The Pandemic
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Kellogg College
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The Need for Conducting Randomized Trials in a Pandemic to Provide High-Quality Evidence: Overcoming the Challenges

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Kellogg College Hub
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DISCLOSURES

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Investments in health organizations: None
Other affiliations:
Member of committees with PHAC, CIHR**,** Cochrane Collaboration Resp Virus Working Group, WHO Infection Prevention and Control Research and Development Expert Group for COVID-19, WHO Health Emergencies Programme COVID-19 GDG, WHO Technical Advisory Group Hand Hygiene, AHS Scientific Advisory Group

Learning Objectives

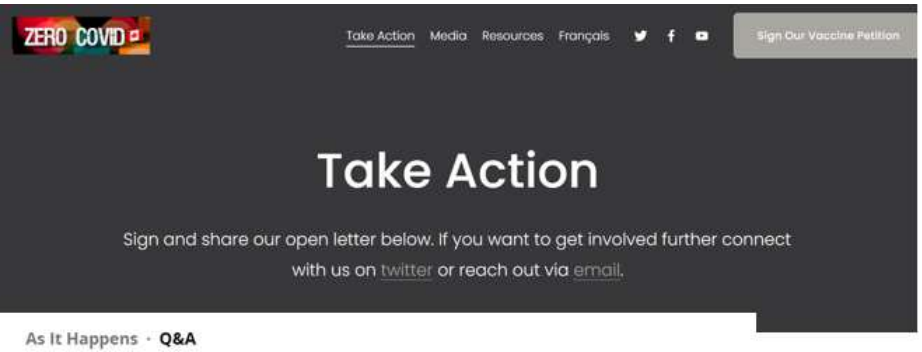
- The polarization of COVID-19
- Background randomized controlled trials (RCTs) vs observational studies
- Why we need RCTs in pandemics/epidemics for multiple types of interventions
- Outline challenges from an example RCT in the COVID-19 era
- Overcoming challenges in conducting randomized trials during a pandemic

Background

- First major pandemic in the modern age **of instantaneous social messaging**
- A pandemic accompanied by **a parallel "infodemic"** *
- Mainstream and social **media** were in **total overdrive**
- Major polarization of views - often **highly emotional**
  - Vaccinations
  - Intervention measures
  - Routes of transmission
- Strong advocacy with differing interpretations of science and countless **strident opinions** – from "No measures" to "COVID-Zero" and complete lockdown
- Occurred **across political spectrum**, mainstream media, social media and among physicians, academics, and scientists

* https://www.who.int/health-topics/infodemic#tab=tab_1

The Polarization of Responses to COVID-19



As It Happens · Q&A

'You don't copy the losers,' says doctor pushing 'COVID-zero' strategy

Dr. Andrew Morris one of several health-care workers calling for 'aggressive' national approach to pandemic

How a national response could address an unprecedented COVID-19 surge across Canada

Federal emergency powers could create more unified approach to pandemic but at what cost?

Adam Miller · CBC News · Posted: Nov 14, 2020 4:00 AM ET | Last Updated: November 14, 2020

Could a national response help control Canada's 2nd wave?

One approach that has been put forth by public health experts is the use of emergency federal powers to co-ordinate our response to the pandemic across the country.

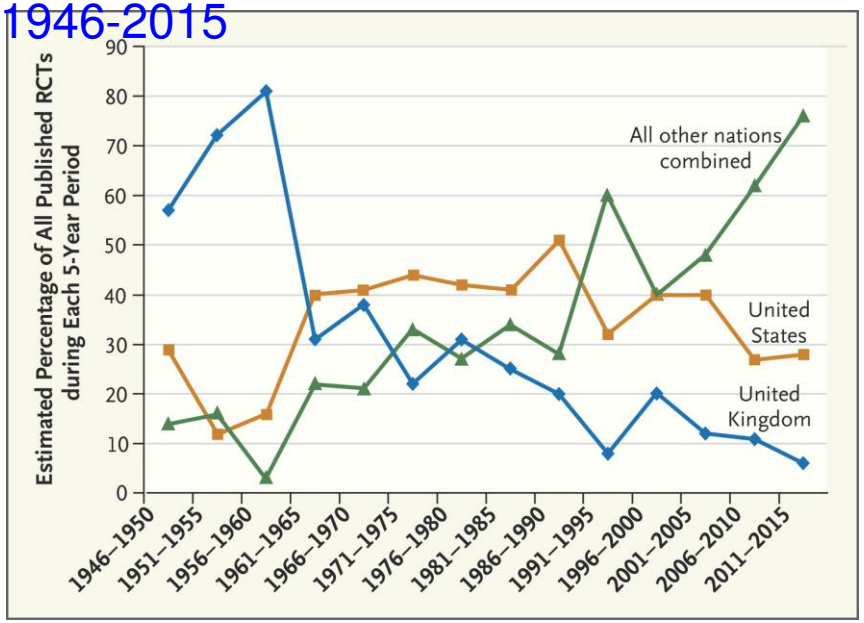
That can be done either by using the Emergencies Act or through the inherent emergency power the federal government has under the Constitution Act.

The Emergencies Act is far-reaching in that it allows the federal government to extend its power over provinces and their health-care systems to deal with the pandemic.

