Design, Implementation and Analysis of Observational Studies

Pragmatics vs Perfection

WHO Meeting
Global research and innovation forum: RESILIENCE against outbreaks and pandemics
October 23-24, 2023

Lindsey R. Baden, MD
Dana-Farber Cancer Institute
Brigham and Women's Hospital
Harvard Medical School

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Dana-Farber Cancer Institute

Gold Standard – RCTs but…

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzal… Cristiano Zerbini, M.D., R… Satrajit Roychoudhury, Ph… Warren V. Kalina, Ph.D., Dav… Laura L. Hammitt, M.D., Özlem Ti… Serhat Ünal, M.D., Dina B. T… Philip R. Dormitzer, M.D., Ph.… and William C. Gruber, M…

ORIGINAL ARTICLE

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

L.R. Baden, H.M. El Sah… S.A. Spector, N. Roupl… J. Solis, A. Brosz, C. Fierr… D. Follmann, M. M… B.S. Graham, H. Benn… S. Han, M. Ivarsson…

ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

J. Sadoff, G. Gray, A. Vandebosch, V. … P.A. Goepfert, C. Truyers, H. Fennema, … K.L. Taylor, M.L. Robb, J. Treanor, D. … M.A. Marovich, K.M. Neuzil, L. Corey, … J. Ruiz-Guiñazú, M. Le Gars, H. Sc… and M. Douoguih, for the …

ORIGINAL ARTICLE

Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine

P.T. Heath, E.P. Galiza, D.N. Baxter, M. Boffito, D. Browne, F. Burns, D.R. Chadwick, R. Clark, C. Cosgrove, J. Galloway, A.L. Goodman, A. Heer, A. Higham, S. Iyengar, A. Jamal… D.F. McAuley, A. Meyrick, A.M. Min… H. Nicholls, O. Osanlou, J. Packham… …aya, R.P. Sheridan, R. Smit… …r, M.E. Viljoen, G. Albert, I… …tson, K. Smith, and S. Toba…

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months

S.J. Thomas, E.D. Moreira, Jr., N. Kitchin, J. Absalon, … J.L. Perez, G. Pérez Marc, F.P. Polack, C. Zerbini, R. Ba… S. Roychoudhury, K. Koury, S. Bouguermouh, W.… R.W. Frenck, Jr., L.L. Hammitt, Ö. Türeci, H. Nell, A. S… P. Liberator, D.B. Tresnan, S. Mather, P.R. Dormitzer, … K.U. Jansen, for the C4591001 Clinical T…

Perspective

JANUARY 14, 2021

Placebo-Controlled Trials of Covid-19 Vaccines — Why We Still Need Them

WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation

ORIGINAL ARTICLE

Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile

Alejandro Jara, Ph.D., Eduardo A. Undurraga, Ph.D., Cecilia González, M.D., Fabio Paredes, M.Sc., Tomás Fontecilla, M.Sc., Gonzalo Jara, B.S.E., Alejandra Pizarro, M.D., Johanna Acevedo, M.S., Katherinne Leo, B.S.E., Francisco Leon, M.B.A., Carlos Sans, B.S.E., Paulina Leighton, B.S.E., Pamela Suárez, B.S.E., Heriberto García-Escorza, M.S., and Rafael Araos, M.D.

Small Molecule Antiviral: Remdesivir

- Gilead: **Compassionate** use – NEJM 10Apr20
  - N=61, open label, hospitalized, hypoxemic. LD200/100mg for 9days
- NIAID-ACTT-1 – NEJM 22May (prelim) and 5Nov20
  - N=1062, RCT-pbo, LD200/100mg 9days, hospitalized
  - **Time to recovery** –median 10 vs 15 days
- Gilead: 5 or 10 days, **Severe** Covid -- NEJM 27May2020
  - N=397, Randomized, **open-label**, hospitalized no IMV
  - Clinical status improvement d14 – 64% in 5D vs 54% in 10D
- Gilead: 5 vs 10 days vs pbo, **Moderate** Covid – JAMA 21Aug2020
  - N=596, RCT-pbo, hospitalized, O2>94%, LD200/100 for 5 or 10d (median 6d)
  - Clinical status d11 – 5d>pbo, 10d~pbo
- WHO-Solidarity: Inpatient – NEJM 11Feb2021, Lancet 02May2022
  - N= 2750 remdesivir (10d)+2708 SOC, RCT-SOC, hospitalized, moderate Covid
  - **Mortality** – 11.0% (14.5%) vs 11.1% (15.6%)
- PineTree: **Outpatient** – NEJM 27Jan2022
  - N=562, RCT, LD200/100 2days. Outpatients
  - Hospitalization/death – 0.7% vs 5.3%

