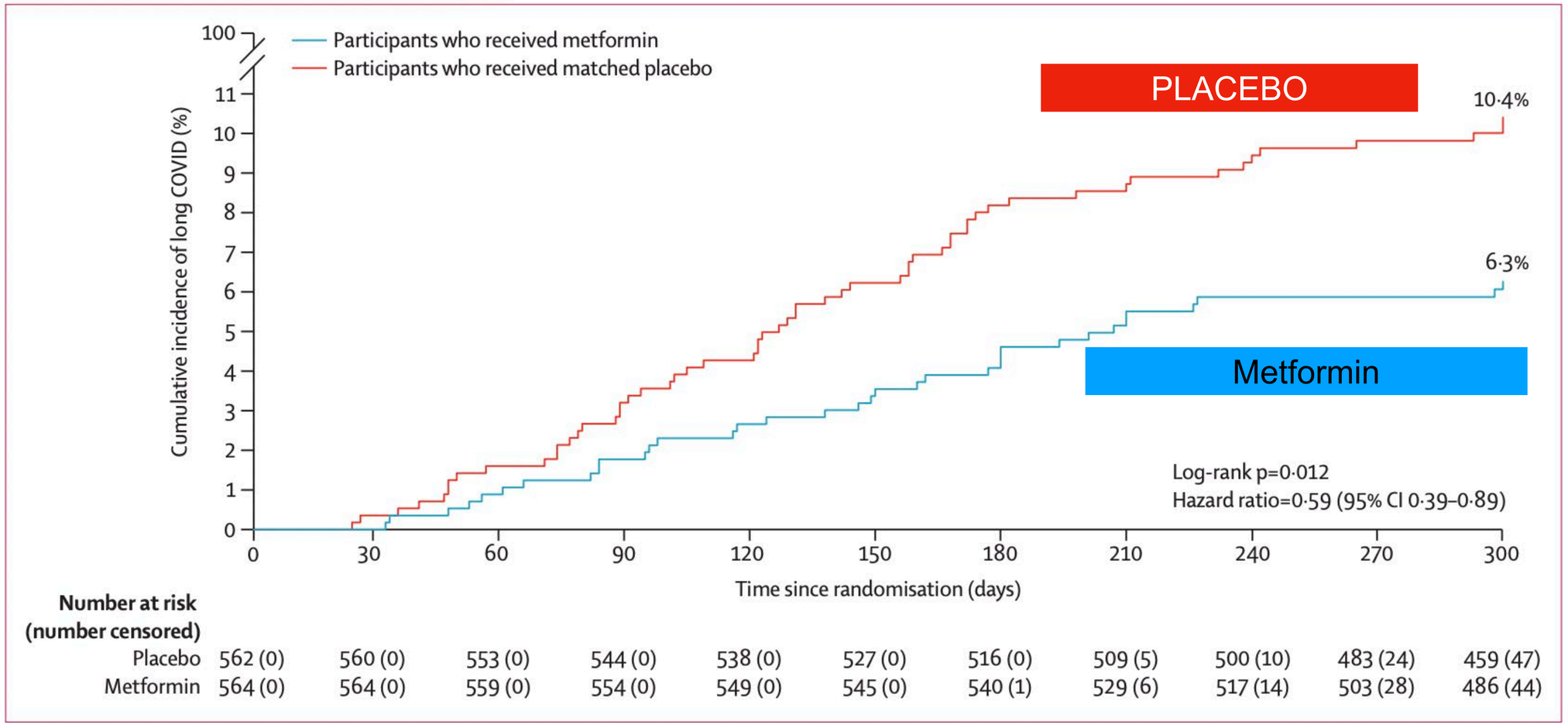

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The therapeutic validation principle.

Applications:

Bramante *et al* Metformin for Long Covid (*Lancet Infectious Diseases*):

•study population had individuals with syndromes similar enough that disease incidence could be modified.

The therapeutic validation principle.

“A treatment can only be effective if there is something to treat.”
“The efficacy of a medical intervention provides evidence that a disease entity has been adequately characterized.”

- **Requirements**:
- High quality data.
  - Prospective
  - Placebo-controlled
  - Blinded
  - Clinical trial (relevant outcomes).

The therapeutic validation principle.

The therapeutic validation of long COVID

Early in the SARS-CoV-2 pandemic, patients alerted medical professionals to post-COVID-19 symptoms that could linger for months. This led to the awareness of post-acute sequelae of SARS-CoV-2, also known as long COVID. In *The Lancet Infectious Diseases*, Carolyn Bramante and colleagues[1] report the results of a prospective, multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial that evaluated the effect of early outpatient COVID-19 treatment on the incidence of long COVID. The authors found that long COVID incidence was reduced by a 14-day course of metformin when initiated early in the acute infection phase. The cumulative incidence of long COVID by day 300 was 6·3% (95% CI 4·2–8·2) in participants who received metformin and 10·4% (7·8–12·9) in those who received matched placebo (hazard ratio 0·59, 95% CI 0·39–0·89; p=0·012).

Varying case definitions for long COVID have been proposed.[2–4] Because of this variation and the overlap with common less understood symptoms or chronic conditions found in the general population, many have expressed concerns that current long COVID definitions are too vague to be medically useful; there are no pathognomonic features, nor are there established reliable biomarkers or tests that can definitively establish the diagnosis.[5] It is feared that some patients have received the diagnosis erroneously and might have other conditions that would benefit from diagnosis and treatment.[6]

Therefore, if confirmed, the findings from the study by Bramante and colleagues[1] are profound and potentially landmark on two distinct counts. First, to our knowledge, this is the first high-quality evidence from a randomised controlled trial to show that the incidence of long COVID can be reduced by a medical intervention, metformin—an inexpensive treatment with which clinicians have ample experience. Second, the authors have, perhaps inadvertently, made an important contribution to medical epistemology. If a new disease has been sufficiently well characterised by clinicians so that it can be successfully modified by a therapy compared with placebo, then the entity must, from a practical standpoint, truly exist. Put differently, a treatment can only be effective if there is something to treat.