Randomized Trials - A Brief History

- Experimental epidemiology early 20th century (experimental/control laboratory animals) evolved to RTs
- Randomization concept **1st time1923**
- First RCT credited to Austin Bradford Hill & colleagues 1948 for TB - bed rest **(BR) vs. BR plus streptomycin**
- **Astounding results** - randomized to the intervention(streptomycin) 6 mo. mortality 4/55 vs 15 /52 in controls
- This UK MRC trial considered a **landmark and turning point bringing RCTs** to the forefront of modern clinical research

Locations of RCT Research Sites 1946-2015



Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81

Bhatt A. Evolution of clinical research: a history before and beyond James Lind. Perspect Clin Res. 2010 Jan;1(1):6-10\
Daniels M, Hill AB (1952). Chemotherapy of pulmonary tuberculosis in young adults; an analysis of the combined results of three Medical Research Council Trials. BMJ 1:1162-68
Crofton J (2004). The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line. JLL Bulletin: Commentaries on the history of treatment evaluation (https://www.jameslindlibrary.org/articles/the-mrc-randomized-trial-of-streptomycin-and-its-legacy-a-view-from-the-clinical-front-line/)

Randomized Trials - A Brief History

- **Polio vaccine trials of 1954** sponsored by the March of Dimes was a large randomized, blinded placebo controlled trial of the **killed Salk vaccine** but with an added natural experiment of observed 'cohort'
- **Controversy** at the time not unlike COVID-19 with **polarized** with some virologists against the killed vaccine
- Concerns raised re: RCTs late1950s being unethical - just rely on expert opinion/case reports/observational studies
- All changed with the **thalidomide tragedy in 1961**, the cause of a **global epidemic of stillbirths and phocomelia**
- Regulatory agencies requiring RCTs by 1970 (FDA)

Meldrum M. "A calculated risk": the Salk polio vaccine field trials of 1954. BMJ. 1998 Oct 31;317(7167):1233-6
Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81

Why a Randomized Trial ?

- **Power** of randomization is an **equal starting point**
- Reduces or even eliminates **known and unknown bias** with allocation to the intervention and controls
- Useful for **multiple types interventions** - pharmacological (medicinal agents, vaccines) non-pharmacological (behaviours, hand hygiene, masking, closures, service delivery and procedures)
- Randomized trials provide the strongest evidence for **causal inferences** and considered the **"gold standard"**
- Still remain some who adhere to non use of RCTs and spilled into COVID-19 era

Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81
Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. N Engl J Med. 2020 Feb 13;382(7):674-678. doi:10.1056/NEJMsb1901642. PMID: 32053307

Randomized Trials vs Observational Studies

- Observational studies **(Obs)** useful for providing knowledge on **causes, pathogenesis** of disease and for **prognosis and diagnosis**
- Events are only observed as they naturally occur in various settings
- **Biases** from differences in patient characteristics, disease severity, and many other **confounders** and inherent in all observational studies
- Adjustments still leave **residual confounding**
- RCTs optimal for prevention, control and treatment of disease

Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. N Engl J Med. 2020 Feb 13;382(7):674-678. doi:10.1056/NEJMsb1901642. PMID: 32053307

Randomized Trials vs Observational Studies

- **Recurrent debates** over the years merits of RTs vs. Obs studies
- Sometimes concordant/sometimes not with many discrepancies
- Examples of **discordance very significant**
- One of the first was **retrolental fibroplasia (RLP**) where case reports, case series and commentaries suggested the poor health of prematurity, birthweight and no oxygen use were causative
- Estimated from1943-53, 7000 children in the US and 10000 globally were blinded - a **global epidemic of blindness**
- **RCT of oxygen therapy** - incidence RLF of 23% in premature infants kept for 28 days in 50% oxygen environment and 7% in infants given oxygen only when clinically indicated - hailed as a benchmark with immediate results

Terry TL: Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens Am J Ophthalmol 1942; 25:203-204;
Kinsey VE, Zacharias L.Retrolental Fibroplasia: Incidence in different localities in recent years and a correlation of the Incidence with treatment given the Infants, JAMA 139:572, 1949.
Flynn JT. Acute proliferative retrolental fibroplasia: multivariate risk analysis. Trans Am Ophthalmol Soc. 1983;81:549-91
Kinsey VE: Retrolental fibroplasia: Cooperative study of retrolental fibroplasia and the use of oxygen. Arch Ophthalmol 1956; 56:481-543.

Randomized Trials vs Observational Studies

- Benson and Hart 2000 NEJM suggested "**little evidence** that estimates of **treatment effects** in **observational** studies reported **after 1984** are ….different from those obtained in RCTs" from a review of 136 studies of 19 treatment effects
- Arguments of assessing methodological rigour, quality and statistical power and the analytic strategy
- **Major failures ensued- HRT** protection from MI, stroke, VTE
- in Obs but ↑ in RTs; **β carotene** protection lung cancer; **Vitamin E** for protective effects CV disease; **cancer registry** obs data vs. RCT data **differed by 55%** for therapeutic efficacy
- Complete reversal of many years of conclusions from observational studies - **? Death of observational epidemiology**

Writing Committee for the Women's Health Initiative randomized controlled trial. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results. JAMA 2002;288:321–3

Sackett DL. The arrogance of preventive medicine. CMAJ. 2002 Aug 20;167(4):363-4

Debbie A Lawlor, George Davey Smith, Shah Ebrahim, Commentary: The hormone replacement–coronary heart disease conundrum: is this the death of observational epidemiology?, Inter J Epi 33(3) 2004, Pages 464–467

