5-14-2021

Forum 5: Understanding Vaccine Efficacy and Effectiveness: A Statistician's Perspective/Open Access STEM research

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Vaccine Efficacy & Effectiveness

A Statistician's Perspective

Dr. Jyotishka Datta, Virginia Tech, Statistics.

"The inspiration of the camel image is that it represents the dedication of the world to bring vaccines to everyone."

- Halloran et al. (2009), *Design & Analysis of Vaccine Studies*

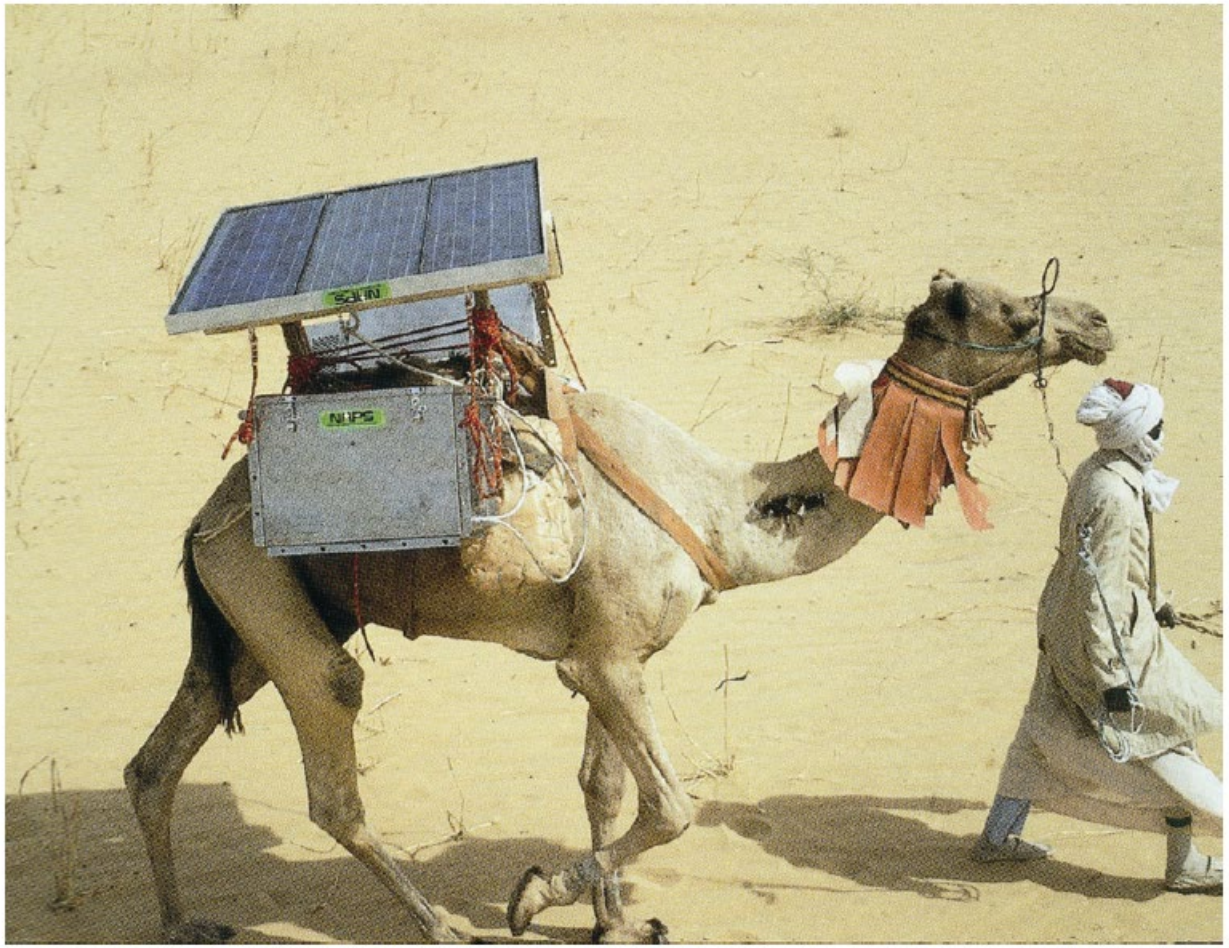

Fig. 0.1 Camel with a refrigerator powered by solar electricity with vaccines being kept in the cold chain. Image courtesy of Naps Systems Oy, Finland.

On May 10, 2021

If the committee endorses the vaccine for that age group, as expected, immunizations in theory could begin immediately. Clinical trials have shown that these children may safely receive the dose already available for adults.

In a clinical trial, Pfizer and BioNTech enrolled 2,260 participants ages 12 and 15 and gave them either two doses of the vaccine or a placebo three weeks apart. The researchers recorded 18 cases of symptomatic coronavirus infection in the placebo group, and none among the children who received the vaccine, indicating that it was highly effective at preventing symptomatic illness.

MATTER

2 Companies Say Their Vaccines Are 95% Effective. What Does That Mean?

You might assume that 95 out of every 100 people vaccinated will be protected from Covid-19. But that's not how the math works.

November 20, 2020, New York Times, Carl Zimmer

Efficacy

- Vaccine efficacy (and vaccine effectiveness), VE, are generally estimated as one minus some measure of relative risk, RR, in the vaccinated group compared to the unvaccinated group:

$$VE = 1 - RR$$

- The groups being compared could be composed of individuals or of populations or communities.

Pfizer

GROUP	GROUP SIZE	NUMBER INFECTED	INFECTION RISK	US POP.
Placebo	21,830	162	162/21830= 0.74%	2.5 million
Vaccine	21830	8	8/21830 = 0.04%	131,000

- Pfizer recruited 43,661 volunteers and waited for 170 people to come down with symptoms of Covid-19 and get a positive test.
- Out of these 170, 162 were from the 'placebo' group and just eight were from the 'vaccine' group.
- (Groups are randomly allocated)

Efficacy

- Recall, VE = 1 – RR = 1 - (risk for vaccine group)/(risk for placebo)
- Placebo group's infection risk: 0.74%
- Vaccine group's infection risk: 0.04%
- VE = 1 – 0.04/0.74 = (0.74 - 0.04)/0.74 = 0.95
- This captures the difference in impact by scaling the percentage point difference in risks by the original infection risk.
- What factors influence efficacy? How do we control for age, gender, ethnicity, co-morbidities etc.?

