Target Trial Emulation: reducing time-varying confounding-by-indication and time-zero biases when evaluating comparative effectiveness in primary COVID-19 vaccine courses on mRNA boosters

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Background

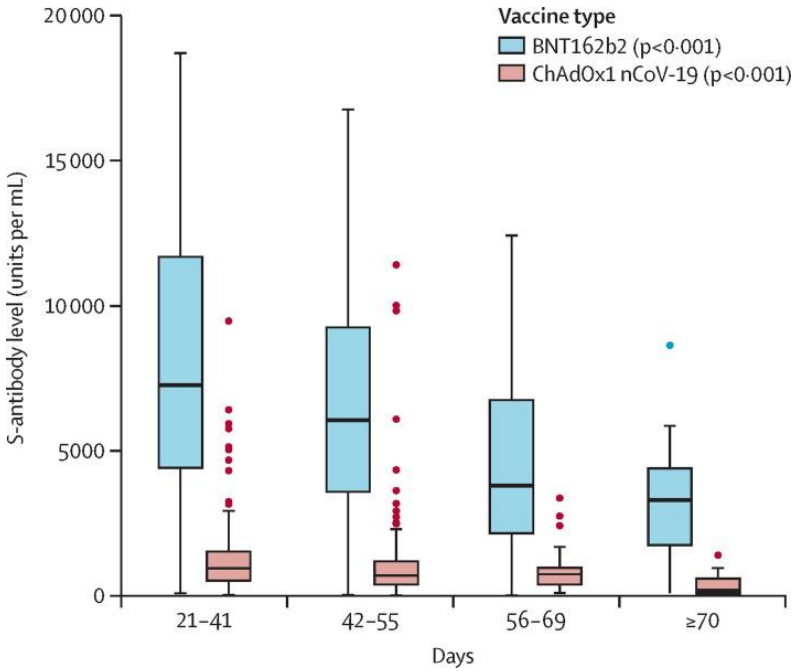
- Vaccination against COVID-19 has prevented deaths worldwide and reduced symptoms in SARS-CoV-2 infected individuals

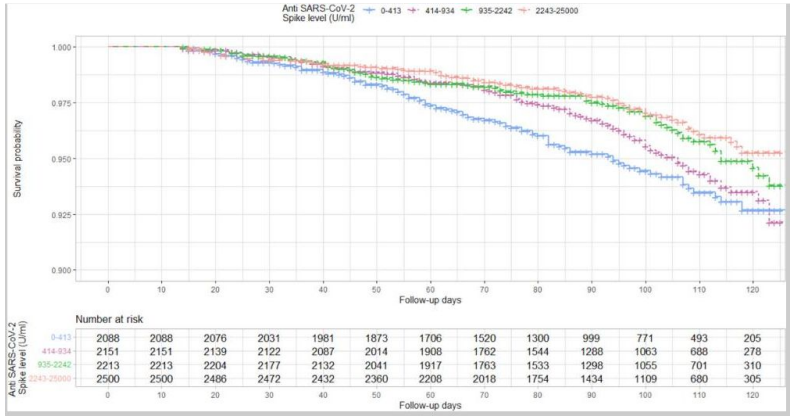
- The two **primary courses** available in the United Kingdom were Oxford AstraZeneca (ChAdOx1) and Pfizer BioNTech (BNT162b2) with two doses being considered a full course

- The first dose of these vaccines were distributed from December 2020 and were prioritised for those who were clinically vulnerable and older individuals with a staggered cohort to younger and healthier individuals

Background Cont

- After time, we realised vaccine induced antibodies were warning and breakthrough infections started to occur
- Related to antibody waning, initial results show that BNT162b2 reduced the risk of vaccination after two doses…perhaps because BNT162b2 produced higher antibody levels when compared to ChAdOX1. HR = 1.35 [95%CI: 1.15 - 1.58] of infection at 266 median follow up
- To counter this, the government introduced booster vaccinations starting in September 2021 (Delta dominant) but only provided mRNA-based vaccines e.g. BNT162b2 and mRNA-1273 (aka Moderna)
- Boosters were prioritised by **clinical vulnerability** and age but then made available to all in December 2021 when Omicron became prominent





Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, Beale S, Fong WLE, Patel P, Kovar J, Hayward AC, Aldridge RW; Virus Watch Collaborative. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet. 2021 Jul 31;398(10298):385-387. doi: 10.1016/S0140-6736(21)01642-1. Epub 2021 Jul 17. PMID: 34274038; PMCID: PMC8285117.