Kordiak J et al. Role of beta-carotene in lung cancer primary chemoprevention: A systematic review with meta-analysis and meta-regression. Nutrients. 2022 Mar 24;14(7):1361. doi: 10.3390/nu1407136

Cook NR et al. A Randomized factorial trial of vitamins C and E and Beta carotene in the secondary prevention of CV events in women: Results from the women's antioxidant cardiovascular study. *Arch Intern Med.* 2007;167(15):1610–1618

Kumar A, Guss ZD, Courtney PT, et al. Evaluation of the use of cancer registry data for comparative effectiveness research. JAMA Netw Open. 2020;3(7):e201198

Randomized Trials in COVID-19

- RCTs for candidate **pharmacological interventions (PIs)** occurred at an **unprecedented rate**
- In **February 2020**, WHO Research Forum COVID-19 recommended evaluation of treatments in large, adaptive randomized trial platform
- **By Apr 21 2020** > **500 clinical trials** were registered globally
- Vast majority were for **antivirals, monoclonal antibodies, plasma, and vaccines**
- Network meta-analysis in **late 2022** identified **17 RCTs** evaluating the efficacy of 16 COVID-19 vaccines in 361,386 participants
- By **March 9 2022**, estimated 11 billion vaccine doses had been administered worldwide.

Thorlund,K et al. A real-time dashboard \ of clinical trials for COVID-19. Lancet Digit Health. 2020 Jun;2(6):e286-e287
Kumar S et al . Efficacy of COVID-19 vaccines: a systematic review and network meta-analysis of phase 3 randomized controlled trials. Pharmacol Rep. 2022 Dec;74(6):1228-1237
WHO Solidarity Trial Consortium et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021 Feb 11;384(6):497-511

NPIs and Lack of Evidence during COVID-19

- **Editorial Nov 2021** for a SR of interventions for COVID-19 found **only one RCT (mask wearing)** of 35 eligible studies on the effectiveness of individual non-pharmacological interventions (NPIs)
- Any success interpreted as the impact of a bundle of correlated interventions
- **Hundreds of PI randomized studies on vaccines and drugs vs a single RCT to that point on NPIs**
- Pointed out only a fraction of the funding designated to non-pharmacological measures

BMJ 2021; 375 doi: https://doi.org/10.1136/bmj.n2729 (Published 18 November 2021) BMJ 2021;375:n2729

Clinical Trials for PIs vs. NPIs during COVID-19

- Scoping review at 18 months into the pandemic for PIs vs NPIs
- 5 databases any country, any setting plus any registered in ClinicalTrials.gov/WHO Inter'l Clinical Trials Registry Platform
- Of > **4000 registered trials** worldwide, **only 41 (1%)** RTs of NPIs to prevent COVID-19 identified
- **9** (22%) published; 26 (63.4%) ongoing or not yet started and 3 (7.3%) completed but not published and 3 (7.3%) withdrawn
- Mainly focused on **PPE** and **testing/screening** and attendance at **music events/concerts**
- Only **9 published on NPIs** c/t 26 RCTs Chloroquine (CQ) or HCQ by 9 months into the pandemic showing harm signal
- Yet an estimated **1.5 billion children globally** were affected by **mandated school closures** and recent 2024 SR suggests school closures not necessary for transmission prevention

Hirt J, Janiaud P, Hemkens LG. Randomized trials on non-pharmaceutical interventions for COVID-19: a scoping review. BMJ Evid Based Med. 2022 Dec;27(6):334-344. doi: 10.1136/bmjebm-2021-111825. Epub 2022 Jan 27.
Neil-Sztramko SE et al. What is the specific role of schools and daycares in COVID-19 transmission? A final report from a living rapid review. Lancet Child Adolesc Health. 2024 Apr;8(4):290-300

Clinical Trials for PIs vs. NPIs during COVID-19

- PubMed search **Feb 2023** to identify published RCTs and ClinicalTrials.gov for ongoing/completed RCTs assessing the effects of **3 PIs vs 5 NPIs**
- PIs require RCTs for recommendation **but NPIs rarely tested** in **RCTs** and **adopted/mandated with minimal evidence**
- Why? Adverse events PIs easily detectable but **NPIs diffuse, ill-defined social, emotional, psychological**
- Authors consider an evidence **double standard**

Non-pharmacological interventions	Ongoing RCTs	Completed RCTs	Ever mandated?
CO2 monitors	0	0	Yes, in some settings[a]
Masks vs. no masks	2	2	Yes
School/sports closures	0	0	Yes
School/building ventilation system upgrades	0	0	Yes
Business closures	0	0	Yes
Pharmacological interventions			
Ivermectin (alone)	8	24	No
Hydroxychloroquine (alone)	8	34	No
Convalescent plasma	16	40	No

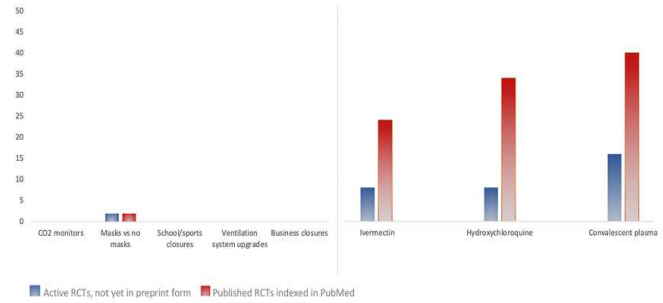


Fig. 1. Ongoing and Published Randomized Controlled Trials for Select Non-Pharmacological vs Pharmacological Interventions for COVID-19.