Forecasting Monoclonal Antibodies (mAb) Utility

Integrate Several Lines of Evidence

- Pathogen and Variant of Concern (VOC)
- *in vitro* activity of mAb
- PK/PD of mAb
- Clinical safety data
- Clinical efficacy data
  - In general vs against a specific VOC
  - Tempo of availability

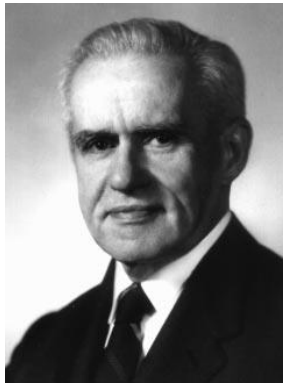
NATIONAL ACADEMY OF SCIENCES

MAXWELL FINLAND

1902—1987

A Biographical Memoir by

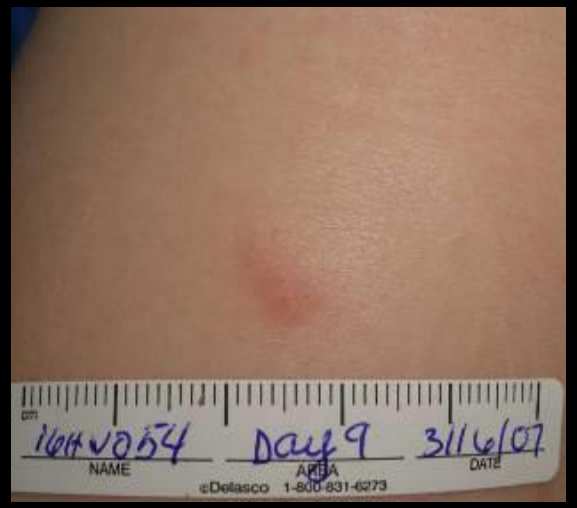
FREDERICK C. ROBBINS



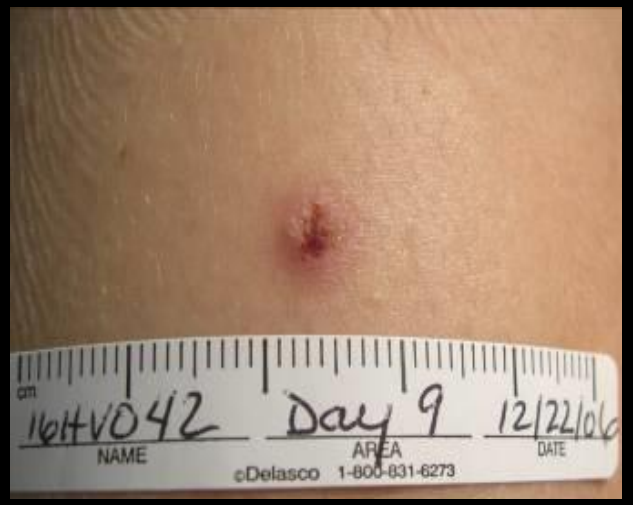
In 1929 Finland was asked by Dr. Nye to join his laboratory at the Thorndike. Thus began one of the most remarkable careers in the field of infectious diseases. The first studies conducted by Max and his associates dealt with pneumonia. At that time the only treatment for pneumococcal pneumonia was administration of type-specific antiserum. The process of treating patients was cumbersome, to say the least. A naso-pharyngeal swab was taken and placed in a tube containing culture medium. After a few hours of incubation when enough bacteria had proliferated, material from the culture was exposed to type-specific antisera. If there was a match between the antiserum and the chemical composition of the polysaccharide on the surface of the bacterium, the capsule would swell and it could be seen with an ordinary light microscope (known as the Quellung reaction). If Quellung occurred, the corresponding antiserum (horse or rabbit) was administered to the patient. The patients usually survived the infection, but they invariably suffered from serum sickness, which could be most unpleasant. Finland and his fellows did a series of studies on the treatment of pneumococcal infection conducted with meticulous care, a hallmark of Finland's research throughout. When sulfonamides became available