We might name this concept the therapeutic validation principle. It is, in a sense, an inversion of Koch's postulates. In the 1880s, Robert Koch showed that if a pathogen isolated from an organism with a particular disease caused the disease when introduced into another, a causative agent had been found. The therapeutic validation principle would state that the identification of an effective treatment (administered to a population suspected to have a condition) inherently confirms the existence of a new or contested entity. A corollary to this is that the evidence must be of sufficient quality to be dispositive. Data from randomised, blinded trials are important to overcome confirmation bias and placebo effects. These features are what distinguish the findings from Bramante and colleagues[1] and make them so compelling.

We usually think of validation—the confirmation of a previous finding—as evidence supporting a particular medical intervention. Here, the construct is inverted; the efficacy of a medical intervention provides evidence that a disease entity has been adequately characterised. This is not to say that the various diagnostic criteria for long COVID now in use are sufficient; however, the present study suggests that these definitions are at least satisfactory to have identified a cohort capable of generating statistically meaningful findings in a high-quality clinical trial. By contrast, if the disease were insufficiently characterised, even the most well-conducted trial would be incapable of producing a positive finding, as it would be nearly impossible to power (ie, the sample size would have to be extremely large for statistical signals to emerge). We cannot modify diseases that do not exist or that are so poorly understood that the affected populations are elusive.

Generally, the concept of the therapeutic validation principle must be correctly applied to be useful. An important corollary to the framework would be that an applied treatment only helps those with a particular disease. A familiar example in clinical practice is the use of nitroglycerin to assess chest pain. If pain resolves after receipt of nitroglycerin, that indicates a coronary cause of the pain. However, analgesics (eg, non-steroidal anti-inflammatory drugs or opioids) that are effective for a variety of conditions do not carry the same implications, nor does the absence of a response necessarily imply the

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Inside Medicine

Did a clinical trial just "prove" that Long Covid really exists?

JEREMY FAUST, MD
JUN 9, 2023

53 6 Share

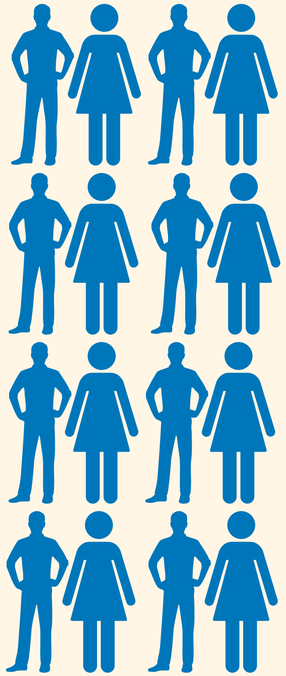
On one hand, there are some who believe Long Covid afflicts 43% of Covid patients. On the other, some commentators say Long Covid is basically psychosomatic.

Neither extreme is correct.

And yet more than 3 years into the pandemic, the search for an objective medical finding that clinches a Long Covid diagnosis—be it blood markers, lung tests, specific cognitive tests, imaging—has come up short. As Derek Lowe wrote in a blog for the journal *Science*, "[S]o far there are no diagnostic findings that would allow you to even say for sure *that post-Covid even exists, biochemically.*"

Not everything has been ruled out. Nothing reliable has been ruled in. Right now, Long Covid diagnoses are made based on our best aggregations of commonly reported symptoms.

PLACEBO



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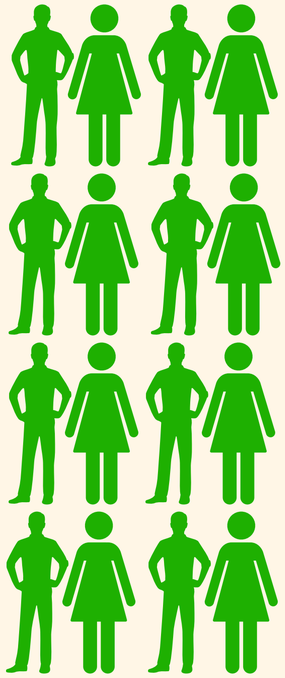