Høeg TB, Prasad VK. An evidence double standard for pharmacological vs.non-pharmacological interventions: Lessons from the COVID-19 pandemic. Contemp Clin Trials Commun. 2023 Jun;33:101108

Failures of Observational Studies in COVID-19

- **Hydroxychloroquine(HCQ)** - global attention after an *in vitro* study reported activity SARS-CoV-2 (a **mechanistic finding**)
- **Small Obs studies** released showing + results and a small RCT suggested ↑ recovery but not stratified by co-morbidities
- Use skyrocketed and **US** granted **emergency approval** 2020
- **April 2021** MA reports ↑ OR all-cause **mortality** for HCQ 1.11 (95% CI: 1.02, 1.20) - Solidarity and Recovery trials; estimated close to **200,000 HCQ deaths** 6 countries 2024 study
- **Ivermectin** followed suit - little to no effect in/outpatients
- **Prone positioning** as NPI MA RCTs suggested ↓ risk intubation but not any 2^0 outcomes as reported in Obs studies SR

Yao X, Ye F, Zhang M, et al. In vitro antiviral actas NPIivity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. doi:10.1093/cid/ciaa237; Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949:105949. doi:10.1016/j.ijantimicag.2020.105949.; Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Epidemiology 2020. doi:10.1101/2020.03.22.20040758.
Axfors, C., Schmitt, A.M., Janiaud, P. et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat Commun 12, 2349 (2021). https://doi.org/10.1038/s41467-021-22446-z
Pradelle A et al. Deaths induced by compassionate use of HCQ during the first COVID-19 wave: an estimate. Biomed Pharmacother. 2024 Feb;171:116055
Ivermectin for preventing and treating COVID-19; CDSR Ivermectin for preventing and treating COVID-19 | Cochrane
Anand S, et al. Effect of awake prone positioning in COVID-19 patients- A systematic review. Trends in Anaesthesia & Critical Care. 2021 Feb;36:17–22.; Weatherald J et al . Efficacy of awake prone positioning in patients with covid-19 related hypoxemic respiratory failure: systematic review and

Juravinski Research Institute

Challenges in Conducting RCTs on NPIs during the COVID-19 Pandemic – A Case Study

World Health Organization

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

- Example of a trial on a NPI and its challenges
- **Pragmatic**, international, multicenter, open-label, **non-inferiority RCT** where HCWs were randomized to either **medical masks or N95** respirators when providing routine care to patients with COVID-19
- REB approvals from 10 boards; DMC established

Medical Masks Versus N95 Respirators for Preventing COVID-19 Among Health Care Workers : A Randomized Trial - PubMed (nih.gov)
Loeb M, Bartholomew A, Hashmi M, Tarhuni W, Hassany M, Youngster I, Somayaji R, Larios O, Kim J, Missaghi B, Vayalumkal JV, Mertz D, Chagla Z, Cividino M, Ali K, Mansour S, Castellucci LA, Frenette C, Parkes L, Downing M, Muller M, Glavin V, Newton J, Hookoom R, Leis JA, Kinross J, Smith S, Borhan S, Singh P, Pullenayegum E, Conly J. Medical Masks Versus N95 Respirators for Preventing COVID-19 Among Health Care Workers : A Randomized Trial. Ann Intern Med. 2022 Dec;175(12):1629-1638. doi: 10.7326/M22-1966. Epub 2022 Nov 29

Acknowledgment: Slides for this trial courtesy of M Loeb MD FRCPC McMaster University

McMaster University

Pragmatic vs. Explanatory RCTs

- Pragmatic trials
  - ✓ consider the **expected imperfect conditions** and **heterogeneity** when interventions are applied in **real-world conditions**
  - ✓ factor in suboptimal adherence, settings, populations, age, and **differences in implementation**
- Explanatory trials
  - ✓ enroll as homogenous a population as possible
  - ✓ aim to further scientific knowledge about the biological basis of an intervention under **optimal circumstances**

Zwarenstein M (2016). 'Pragmatic' and 'Explanatory' attitudes to randomized trials. JLL Bulletin: Commentaries on the history of treatment evaluation (https://www.jameslindlibrary.org/articles/pragmatic-and-explanatory-attitudes-to-randomized-trials/
Sackett DL. Explanatory and pragmatic clinical trials. Pol Arch Med When 2011; 121: 259-263.

Interventions

Medical Mask group

- HCWs instructed to use the ASTM **medical mask for routine care**
- Could use N95 respirator based on risk assessment and were required to N95 during AGMPs
- **Universal use** (all activities,
- patient related or not)

N95 respirator group

- HCW instructed to use fit-tested NIOSH approved **N95 respirator for routine care**
- **Universal use** (all activities, patient related or not)

Pre-trial survey

- Of 111 responses, 75.5% reported that RCT evidence of medical masks versus N95 respirators would be helpful to inform policy
- **Demonstrated equipoise**