Classification of Dryvax Takes

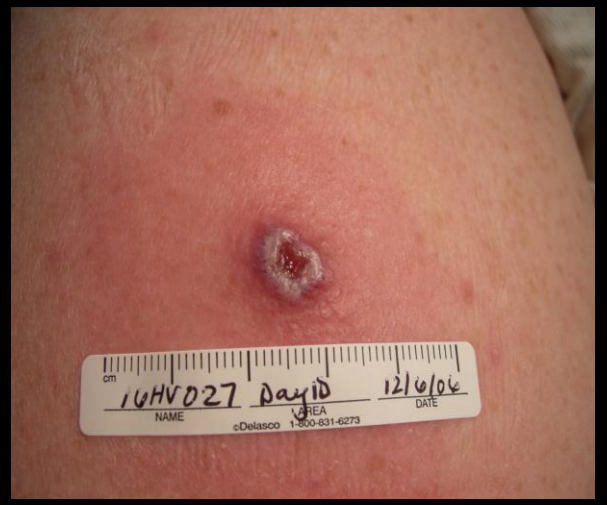
Category 1



Category 2

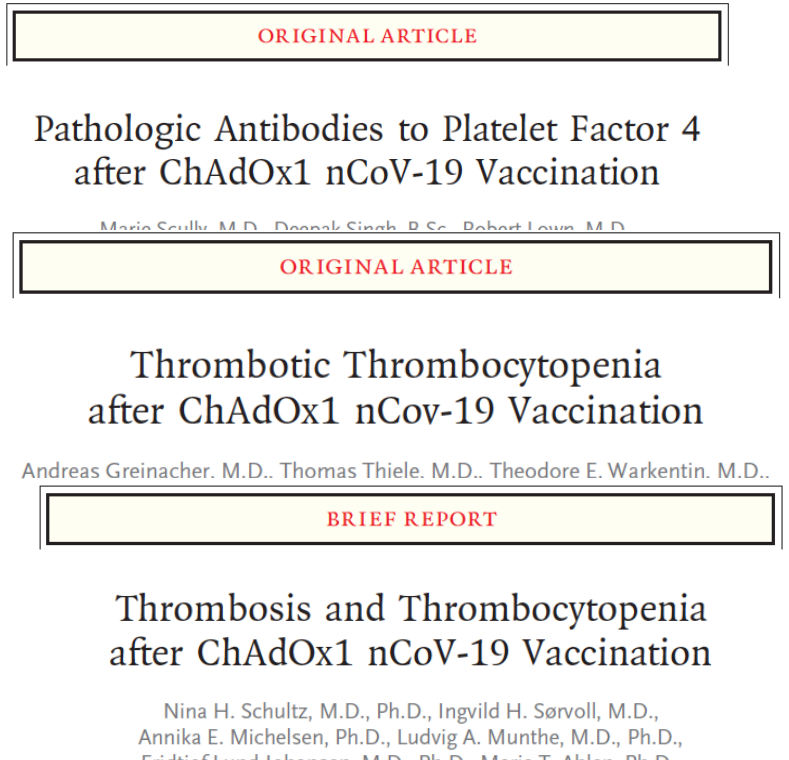


Category 3



Observational Studies Needed to Fill in Gaps

- Safety
  - Event frequency
  - Large databases (healthcare systems), voluntary reporting (VAERS)
  - Sorting out from background rates
    - Reactivation zoster, Bell's palsy
    - Serious
      - TTS, anaphylaxis, myocarditis
- Defining rates
  - Numerator
  - Population specific



ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4
after ChAdOx1 nCoV-19 Vaccination

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia
after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher. M.D.. Thomas Thiele. M.D.. Theodore E. Warkentin. M.D..