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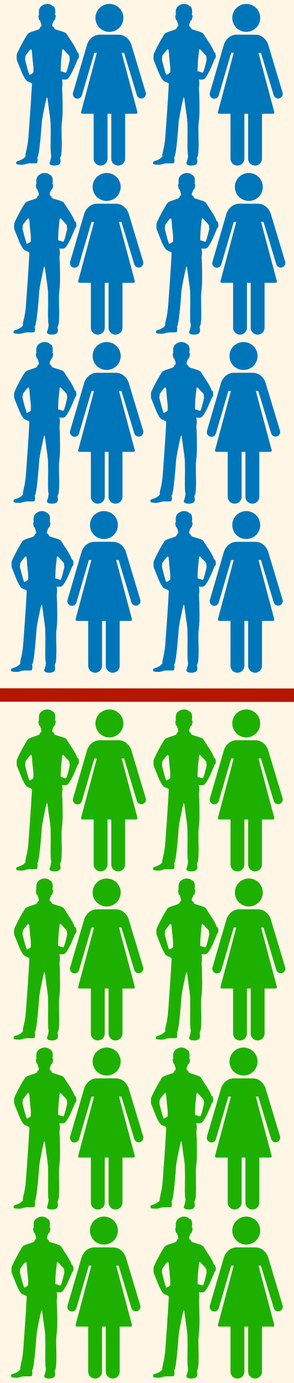
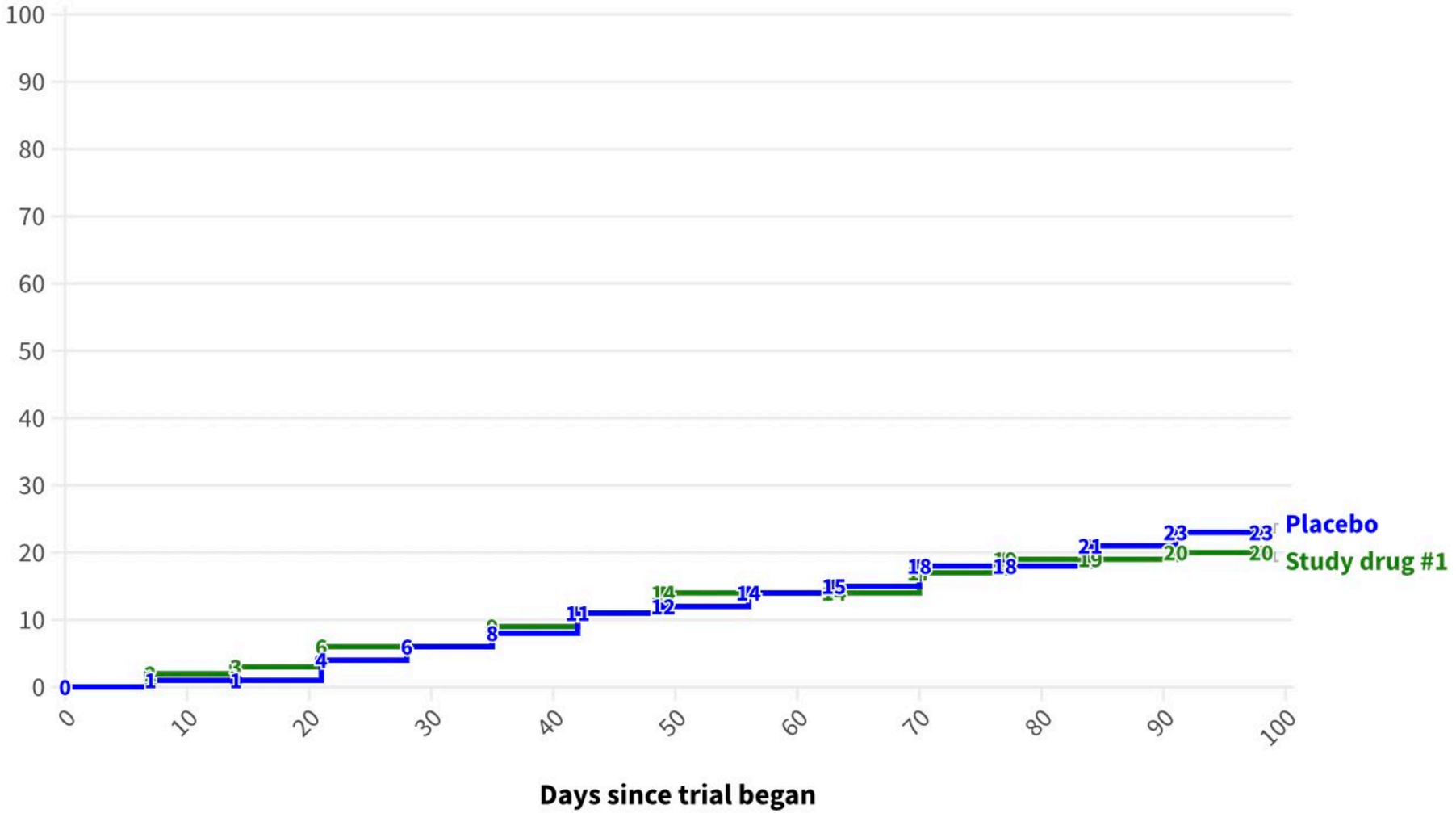
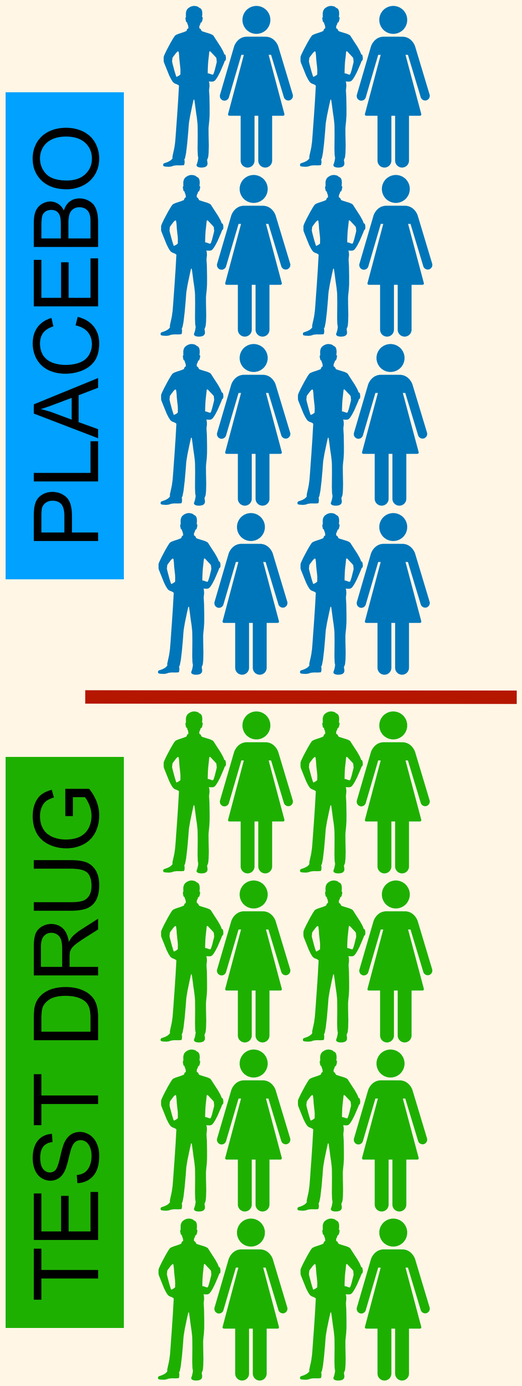


Does a drug being studied decrease symptoms by 10% or more?