What does 95% COVID-19 vaccine efficacy really mean?

It is imperative to dispel any ambiguity about how vaccine efficacy shown in trials translates into protecting individuals and populations. The mRNA-based Pfizer[1,2] and Moderna[3] vaccines were shown to have 94–95% efficacy in preventing symptomatic COVID-19, calculated as 100 × (1 minus the attack rate with vaccine divided by the attack rate with placebo). It means that in a population such as the one enrolled in the trials, with a cumulated COVID-19 attack rate over a period of 3 months of about 1% without a vaccine, we would expect roughly 0·05% of vaccinated people would get diseased. It does not mean that 95% of people are protected from disease with the vaccine—a general misconception of vaccine protection also found in a *Lancet Infectious Diseases* Editorial.[4]

In the examples used in the Editorial, those protected are those who would have become diseased with COVID-19 had they not been vaccinated. This distinction is all the more important as, although we know the risk reduction achieved by these vaccines under trial conditions, we do not know whether and how it could vary if the vaccines were deployed on populations with different exposures, transmission levels, and attack rates.

Simple mathematics helps. If we vaccinated a population of 100 000 and protected 95% of them, that would leave 5000 individuals diseased over 3 months, which is almost the current overall COVID-19 case rate in the UK. Rather, a 95% vaccine efficacy means that instead of 1000 COVID-19 cases in a population of 100 000 without vaccine (from the placebo arm of the abovementioned trials, approximately 1% would be ill with COVID-19 and 99% would not) we would expect 50 cases (99·95% of the population is disease-free, at least for 3 months).

Accurate description of effects is not hair-splitting; it is much-needed exactness to avoid adding confusion to an extraordinarily complicated and tense scientific and societal debate around COVID-19 vaccines.

I declare no competing interests.

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1 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020; 383: 2603–15.
2 Pfizer. Pfizer-BioNTech COVID-19 vaccine (BNT162, PF-07302048). Vaccines and Related Biological Products Advisory Committee briefing document. https://www.fda.gov/media/144246/download (accessed Jan 29, 2021).
3 US FDA. Vaccines and Related Biological Products Advisory Committee meeting December 17, 2020. https://www.fda.gov/media/144434/download (accessed Jan 29, 2021).
4 The Lancet Infectious Diseases. An exceptional vaccination policy in exceptional circumstances. *Lancet Infect Dis* 2021; **21**: 149.

Lancet Infect Dis 2021
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February 17, 2021
https://doi.org/10.1016/S1473-3099(21)00075-X

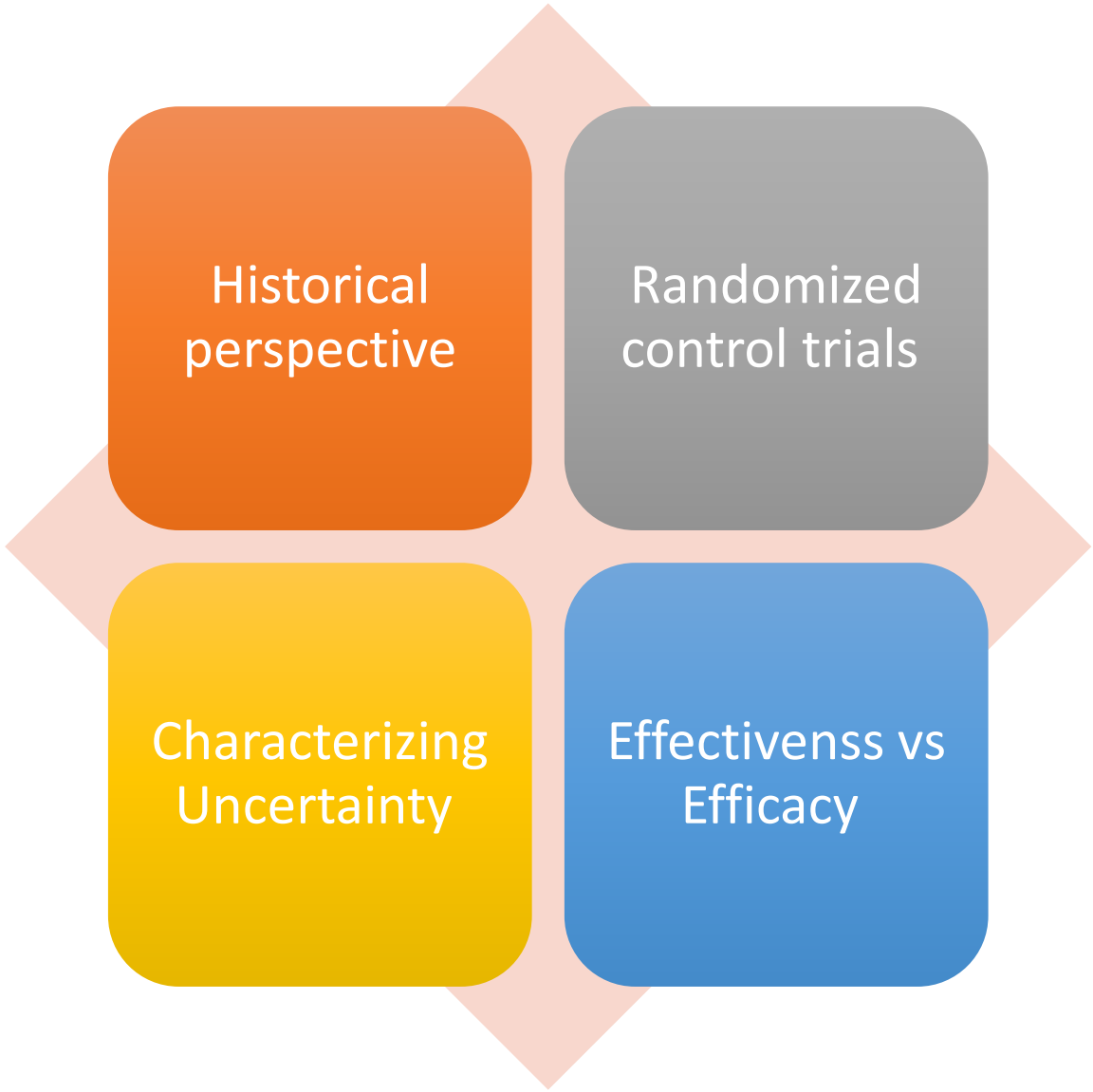
Piero Olliaro, "What Does 95% COVID-19 Vaccine Efficacy Really Mean?"