BRIEF REPORT

Thrombosis and Thrombocytopenia
after ChAdOx1 nCoV-19 Vaccination

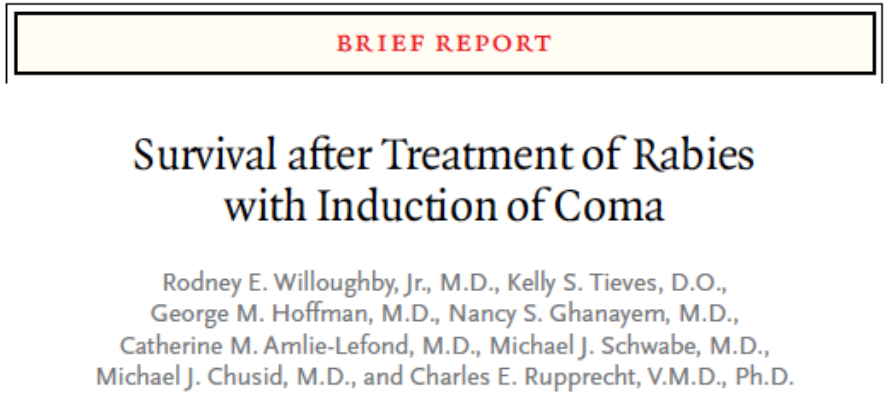
Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D.,
Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D.,

Observational Studies Needed to Fill in Gaps

- Special populations
  - Immunocompromised patients, pregnancy, children
- Durability
  - *in vitro* (antibody titers) vs clinical activity (outcome of interest)
  - Boosting, interval
- Determine a Correlate of Protection (CoP)
  - ?Neutralizing antibody titer (nAb)
- Pathogen evolution
  - Variants
  - Implications for vaccines, monoclonal antibodies, small molecule antivirals

Observational Designs

- Case series
- Case control
- Cohort
  - Large databases (healthcare system, country wide)



BRIEF REPORT

Survival after Treatment of Rabies with Induction of Coma

Rodney E. Willoughby, Jr., M.D., Kelly S. Tieves, D.O., George M. Hoffman, M.D., Nancy S. Ghanayem, M.D., Catherine M. Amlie-Lefond, M.D., Michael J. Schwabe, M.D., Michael J. Chusid, M.D., and Charles E. Rupprecht, V.M.D., Ph.D.

NEJM 2005

Some Key Confounders/Biases

- Understanding of illness caused by pathogen (and VOCs)
  - Direct viral effects, immunopathogenesis, tempo
- Variable infrastructure across settings
  - Variable prevention/treatment over time
- End point of interest
  - Infection; hospitalization; mortality
  - Availability and reasons for SARS-CoV-2 testing; reasons for hospitalizations; reasons for discharge; availability of supportive care
- Data availability/completeness
  - Variable data collection in medical record
  - Accuracy: variable definitions used across settings
- Human behavior
  - Patient, practitioner, health system
- Speed

Design Challenges

14September 2023 – WHO Meeting

1. Confounding
2. Healthy Vaccinee Bias
3. Misclassification
4. Selection Bias
5. Biases for Test Negative Design (TND)
6. Differential depletion of susceptibles
7. Waning immunity

Observational Designs

- Causal inference from observational data
  - Bradford Hill (9) Criteria
    - Strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, analogy
- Design innovations
  - Comparator group selection (access, EMR)
  - Propensity weighting
  - Emulated randomized (targeted) trials

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS (*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a

I wonder whether the pendulum has not swung too far - not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the USA where, I am told, some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary - because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the t table diverts attention from the inadequacies of the fare.

The International Journal of Biostatistics

Volume 4, *Issue* 1 2008 *Article* 22

Causal Inference from Longitudinal Studies with Baseline Randomization

American Journal of Epidemiology

Vol. 183, No. 8
DOI: 10.1093/aje/kw254
Advance Access publication: March 18, 2016

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

* Correspondence to Dr. Miguel A. Hernán, Department of Epidemiology, 677 Huntington Avenue, Boston, MA 02115 (e-mail: miguel_hernan@post.harvard.edu).

Clinical Review & Education

JAMA Guide to Statistics and Methods

Target Trial Emulation
A Framework for Causal Inference From Observational Data

Miguel A. Hernán, MD, DrPH; Wei Wang, PhD; David E. Leaf, MD, MMSc

ORIGINAL ARTICLE

Inhaled Fluticasone Furoate for Outpatient Treatment of Covid-19

David R. Boulware, M.D., M.P.H., Christopher J. Lindsell, Ph.D., Thomas G. Stewart, Ph.D., Adrian F. Hernandez, M.D., M.H.S., Sean Collins, M.D., Matthew William McCarthy, M.D., Dushyantha Jayaweera, M.D., Nina Gentile, M.D., Mario Castro, M.D., M.P.H., Mark Sulkowski, M.D., Kathleen McTigue, M.D., M.P.H., G. Michael Felker, M.D., M.H.S., Adit A. Ginde, M.D., M.P.H., Sarah E. Dunsmore, Ph.D., Stacey J. Adam, Ph.D., Allison DeLong, B.S., Geo… Rhonda Wilder, M.S., S… Susanna Naggie, M.D., M…