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Challenges answering following question: Are mRNA vaccines compatible with non-mRNA vaccines e.g. Chimpanzee adenovirus vaccines?

1) Prioritising distribution based upon age+clinical vulnerability means those who are older have longer follow up and were more likely to receive Pfizer as their primary course

2) Those who received Oxford AstraZeneca were more likely to be infected between dose 2 and dose 3 - Those who survived could have done so due to survivor's bias and also have natural immunity in addition to a booster

3) Booster campaign started during a time where the Delta variant was the dominant strain, but then Omicron (higher rates of immune escape) became the dominant strain..impacted younger people

4) Those vaccinated earlier prior to Omicron may have longer for their antibodies to wane…

Therefore, the risk of infection at day 1 of follow up during Delta is not the same as the risk of infection at day 1 of follow up during Omicron! i.e Time Varying Confounding by indication via Time Zero Bias

Method - Target Trial Emulation

Trial emulation aims to reduce time-varying confounding by indication by using three primary components:

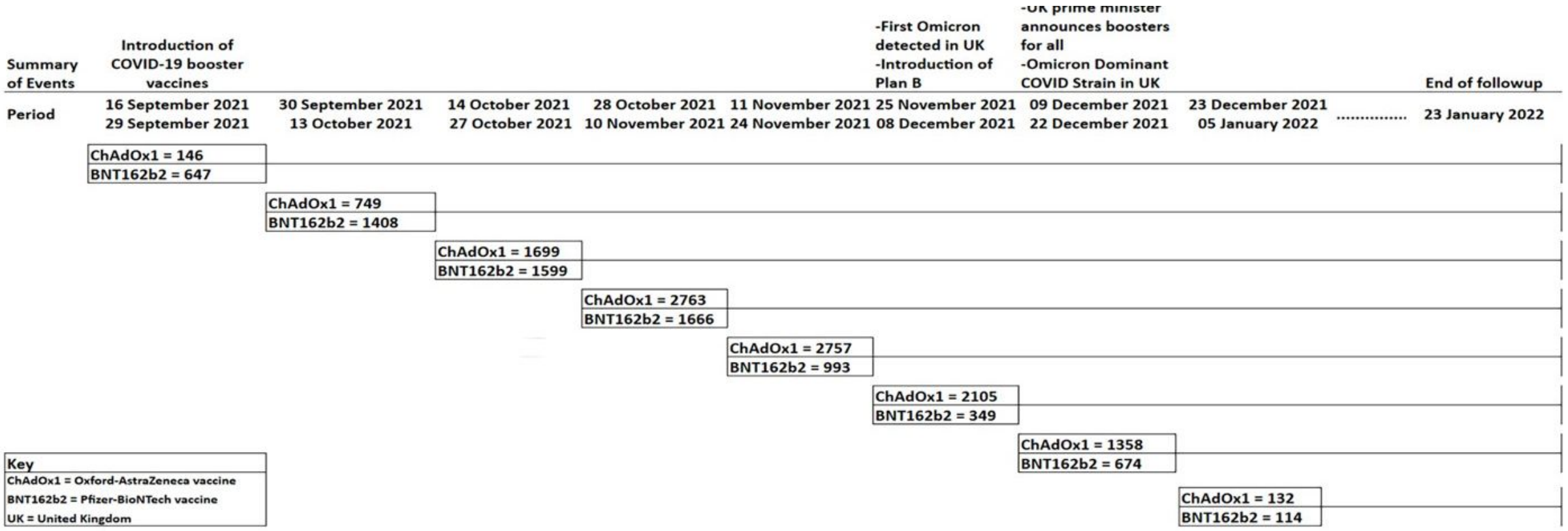
1) **Consider incident users of an intervention or use a wash-out period to remove effects of prior treatment - in our case, prior infection reduces risk of breakthrough infections**
2) **Use an intention to treat analysis and ignore changes in treatment strategy. In our case, we're comparing primary courses of ChAdOX1 with an mRNA booster dose, against a regime of 3 booster doses**
3) **Finally, we need to consider what an appropriate time-zero is.**