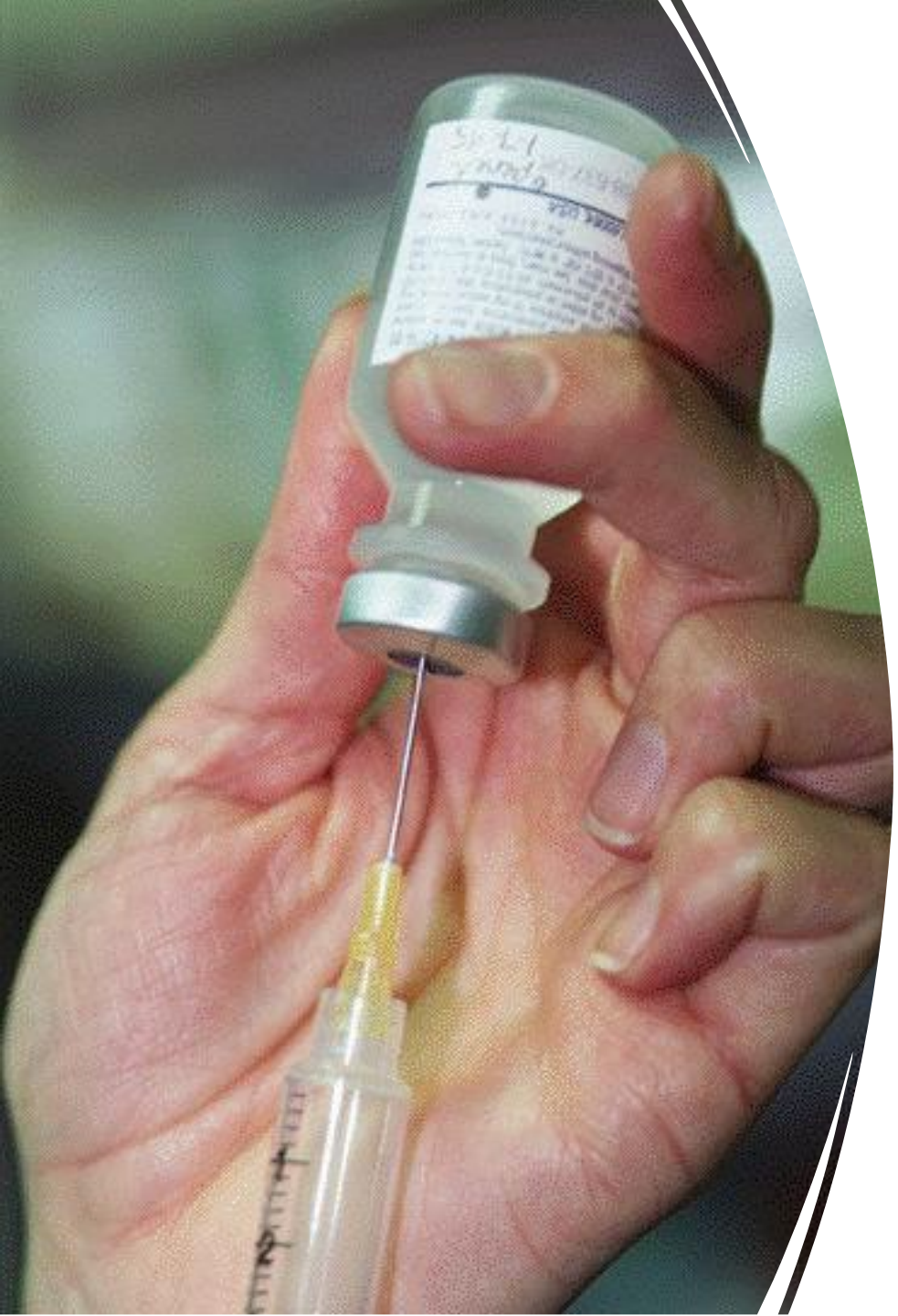
Quote from the letter

- "The mRNA-based Pfizer and Moderna vaccines were shown to have 94–95% efficacy in preventing symptomatic COVID-19, calculated as 100 × (1 minus the attack rate with vaccine divided by the attack rate with placebo)."
- "It means that in a population such as the one enrolled in the trials, with a cumulated COVID-19 attack rate over a period of 3 months of about 1% without a vaccine, **we would expect roughly 0·05% of vaccinated people would get diseased."**
- **"It does not mean that 95% of people are protected from disease with the vaccine**—a general misconception of vaccine protection also found in a Lancet Infectious Diseases Editorial."

Piero Olliaro, "What Does 95% COVID-19 Vaccine Efficacy Really Mean?"

Digging deeper





History of vaccines

History of vaccines

- The word vaccine was derived from Latin word 'vacca' for cow*, when English physician Edward Jenner introduced cowpox-based vaccine against smallpox in 1796.
- Apparently, that story was probably not correct. As an NEJM article showed in 2017 (by analyzing historical containers), the vaccine used to prevent small-pox was horse-pox, and maybe ... we should have called it 'equusine'.