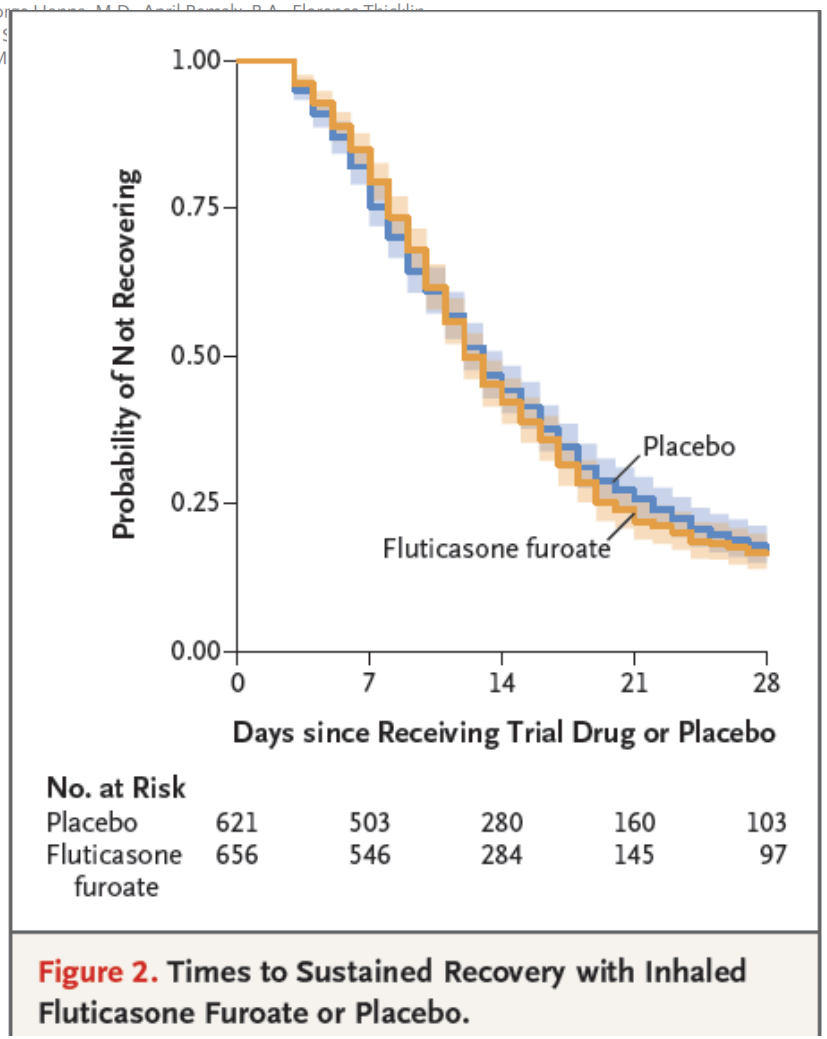
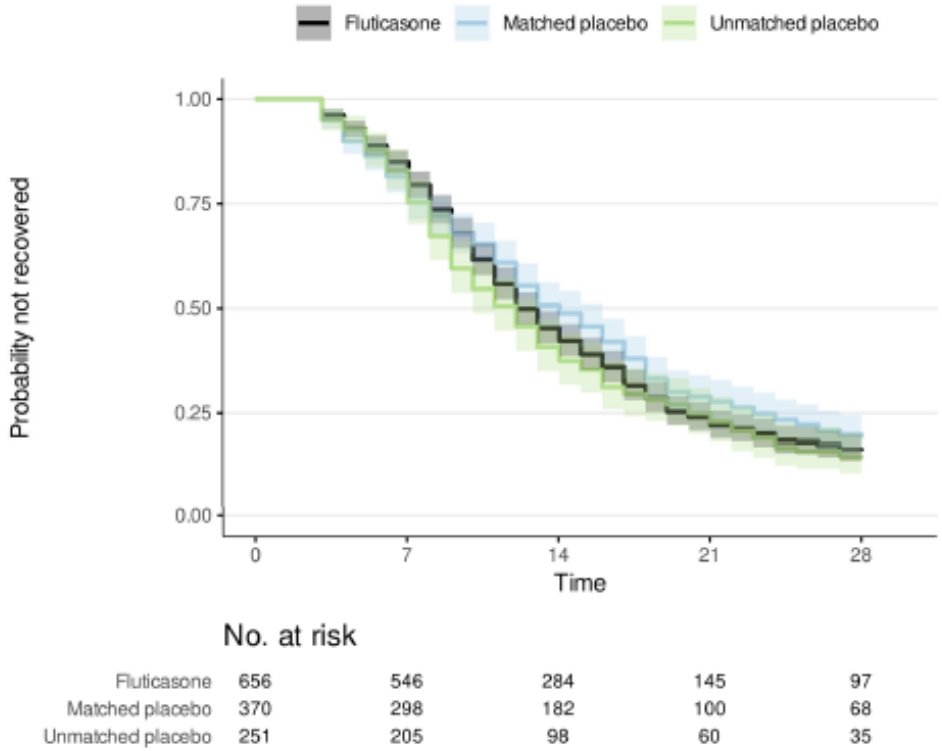