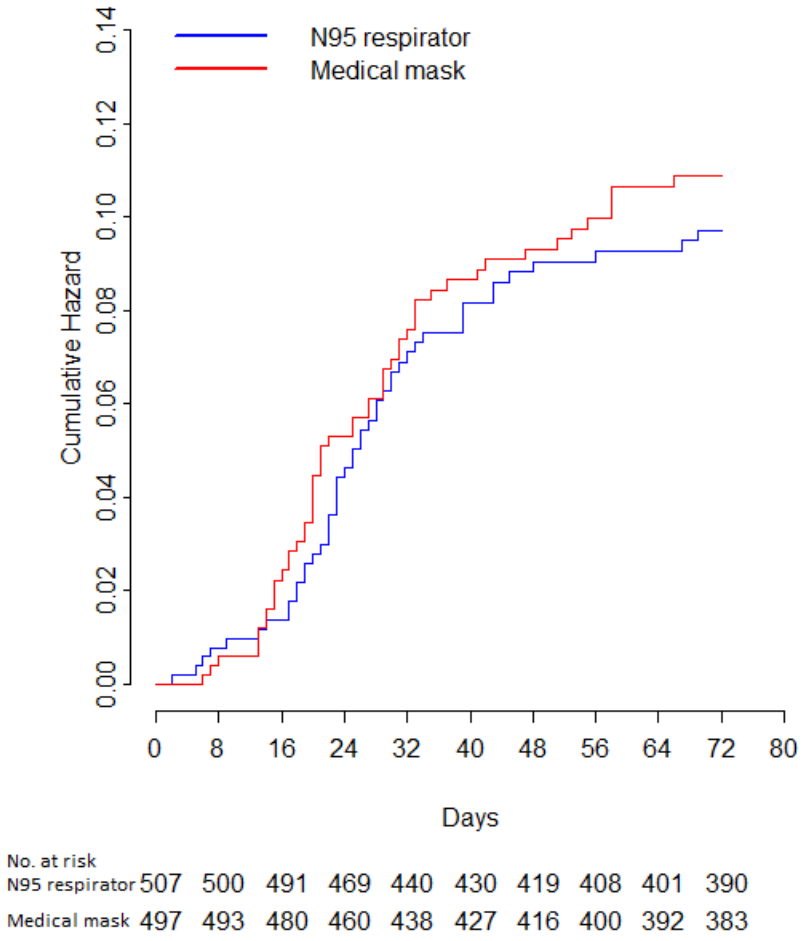
Primary Outcome and Summary

	Medical Mask	N95 Respirator	
RT-PCR confirmed COVID-19			**HR (CI 95%)**
ITT	**52/497 (10.46)**	**47/507 (9.27)**	**1.14 (0.77-1.69)**
PP	52/446 (11.66)	47/452 (10.40)	1.13 (0.76-1.68)

Absolute difference 1.19% (95%CI -2.5% to 4.9%)

- **Medical masks were shown to be noninferior to N95 respirators** for preventing COVID-19
- 2^0 outcomes consistent with 1^0 outcome
- Strengths - **high rate of follow up and adherence, exposure to original strain and VOCs**, variety of settings (**HICs** and **LMICs**) , **exposures balanced**; **90% power** at n=875; enrolled 1004
- Limitations were **auditing by monitors**, **some infections likely acquired by household or community** exposure, **self-reported** exposures, limited sample for seroconversion analysis