Historical Perspectives

"The fundamental logic behind today's vaccine trials was worked out by statisticians over a century ago."

Section of Epidemiology and State Medicine.

June 4, 1915.

Dr. W. H. Hamer, Vice-President of the Section, in the Chair.

The Statistics of Anti-typhoid and Anti-cholera Inoculations, and the Interpretation of such Statistics in general.

By Mr. Major Greenwood, jun., and Mr. G. Udny Yule.

Through the centuries

- After nearly a 100-years of hiatus, at the end of the 19th century, inoculations against cholera, typhoid, plague (caused by bacteria) and rabies (caused by a virus) were developed
- By the early 20th century, legendary statisticians **Karl Pearson**, **Major Greenwood, and Udny Yule** were deeply engaged in discussions of assessing these vaccines in the field.
- 1920's: Pertussis, diptheria, tetanus, and bacille Calmette-Gu´erin against tuberculosis
- 1930's: yellow fever, influenza, and rickettsia vaccines
- Post-war: polio, measles, mumps, rubella, varicella, and adenovirus.

Greenwood & Yule (1915) paper

- Famous opening line:

- “Hardly any subjects within the range of preventive medic ine is of more immediate importance than the methods of prophylaxis which ought to be adopted with respect to typhoid fever and cholera”

TABLE I.—ANTI-TYPHOID COMMITTEE'S DATA.

First arrangement.

	Not attacked	Attacked	Total
Inoculated	10,322	56	10,378
Not inoculated	8,664	272	8,936
Total	18,986	328	19,314

$\chi^2 = 180{\cdot}36$, P = less than 0·0001.

TABLE II.—ANTI-TYPHOID COMMITTEE'S DATA.

Second arrangement.

	Not attacked	Attacked	Total
Inoculated	6,759	56	6,815
Not inoculated	11,396	272	11,668
Total	18,155	328	18,483

$\chi^2 = 56{\cdot}23$. P = less than 0·0001.

Fig. 1.1 Two tables from the original Greenwood and Yule (Proc R Soc Med, 8(part 2):113–194, 1915) paper containing data on anti-typhoid inoculations and attack rates in the military. The two tables represent two differing arrangements of the data. Reprinted with permission of the Royal Society of Medicine.

Why two tables?

- Whether to “class as inoculated those who were so at the date of the last return made or only those actually inoculated at the time of arrival on the foreign station” ?

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Why two tables?

- In the former case, there may be an *exaggeration* of the “number of men who were inoculated during the whole exposure to infection,”
- In the latter case, one would *underestimate* it “because many inoculations were done shortly after arrival”
- How to adjust for this *effect*?
- Pre-date formal 'randomized studies'

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Poliomyelitis vaccine

- In 1954, an enormous field study - total of 1,829,916 children participated in the nationwide study.
- *Observed* control study.
- "to administer vaccine to children in the second grade of school; the corresponding first and third graders would not be inoculated, but would be kept under observation for the occurrence of poliomyelitis in comparison with the inoculated second graders”
- not a blinded study + effect of age might lead to bias !!

Poliomyelitis vaccine

- The plan was changed in mid-stream. In the second plan, called the Placebo Control Study, “children of the first, second, and third grades **would be combined**. **One half** would receive vaccine; the other matching half, **serving as strict controls**, would receive a solution of similar appearance (placebo)”
- Despite flaws, this vaccine had 72% efficacy.
- The Salk (injected) and Sabin (oral) polio vaccines have been 'transformative' - three polio virus strains has been eliminated in *most* countries of the world.

Randomized Controlled Trials

Randomized clinical trial

- Double-blinded randomized controlled trial (RCT)
- Group of participants placed either in a control group or experimental, completely at random, people going in are not aware of which group they're in, neither the researchers.
- The idea is that the experimental & control groups would be similar in terms of potential factors, such as, age, gender, ethnicity etc.
- Keep in mind: There could be issues of ethics ("necessary to know if the vaccine was better than what was available at the time")
- Other types of biases, too.

Details from Pfizer's website

"*Efficacy was consistent across **age, gender, race and ethnicity** demographics; observed efficacy in adults over 65 years of age was over 94%"*

"*The **Phase 3 clinical trial** of BNT162b2 began on July 27 and has enrolled 43,661 participants to date, 41,135 of whom have received a second dose of the vaccine candidate as of November 13, 2020".*

"*Approximately 42% of global participants and 30% of U.S. participants have **racially and ethnically diverse backgrounds**, and 41% of global and 45% of U.S. participants are **56-85 years** of age."*

Trial Enrollment

The landmark phase 3 clinical trial enrolled **46,331** participants at **153** clinical trial sites around the world.

Trial Geography

Our trial sites are located in **Argentina, Brazil, Germany, Turkey, South Africa** and the **United States.**

Participant Diversity

Approximately **42%** of overall and **30%** of U.S. participants have diverse backgrounds.

Participants	Overall Study	U.S. Only
Asian	5%	6%
Black	10%	10%
Hispanic/Latinx	26%	13%
Native American	1.0%	1.3%