Figure 2. Times to Sustained Recovery with Inhaled Fluticasone Furoate or Placebo.

Figure S4. Kaplan-Meier plot of time to recovery with matched and unmatched placebos



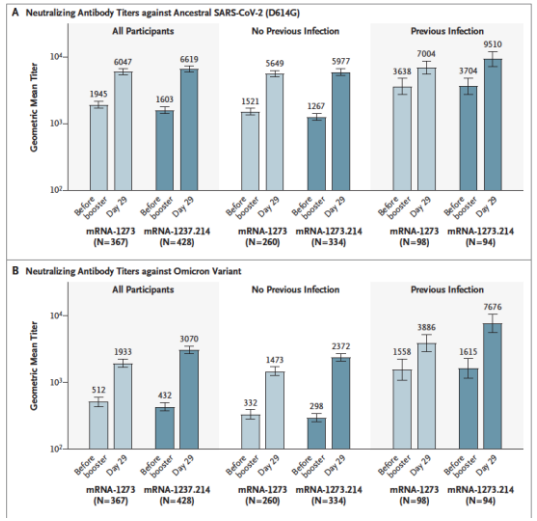
Kaplan-Meier curve for time-to-recovery primary endpoint stratified by treatment and type of placebo. This exploratory analysis used a 3-level treatment variable (active, matched placebo, unmatched placebo) in place of the pre-specified 2-level treatment variable (active versus placebo with matched and unmatched placebos combined). The unadjusted, log-rank test comparing the 3 groups resulted in a p-value of 0.1. Excluding the active group and comparing just the 2 placebo groups resulted in a p-value of 0.04. The covariate-adjusted Cox model with the 3-level treatment variable resulted in a 2 degree of freedom chunk test p-value of 0.01, suggesting possible heterogeneity between the placebo groups. The covariate-adjusted Cox model was consistent with the Kaplan-Meier curves in that the time to recovery for the active treatment group fell in between the time to recovery profiles of the two placebo groups. Specifically, the treatment effect hazard ratio when compared with matched placebo was 1.12 (95% CI: 0.97, 1.30). When compared with the unmatched placebo, the hazard ratio was 0.85 (95% CI: 0.72, 1.00). On the absolute scale, the unadjusted estimate of median time to recovery was 12 days (95% CI: 12, 13) for the active arm, 14 days (95% CI: 13, 16) for the matched placebo arm, and 12 days (95% CI: 10, 13) for the unmatched placebo arm.

Boulware et al. NEJM 2023:389;12:1085-95 21Sept2023

Conclusions

- For Safety observational data essential
  - Ability to detect rare events (i.e., <1:1,000,000)

- For Efficacy need a mix (totality) of data sources
  - Utilize multiple lines of evidence
    - Mechanistic, pre-clinical, observational, clinical, and RCT
  - Ethical
  - Efficacy end point
  - Define critical settings
  - Big data does not equal unbiased/unconfounded data
  - Develop a meaningful CoP
  - Utilize randomization when possible
  - Novel designs raise novel threats to validity



NEJM 16Sept2022