Details of the trial emulation framework used to conceptualize the observational study as a controlled trial

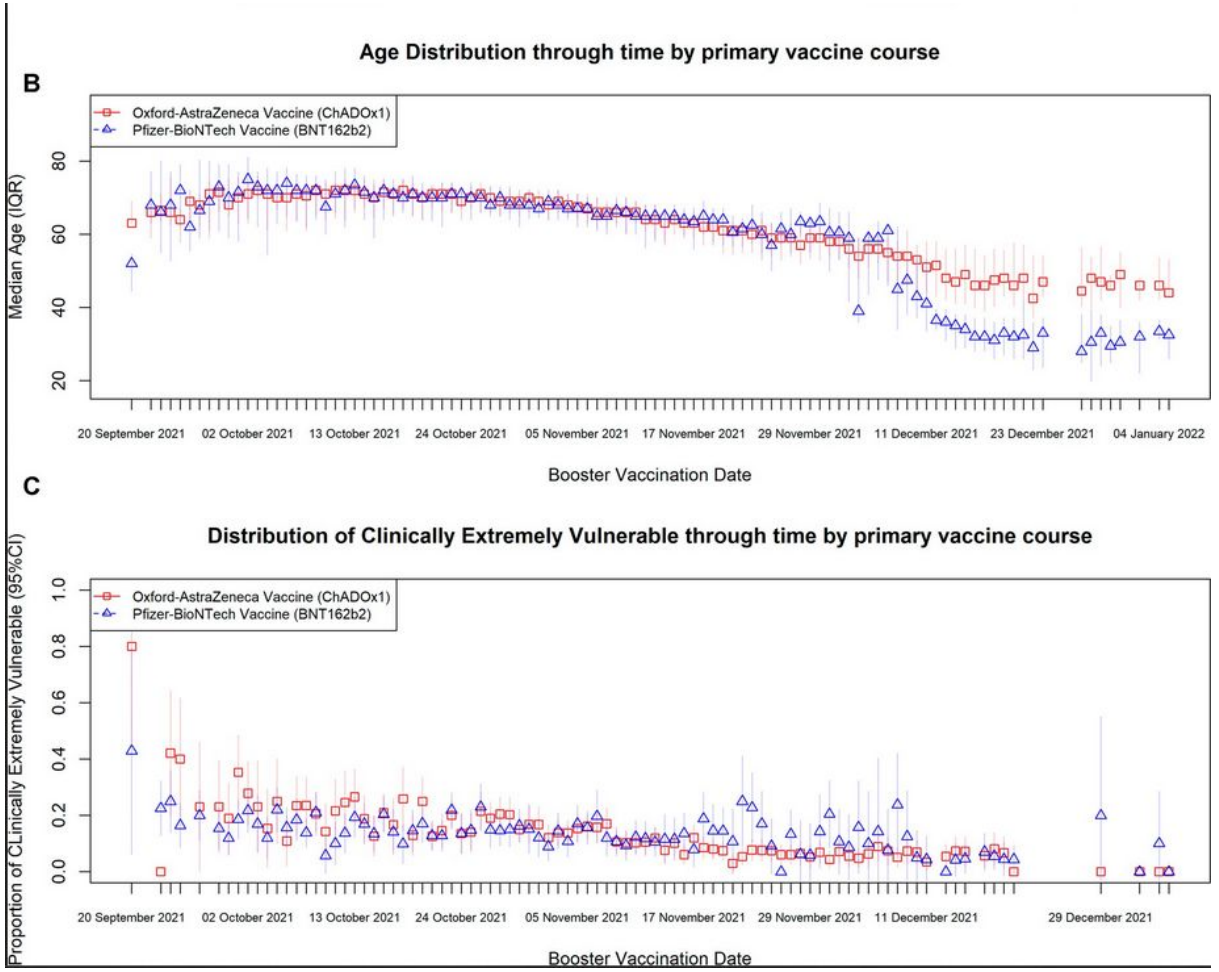
	Ideal randomised controlled trial	**Trial emulation**
Eligibility criteria	• At least 18 years old • No prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection • Two doses of the SARs-CoV-2 vaccine	• At least 18 years old when vaccinated • No recorded SARS-CoV-2 infection prior to booster vaccination date, defined usi Spike protein before 2021 • Two doses of the SARs-CoV-2 vaccine
Recruitment period	16 September 2021 to 05 January 2022	16 September 2021 to 05 January 2022 split by 14-day intervals: • Cohort 1: 16 September 2021 to 29 September 2021 • Cohort 2: 30 September 2021 to 13 October 2021 • Cohort 3: 14 October 2021 to 27 October 2021 • Cohort 4: 28 October 2021 to 10 November 2021 • Cohort 5: 11 November 2021 to 24 November 2021 • Cohort 6: 25 November 2021 to 08 December 2021 • Cohort 7: 09 December 2021 to 22 December 2021 • Cohort 8: 23 December 2021 to 05 January 2022
Follow-up duration	From 16 September 2021 to 23 January 2022	From recorded booster vaccination date until 23 January 2022
Outcome	i. Positive PCR test for SARS-CoV-2 ii. Positive LFT for SARS-CoV-2	iii. Positive PCR test for SARS-CoV-2 (self-reported or linked data) iv. Positive LFT for SARS-CoV-2 (self-reported or linked data)
Treatments to be compared	Booster dose with primary course of the Oxford-AstraZeneca vaccine (ChAdOx1) Booster dose with a primary course of the Pfizer-BioNTech vaccine (BNT162b2)	Booster dose with primary course of ChAdOx1 Booster dose with a primary course of BNT162b2
Estimand	Intention to treat based upon primary course	Intention to treat based upon primary course
Analysis plan	Survival analysis (Kaplan–Meier estimator)	Survival analysis (pooled multivariable Cox proportional hazard models)