INSIDEMEDICINE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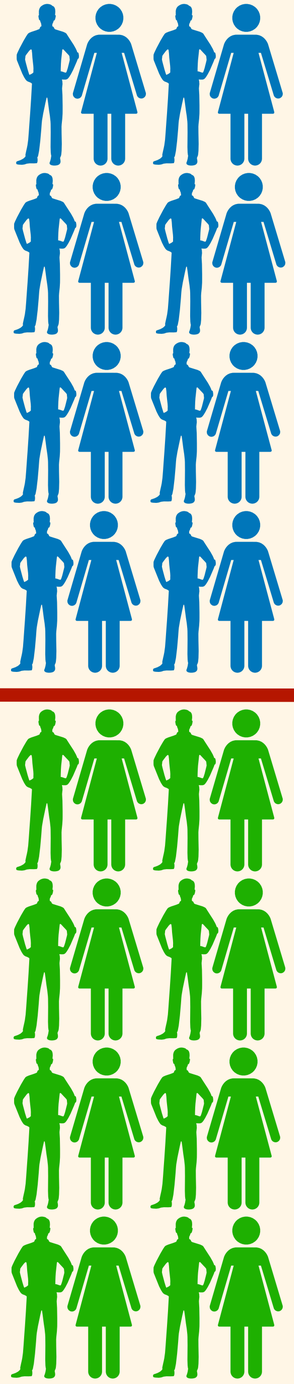

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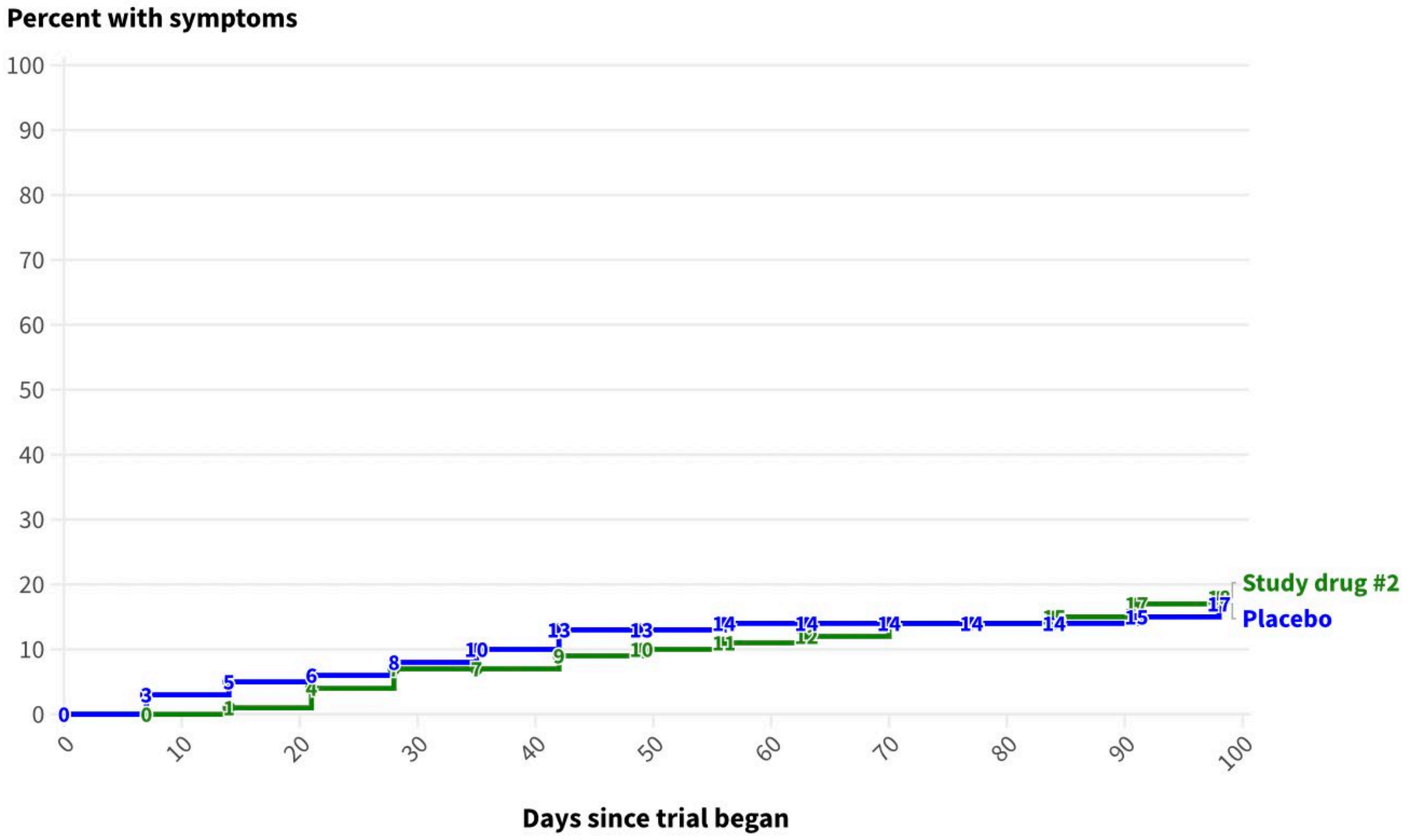


INSIDEMEDICINE

Case study:
Pre-exposure prophylaxis (PREP) for HIV

What is our study population?