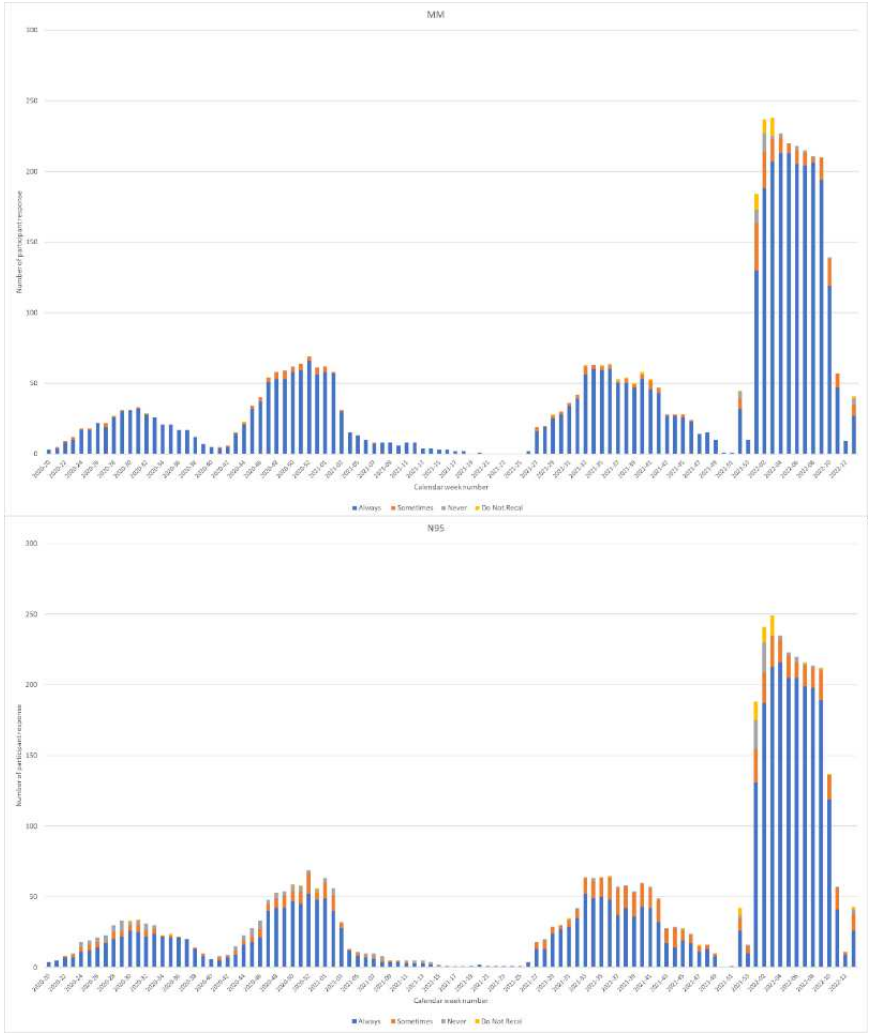
ITT Survival Curves/Secondary Outcomes



	Medical Masks	N95 resps	HR (95%CI)
ARI			
ITT	25/497 (5.03)	30/507 (5.92)	0.84 (0.50-1.44)
PP	24/446 (5.38)	29/452 (6.42)	0.84 (0.49-1.44)
LRTI or pneumonia*			
ITT	3/497 (0.60)	3/507 (0.59)	1.03 (0.21-5.01)
PP	3/446 (0.67)	3/452 (0.66)	1.02 (0.21-5.06)
Absenteeism			
ITT	48/497 (9.66)	45/507 (8.88)	1.08 (0.72-1.62)
PP	43/446 (9.64)	39/452 (8.63)	1.10 (0.72-1.70)
			OR (CI 95%)
Seroconversion			
ITT		19/180 (10.56)	0.93 (0.53-1.95)
PP	18/146 (12.33)	17/140 (12.14)	1.02 (0.47-2.21)
Laboratory confirmed infection			
ITT	71/497 (14.29)	66/507 (13.02)	1.11(0.78-1.60)
PP	70/446 (15.70)	64/452 (14.16)	1.13 (0.78-1.63)

*** No ICU admissions or deaths**

Implementation Adherence: Self Reported and Directly Observed Adherence to Masks



- Of 118 participants observed in the medical mask group, 116 **(98.3%)** were reported by monitors to be adherent to their assigned mask
- Of 117 in the N95 respirator group, 113 **(96.6%)** were reported to be adherent to their assigned mask

Comments Published in Annals

- **Unethical** because transmission is by aerosol inhalation
- Trial was **flawed** - **no control** group
- Masking is a complex intervention and **RCTs are not superior to other forms of evidence** for NPIs
- Respiratory **protection** was **not used continuously-** the RCT was testing close-contact transmission alone
- Concern about one of the 15 **surgical masks** used in the RCT not meeting **ASTM standards**
- Differences in **sub-groups even though post hoc**
- Concerns about **fit-testing**

Comments Published in Annals

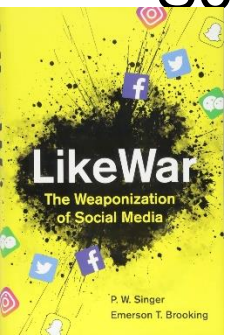
- Study was **not adequately powered** and **N95s** were **used intermittently**
- There were "**multiple biases**" a **subgroup** analysis for Canada should have been conducted, concerns about an ↑ in **sample size** and a **"change"** in outcomes
- **Lack of equipoise** was a major item repeatedly raised
- Concern about **24 months** fit-testing criterion and facial hair in N95 respirator users
- Use of surgical masks was evidence that study sites did **not** have an **appropriate "program"** in place
- Absence of **occupational hygiene** expertise, PAPRs should have been used in Egypt
- **Modifications to trial** registry on December 21, 2022

Challenges in this NPI RCT
A Microcosm Gaze into the Macrocosm

- Logistical
  - Sheer sample size issues for adequate power
  - Consenting at the individual level in a pandemic
  - Difficulty obtaining N95 respirators (procurement) due to supply chain challenges in all countries
  - Refusal of participation-individual/community/institution
  - Varying levels of recruitment at study sites
  - Protocol adjustments
- Financial
  - Securing additional funding
- Communication
- Confidentiality

Challenges in this Trial
A Microcosm Gaze into the Macrocosm

- Bias against use of RCTs in a pandemic
  - **Harassment of investigators** at Coordinating Centre and at Study Sites
  - **Misinformation** during/after the RCT; highly organized **campaign to discredit** the RCT to McMaster, HREBs, CIHR through social media, **letter writing campaigns** to University/Hospital **ethics boards** to halt an **unethical study** placing HCWs at risk
  - **Misconduct/ethics allegations** with letters to the Tri-council Federal Office Panel on the responsible conduct of research Ottawa, Canada that was placed in the public domain on Twitter REBTri_council_letterrevisedfinal19Apr2021final.pdf (healthcareworkersaustralia.com) requesting "for the study to be **decoded** immediately/**formal letters** of **apology** to be sent to participants by the investigator"
  - **Advocacy to limit recruitment** - **letter writing to Union leadership** in some provinces to write their members to inform them to not enroll
- Timeliness
  - **Dynamic changes** in a rapidly changing setting eg vaccine rollout
- Social media



Constant criticism, well organized, **vigorous** (especially physicians and academics), **no equipoise**, **unethica**l, endangering lives, anti-HCW, **contact us if concerns**, encouraging letters to Secretariat for Responsible Conduct Research, **personal attacks** on investigators