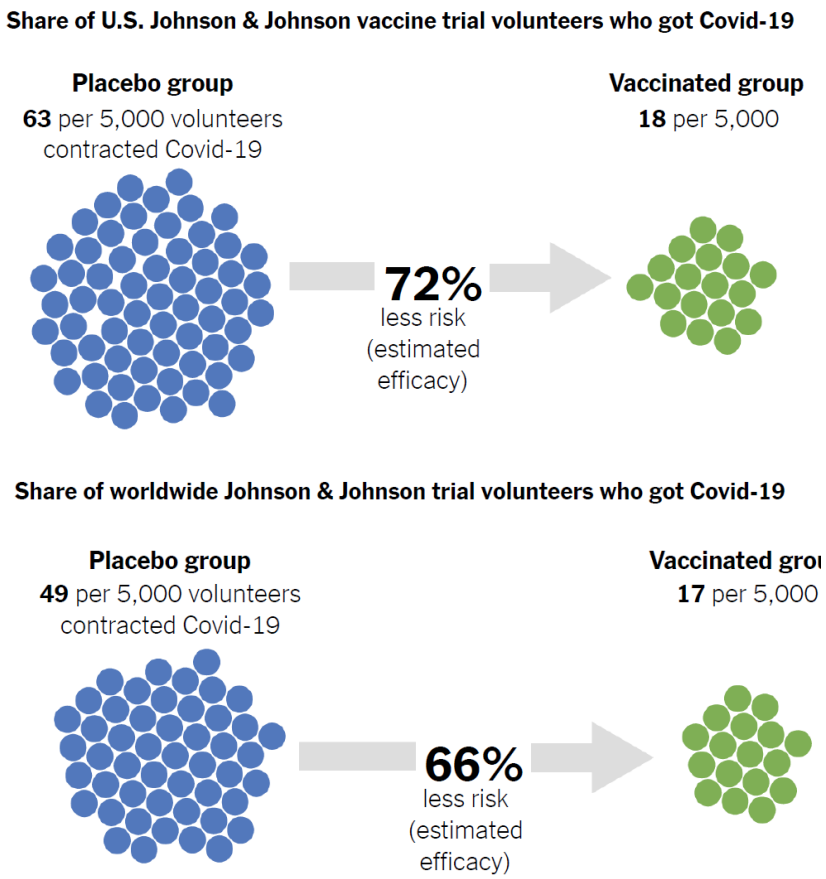
49.1% of participants are male and **50.9%** are female

Participant Age

Ages 12-15	2,259
Ages 16-17	754
Ages 18-55	25,427
Ages 56+	17,879

Efficacy depends on a lot of things!

- Where? J&J conducted trials in US, Latin America, South Africa.
- Overall efficacy lower than US-specific efficacy.
- In South Africa, trials took place after a new variants B.1.351 emerged, affecting the efficacy.
- But it didn't make it useless (SA efficacy ~ 64%)
- Also, when do we look at outcomes? J&J has 85% efficacy against severe cases.

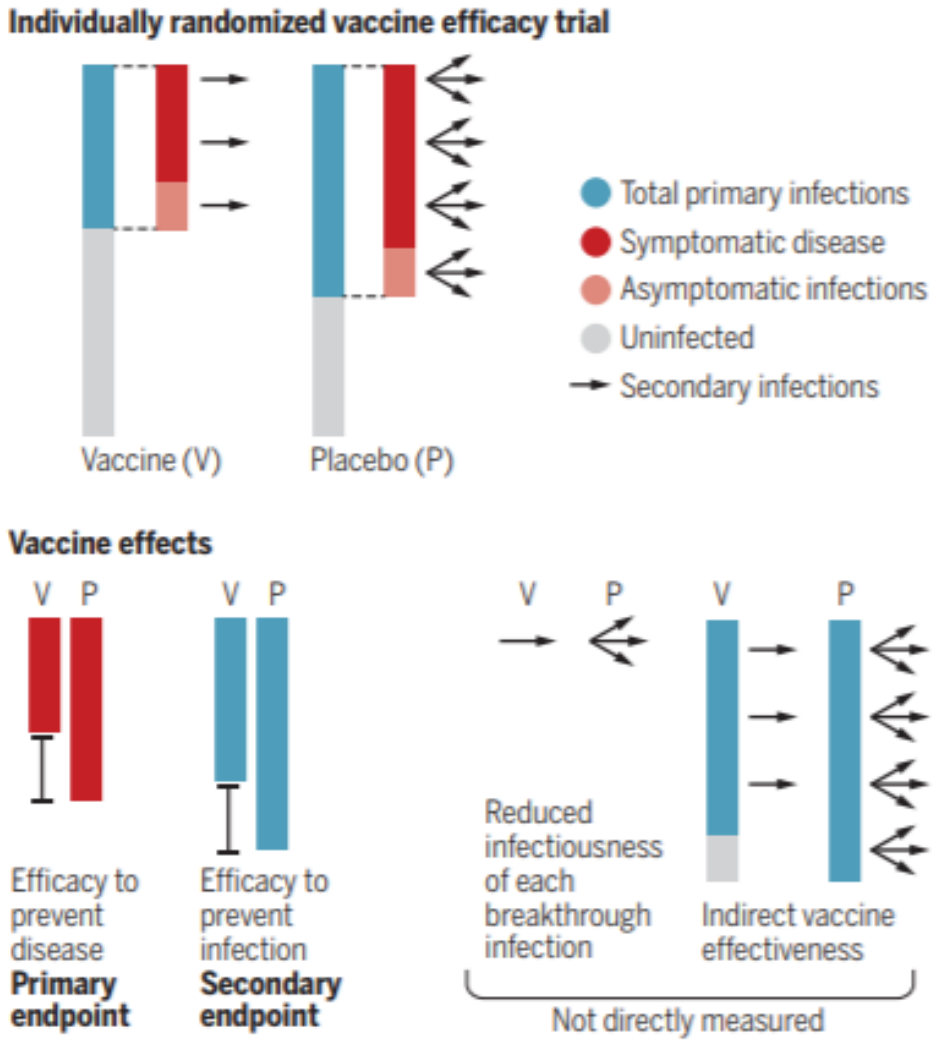


Direct & Indirect effects

- Safe & effective vaccine strategy offers both

  (1) direct protection (high-risk) and

  (2) indirect (reduce transmission for those in contact with high-risk).