What is our study population?

What are our goals?

1. Difference ≥1% (absolute)

2. Number needed to treat to prevent 1 bad outcome: less than 500

50,000 people

(Everyone, regardless of risk)

50,000 people

(Everyone, regardless of risk)

50% placebo
50% PREP

Outcome

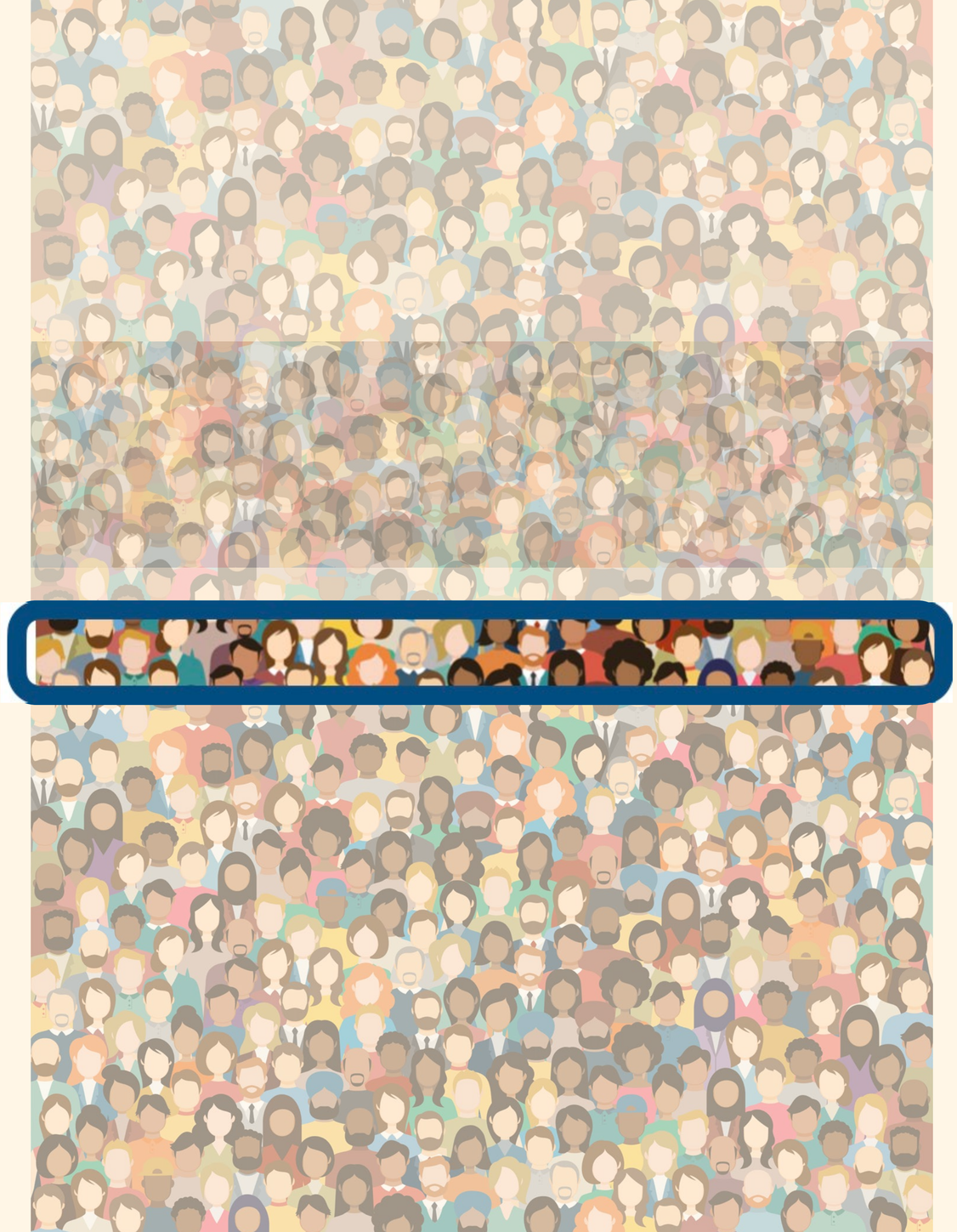
Placebo	PREP
49,995 (-)	49,997 (-)
5 (+)	3 (+)
0.01% (+)	0.006% (+)