Named a Best Book of the Year 2018
By Amazon and *Foreign Affairs* Magazine

Challenges to Randomized Trials in a Pandemic

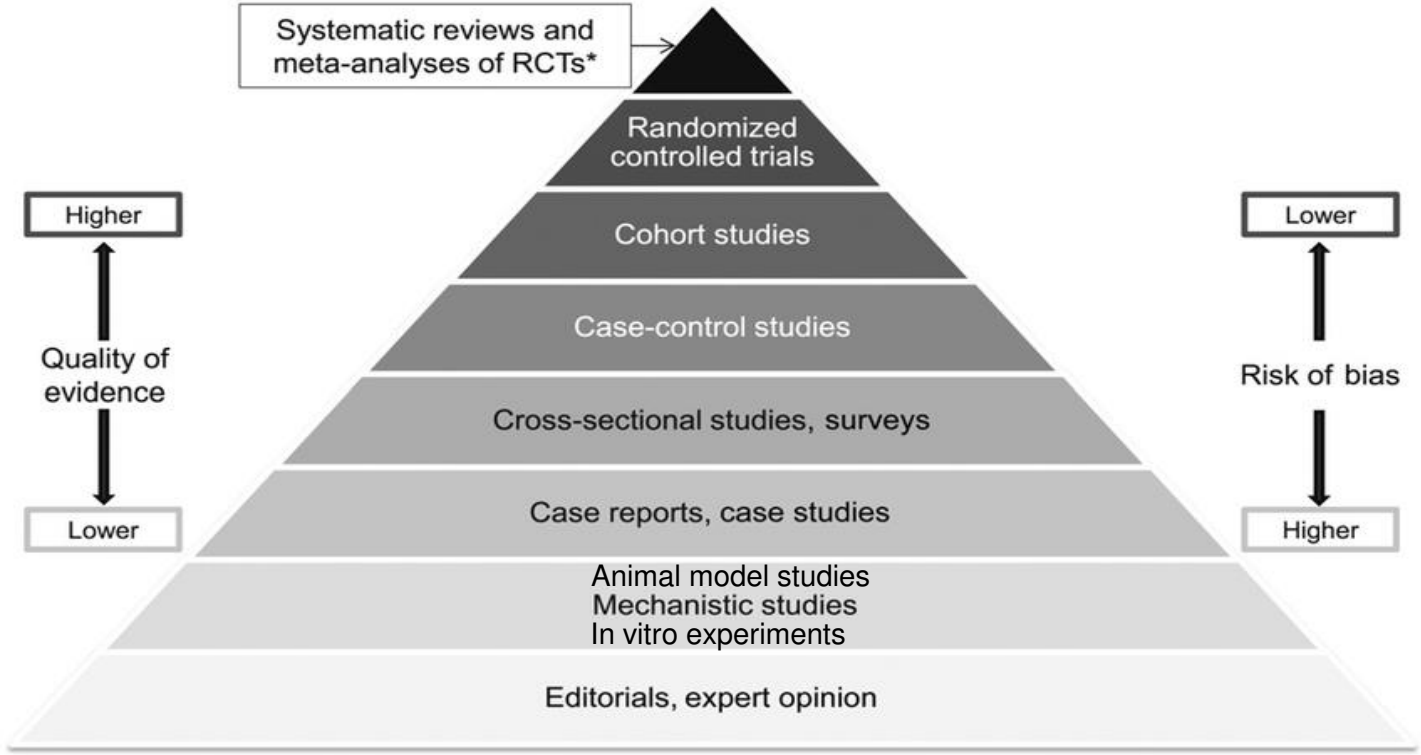
- **Fundamental opposition** by some scientists, academics and policy makers to NPI randomized trials in a pandemic

  RCTs for NPIs for "infectious diseases such as **COVID-19 are particularly challenging**", **too complex/too many ethical** issues; "**policy approaches** to SARS-CoV-2**… made trials of** individual **NPIs almost impossible**" Royal Society (UK) August 2023

  - **Confirmation bias**
    - "tendency to search for, **interpret, favor, and recall information** in a way that **confirms** or **supports one's prior beliefs**"; only select /process information to support their point of view – often an **insuperable belief** and **highly emotional**
  - **Intellectual bias**
    - ''academic activities that create the potential for an **attachment to a specific point of view** that could unduly **affect** an individual's **judgment**…."

- Other authors suggest **value in RCTs** for feasibility and inclusion in meta-analyses even if underpowered; and others consider **ethically obligatory** if any uncertainty benefits/harms

Royal Society Aug 2023 royalsociety.org/npi-impact-on-covid-19
Fretheim A. COVID-19: underpowered randomised trials, or no randomized trials? Trials. 2021 Dec;22(1):234.
Haber et al. Much ado about something: a response to "COVID-19: underpowered randomised trials or no RTs?"Trials. 2021 22:780
Akl EA, El-Hachem P, Abou-Haidar H, Neumann I, Schünemann HJ, Guyatt GH. Considering intellectual, in addition to financial, conflicts of interest proved important in a clinical practice guideline: a descriptive study. J Clin Epidemiol. 2014 Nov;67(11):1222-8
Wikipedia and Confirmation bias - Catalog of Bias CEBM Oxford
Barosa M, Jamrozik E, Prasad V. The ethical obligation for research during PHEs: Insights from the COVID-19 Pandemic. Med Health Care Philos. 2024 Mar;27(1):49-70;



Placing randomized trials above other types of research such as observational, lab and modeling studies, has interfered with the COVID response. A randomized trial approach that allows a few studies to cancel out a huge body of research from other disciplines has no basis in science.