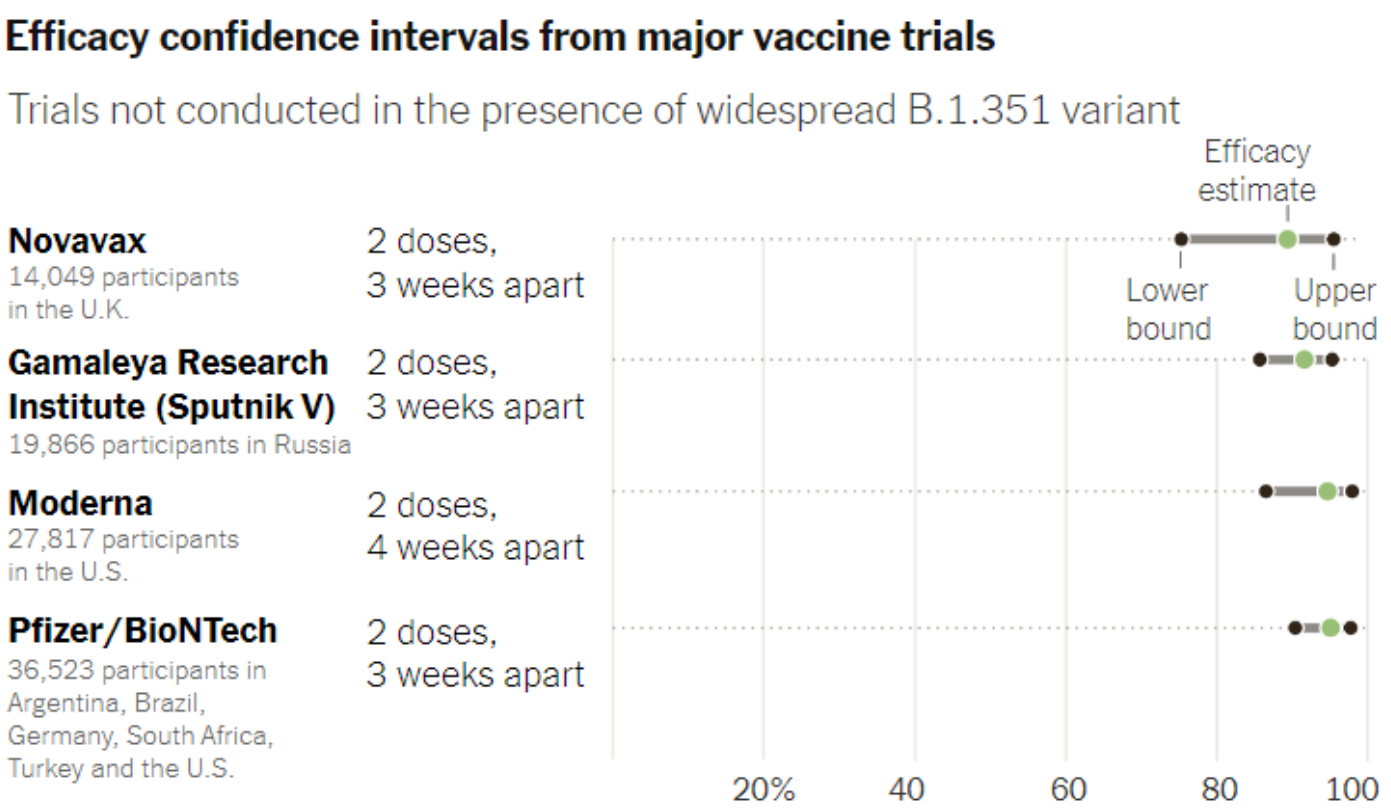
Marc Lipsitch and Natalie E. Dean, "Understanding COVID-19 Vaccine Efficacy", Science.

Strategy

- Elderly & people with comorbidities are at greatest risk - age structured mathematical models.
- Need to know well the vaccine works in which groups.
- Phase 3 trials provide insights about individual level efficacy & safety.
- However, assessing subgroup-specific efficacy is often challenging, and needs more work.
- For example, blinded follow-up studies can provide evidence on long-term safety, efficacy & age-specific effects.