Results - Numbers analysed through time

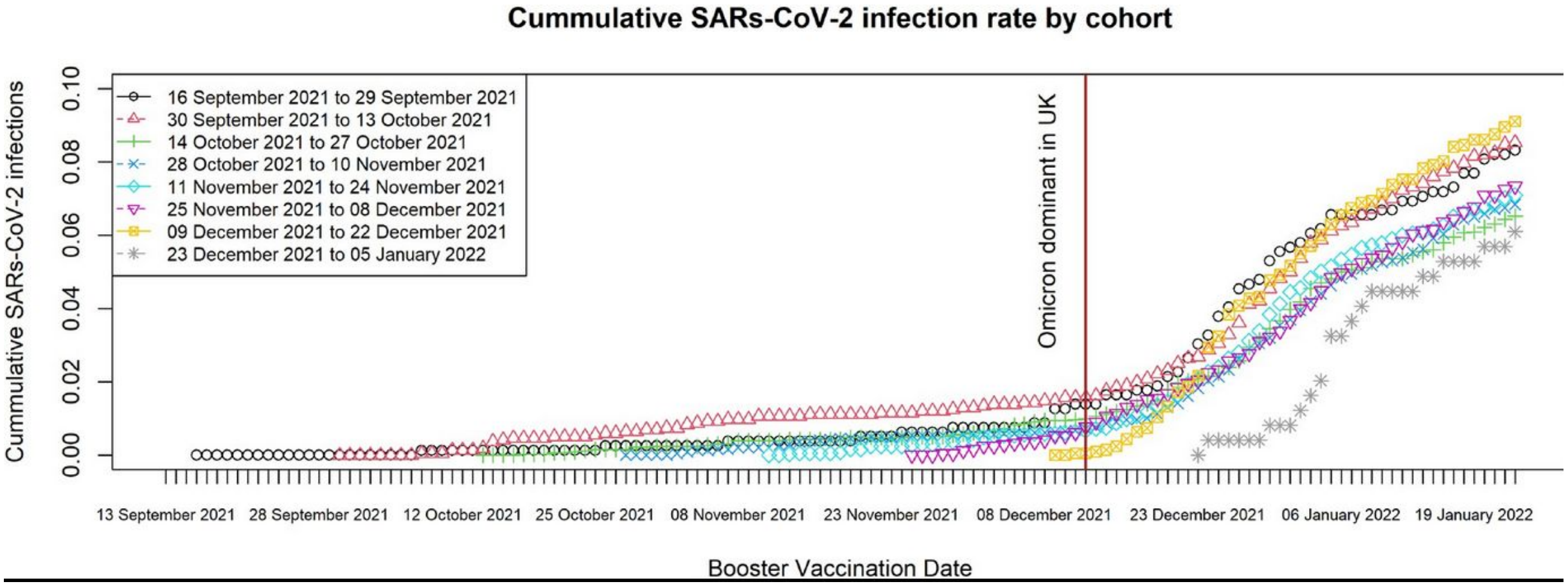
Total = 19,159; Pfizer = 7,450; Oxford = 11,709