Difference=0.004%

Number needed to treat=25,000

200 people

50% placebo
50% PREP

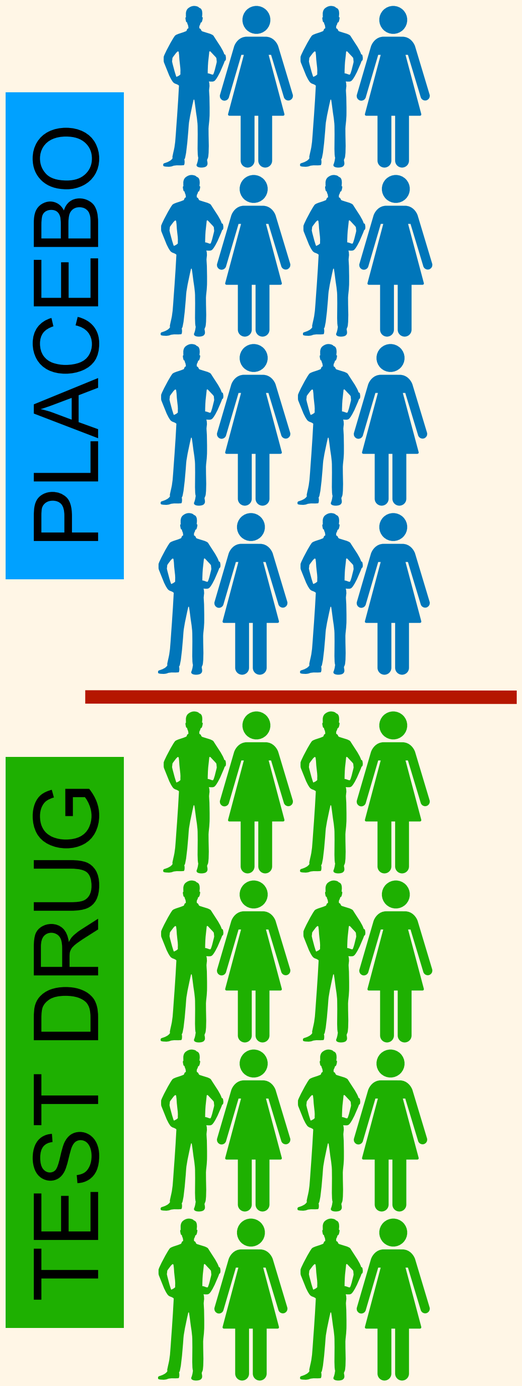


Outcome

Placebo	PREP
195 (-)	197 (-)
5 (+)	3 (+)
2.5% (+)	1.5% (+)

Difference=1%

Number needed to treat=100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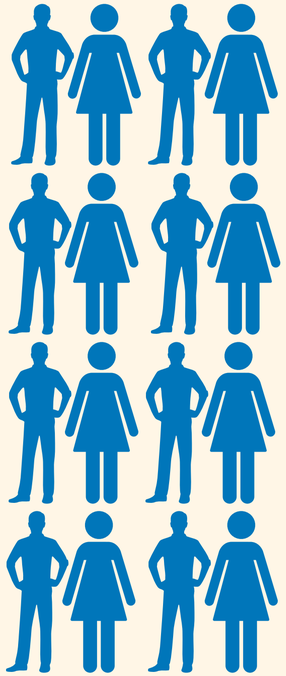

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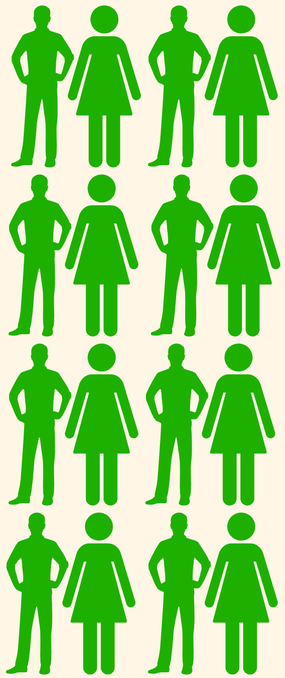

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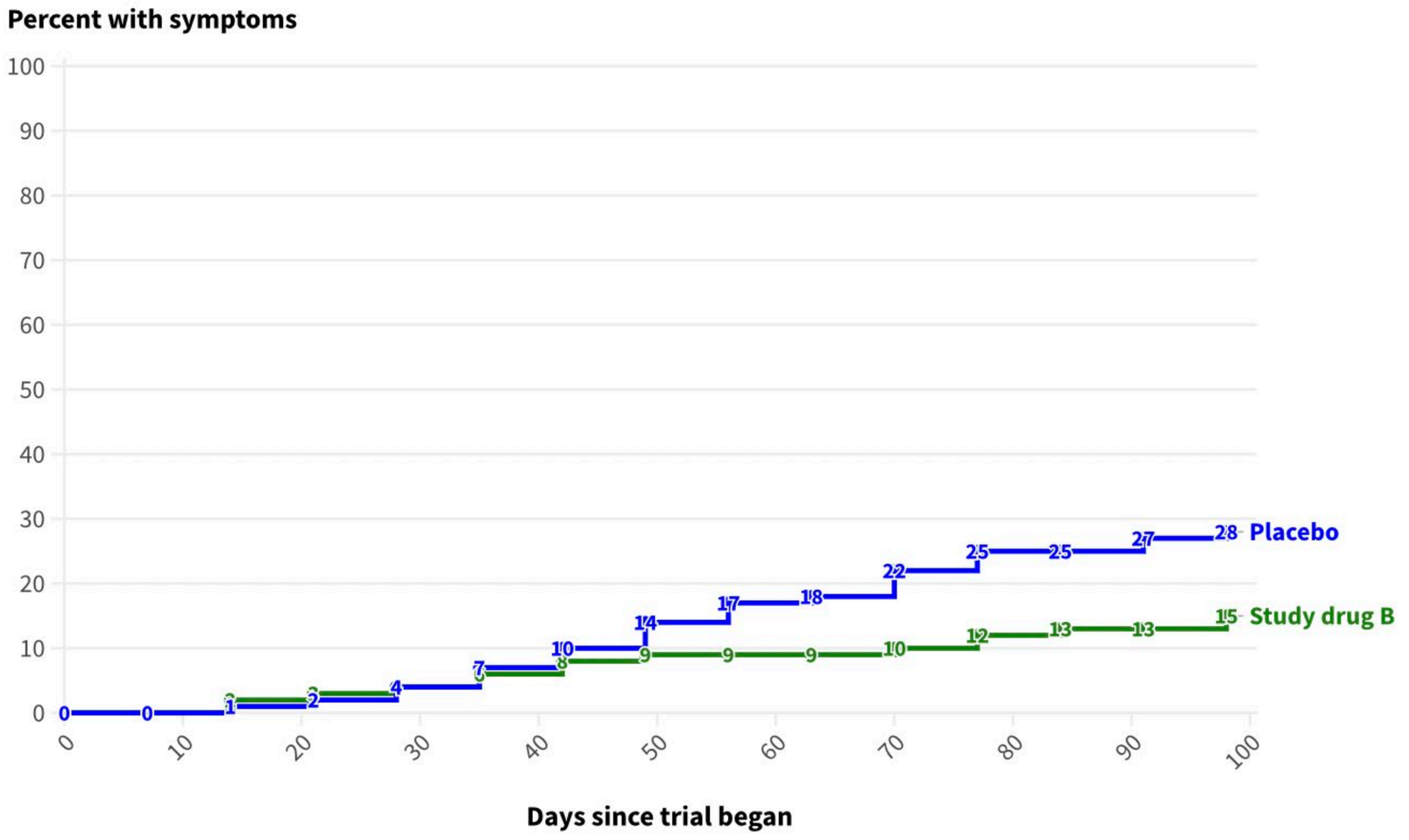