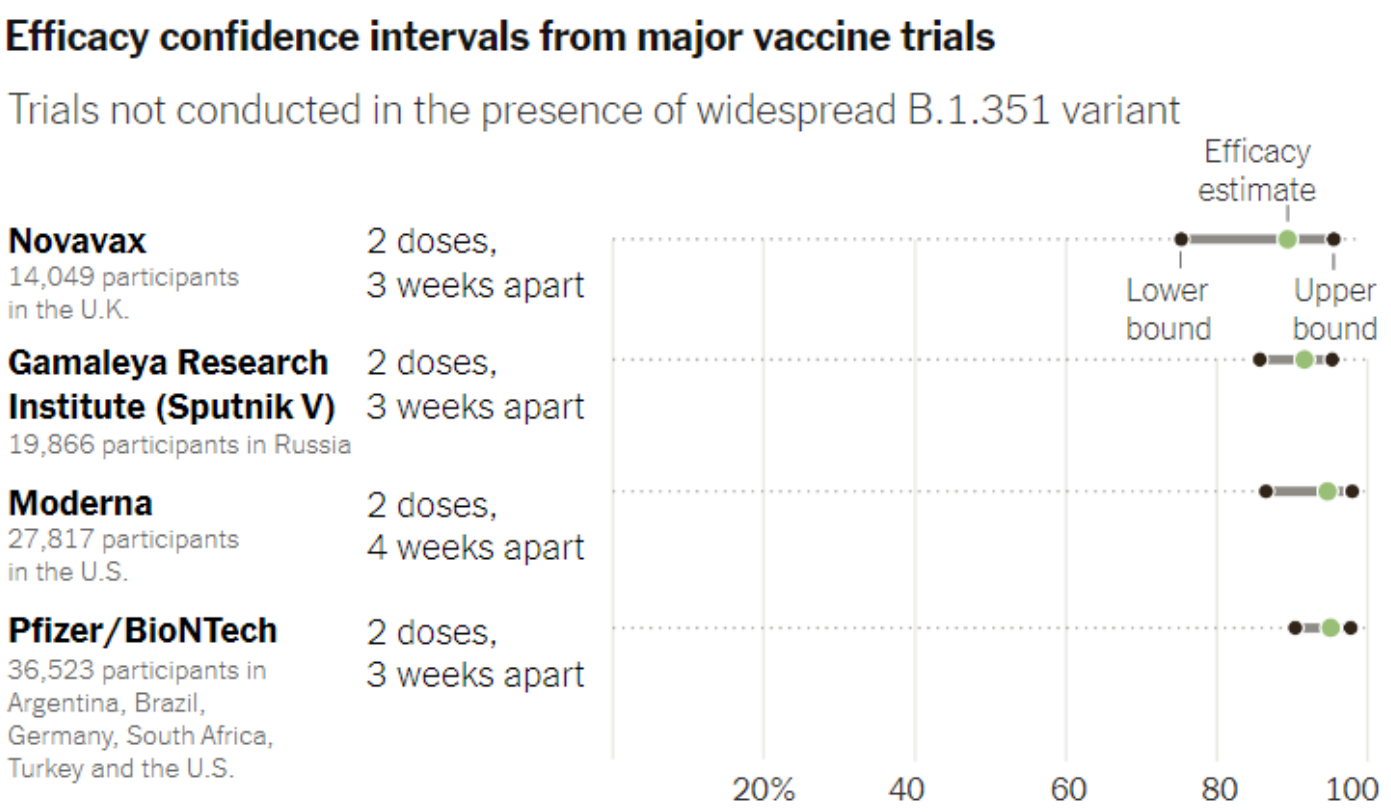
Uncertainty

Uncertainty



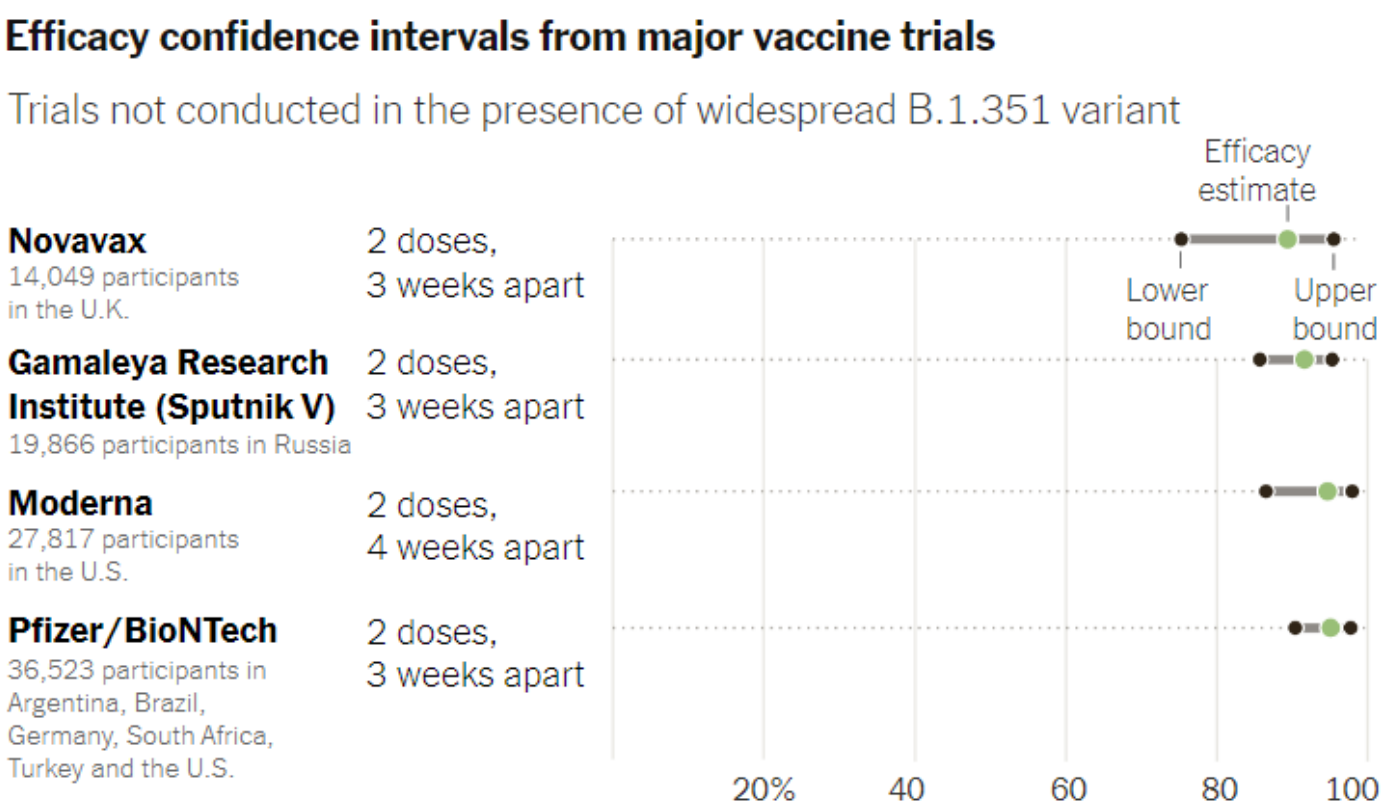
- The efficacy numbers you see (e.g., 95%) are point estimates.
- For the general population, there will be 'uncertainty' - reflects the difference between the subjects under trial and the large population.
- 95% confidence intervals.

Uncertainty



- One way to think about 95% CI's is that if you conduct 100 such similar studies, 95 of them would contain the efficacy value.
- FDA's threshold: efficacy no less than 50% & lower limit of CI cannot be lower than 30%
- Fortunately, all the major vaccines surpassed that.

Uncertainty



- The last thing to note about CI's is that if there's a large overlap between two CI's, then their difference is not statistically significant.
- In case of vaccines, it means that the point estimates of the efficacy values might be different, but if the CI's overlap, their efficacies are not really distinguishable.
- There are other factors as well.

How do vaccines compare?

- It is very difficult to compare vaccines.
- Vaccines were tested on different groups of people, during different stages of pandemic.
- They were also measured in different ways – e.g., J&J 28 days after a single dose, while Moderna 14 days after a second dose.
- All these vaccines have a high efficacy against hospitalization & death.