Sci American May 2023 Opinion. https://www.scientificamerican.com/article/masks-work-distorting-science-to-dispute-the-evidence-doesnt/

Ten priority research activities/themes to combatting future outbreaks and pandemics

- Increase resources for research/innovation worldwide
- **If there is uncertainty* give randomization the opport-unity to yield trustworthy evidence**
- Expand the use of simple large platform trials employing core protocols
- **Consider generating large-scale randomized evidence during epidemics/pandemics**

* Recent African study **harms**: economic slowdown, job losses (women), ↑ sexual violence, ↑ teen pregnancies, ↓ mental health, ↑ waste

Diallo I et al. Unintended consequences of implementing non-pharmaceutical interventions for the COVID-19 response in Africa: experiences from DRC, Nigeria, Senegal, and Uganda. Global Health. 2023 Jun 6;19(1):36.

Global Research and Innovation for Health Emergencies

Building the world's resilience against future outbreaks and pandemics

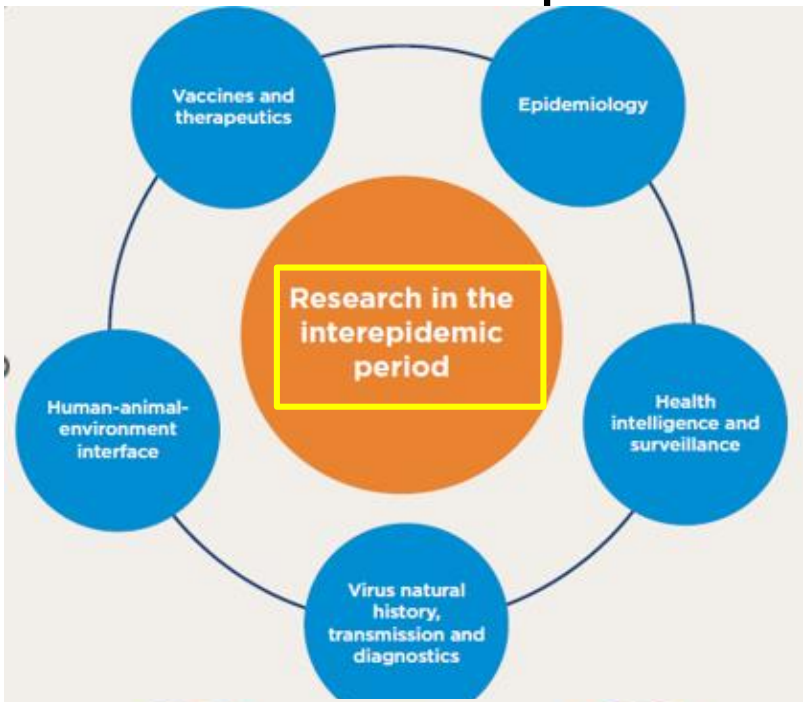
October 2023

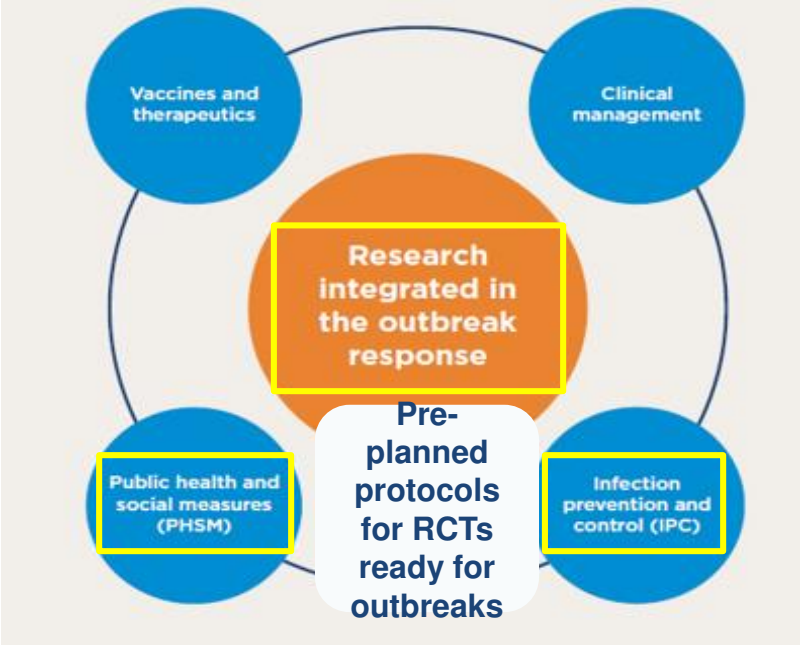
The 3rd Global Research and Innovation Forum
23-24 October 2023

World Health Organization

R&DBlueprint
Powering research to prevent epidemics

Future research priorities





The Pandemic
EVIDENCE Collaboration

Overcoming the Challenges

Kellogg College
University of Oxford

- Advocate for financial resources to deploy randomized trials (RTs) for PIs /NPIs **early, equitably, and energetically (the 3 Es)** within pandemics/epidemics
- Build **resiliency and preparedness** to allow for RTs of NPIs within pandemics, epidemics and endemic settings
- Ensure all **benefits and harms of interventions** are considered including physical health, mental health, social health and economic impacts short/medium/long range
- Establish and sustain **'oven-ready' research protocols** to facilitate the **rapid launch** of NPI RTs during a pandemic/epidemic with **ethical approval**
- Build **partnerships and co-operation** wherever feasible

Questions

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