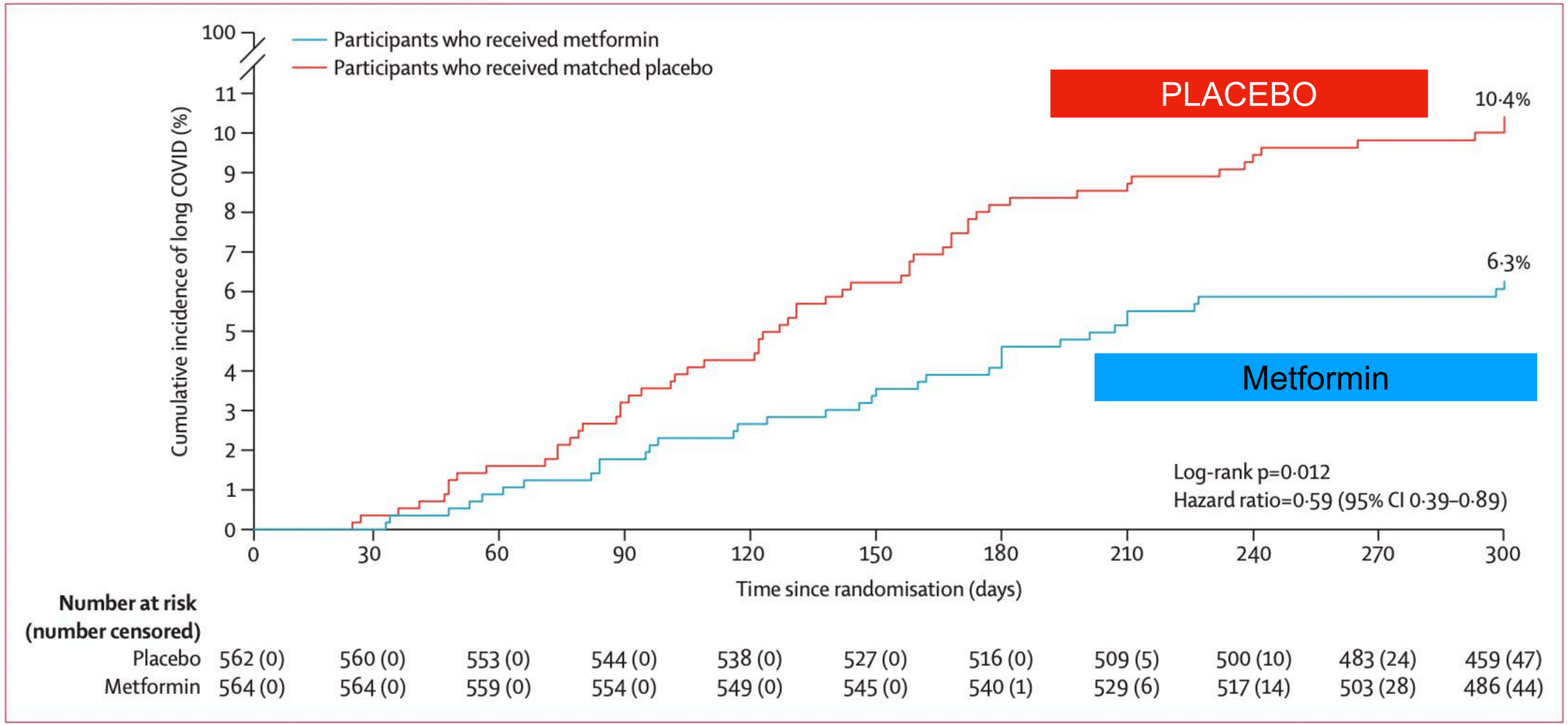

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The challenge…

Option #1: Big tent

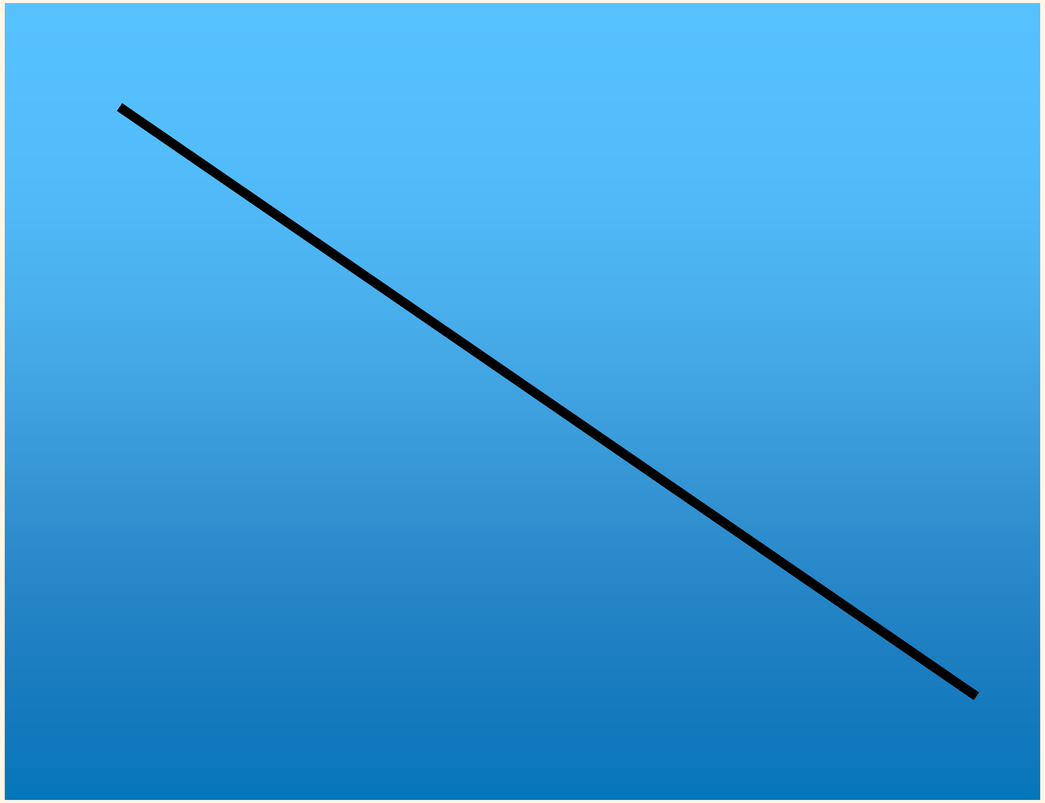
Option #2: Multiple smaller tents

Every disease is a construct. What is the point of the construct?

- Identify illness/ validate suffering
- Find preventions and treatments

The search for treatments for incompletely understood illnesses.

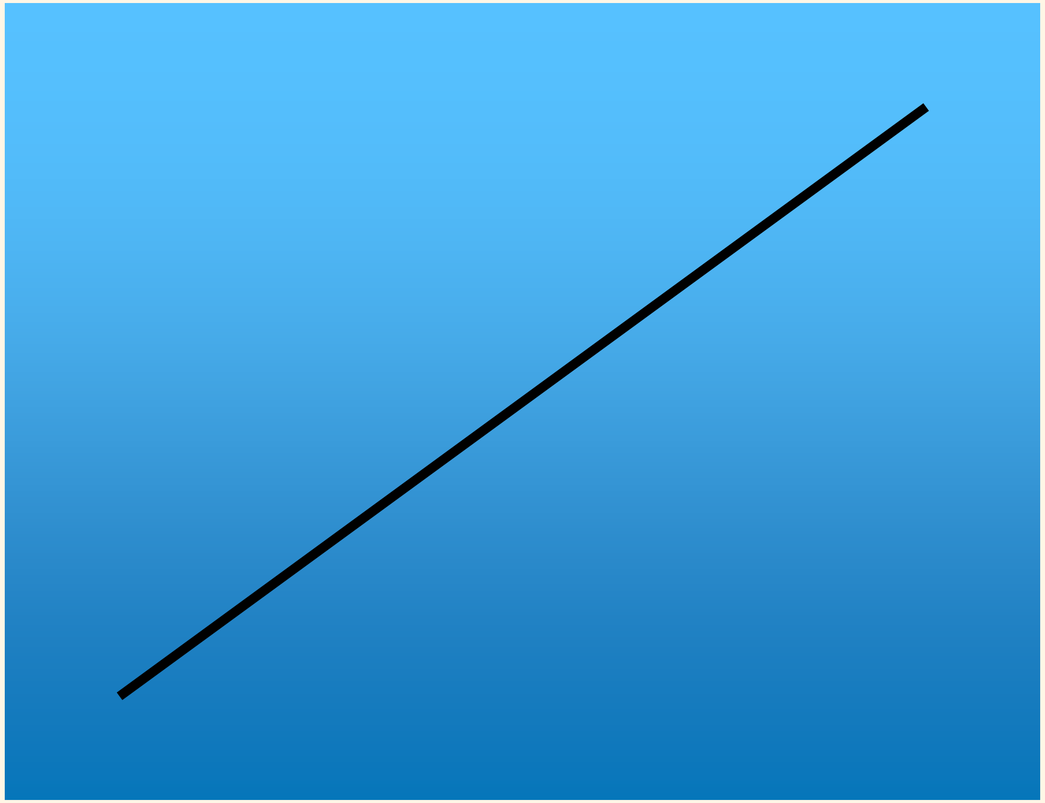
Likelihood of finding an effective treatment



Inclusiveness of definition

The search for treatments for incompletely understood illnesses.

Likelihood of *mistakenly dismissing* an effective treatment



Strict/narrow Liberal/wide

Inclusiveness of definition

The stakes are high.

Diagnosis and treatment mismatches.

- **Sepsis phenotypes (missed opportunity)**

The stakes are high.

Diagnosis and treatment mismatches.

- **Myocardial infarction versus aortic dissection (harm)**

The challenge, the tension, the mission:

Desire to be inclusive *versus* desire to find therapies.