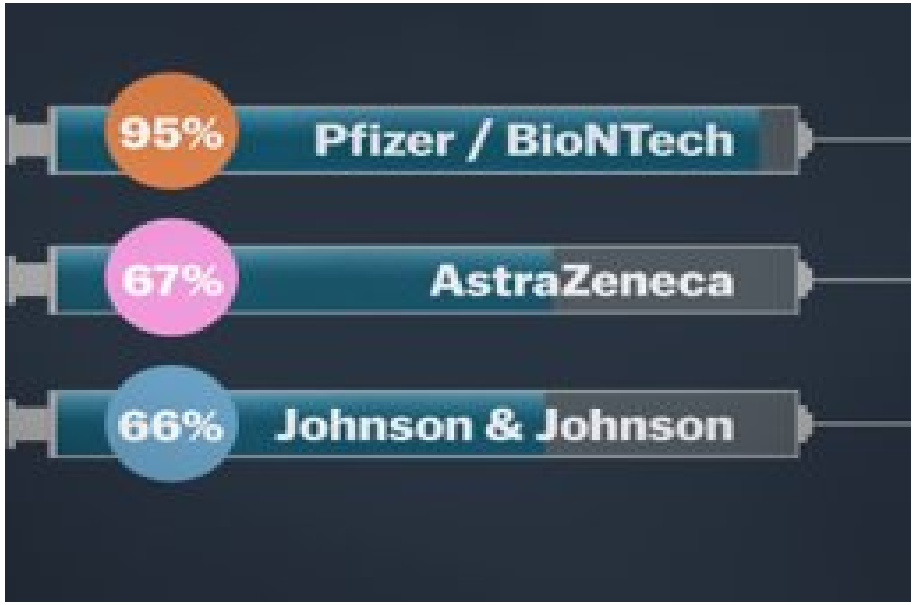


Image from Vox video

Effectiveness

A clinical trial is not the final destination, but just a start.

Researchers follow the effects of vaccine on the large popoulation for a long time.

Then, the quantity to look at is called "effectiveness" - the relative reduction of risk in 'real world', millions or billions of people.

Early studies show that the vaccines are also quite effective.

Final remark

"A tale of personal perseverance"

- Katalin Karikó was dismissed, ignored, unable to get grants and demoted. Had a cancer scare & her husband was stuck in Hungary sorting out visa issues.
- For three decades, she refused to quit.
- Ask yourselves, why did it have to be this way, and how many Katalin Karikos have quit?

"I thought of going somewhere else, or doing something else," Karikó said. "I also thought maybe I'm not good enough, not smart enough. I tried to imagine: Everything is here, and I just have to do better experiments."

Katalin Karikó, a senior vice president at BioNTech overseeing its mRNA work, in her home office in Rydal, Penn. *Jessica Kourkounis for The Boston Globe*

In time, those better experiments came together. After a decade of trial and error, Karikó and her longtime collaborator at Penn — Drew Weissman, an immunologist with a medical degree and Ph.D. from Boston University — discovered a remedy for mRNA's Achilles' heel.

Damian Garde, "The Story of MRNA: How a Once-Dismissed Idea Became a Leading Technology in the COVID Vaccine Race"

References

- Piero Olliaro, “What Does 95% COVID-19 Vaccine Efficacy Really Mean?” (**Blackboard**).
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Questions

The Role of Open Access in COVID-19 Vaccine Research

Angie Ohler, Associate Dean for Content and Digital Initiatives

UNIVERSITY OF ARKANSAS | University Libraries

Overview

Open Access

- What
- Why

Community Response

- Open Science
- Controversy

Future Directions

- Public Discourse
- Cultural Shifts

Open Access

What is Open Access?

- OPEN = IMPACT
- Open Access Publishing
  - Open access (OA) refers to freely available, digital, online information. Open access scholarly literature is free of charge and often carries less restrictive copyright and licensing barriers than traditionally published works, for both the users and the authors.
  - While OA is a newer form of scholarly publishing, many OA journals comply with well-established peer-review processes and maintain high publishing standards.
- Digital Repositories like ScholarWorks@UARK
- Funding agencies are getting serious about compliance, and that means publicly funded research must be made available OA

Why Open Access?

- Higher visibility for University of Arkansas authored works, with higher citation rates and greater impact in the field and beyond.
- Publishing with established journals and presses using trusted peer review processes.
- Opportunities to establish a strong early career publication record for tenure track faculty and student authors.
- Helps those authors in disciplines who do not otherwise have grant funding to pay for publication fees.

Community Response to the Pandemic

Open Science

- Public outcry from the scientific and research community
- Taxpayer funded research should be freely available
- Data sharing and open peer review
- Full access to all research and publication

Controversy

- Quantity versus quality
- Other models for peer review
- *The Lancet* retraction
- bioRxiv preprint server retraction

Public Discourse

- Scholarly Publication in Historical Context
- Societal Impact

Cultural Shifts

- Is this a permanent change?
- Should it be?

FAQ for Open Access Publishing Fund

- **When will the program begin?** July 1, 2021
- **Is this a one time ask?** Yes, this is a pilot program, and we will be assessing it for continuing.
- **Is there a plan for dedicated funding?** Most research-intensive universities have had open access grant programs for a long time. These programs are typically centered within academic libraries and are funded every year by a combination of funding from partners across campus.
- **Will there be limits on the number of asks, the total amount of requests, the frequency of asks, etc.?** We will limit the requests per author to one per year to make sure the funding covers as many authors as possible.
- **Open to students?** Yes, open to all institutional authors.
- **Are there caps on the grant amount?** Open access grant funds at large universities typically cover between $1500 to $3000 per book or journal article funding request. We will cover up to $2000.
- **How will the funding be managed?** As with other research institutions, the Libraries will administer the open access funds and the program will have clearly defined rules as to who is eligible, what publications are covered, and guidelines for applying. These will be posted on the Office of Scholarly Communications page.

Questions?