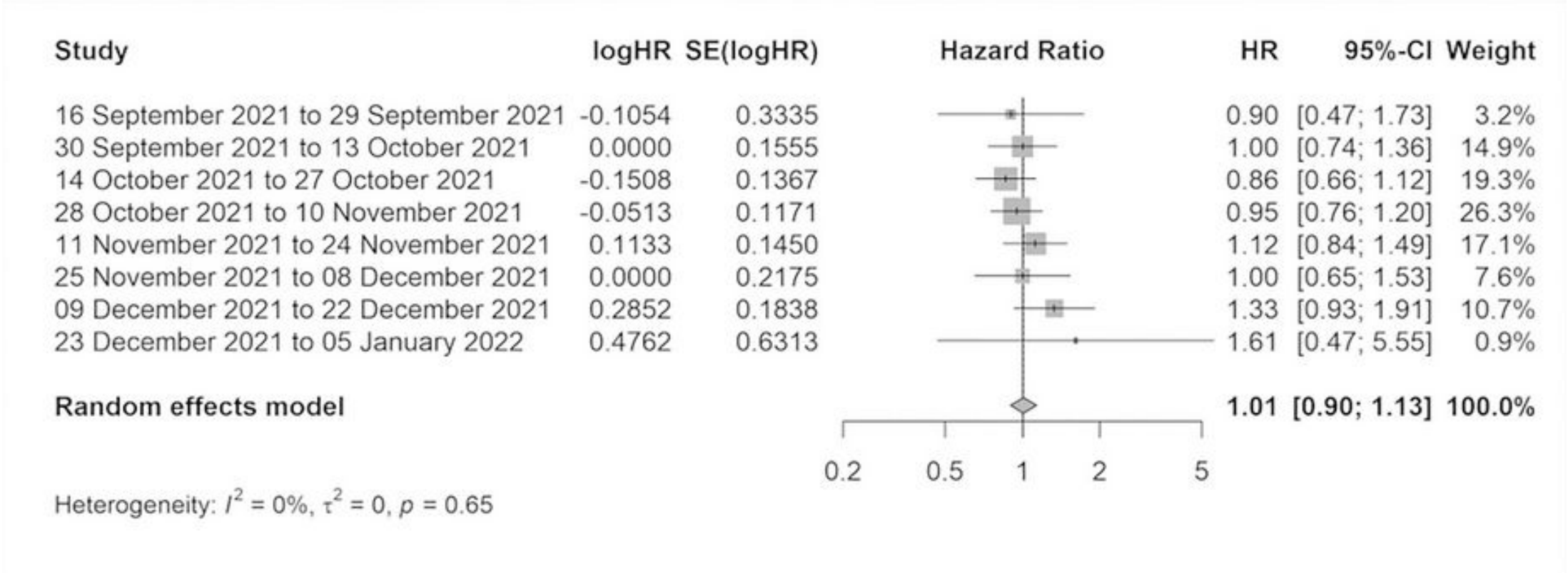
Results - Age and Clinical Vulnerability through time



Results - Infection Rates through time



Results - Pooled multivariable Hazard Ratios



HR adjusted for: Age (continuous), Sex (female, male), minority ethnic status (White British,Ethnic Minority), Clinically Vulnerability (Clinically extremely vulnerable, Clinically vulnerable, None Identified) and Deprivation (Index of Multiple Deprivation Quintile)

Results Sensitivity Analysis

Description of Analysis	**Updated Hazard ratio** **<1: BNT162b2 better** **>1: ChADox1 better** **=1:no difference**
Primary Analysis - 19000-ish participants	1.01 (95%CI: 0.90 to 1.13)
Did not remove those with prior SARs-CoV-2 infections - adjusted for prior infection Requested by reviewers due to breakthrough infection rates	1.02 (95% CI: 0.91 to 1.14)
Only analysed those boosted with BNT162b2. Those receiving ChADOX1 were more likely to receive mRNA-1273 compared to those with a primary course of BNT162b2	1.06 (95% CI: 0.90 to 1.25)
Only used data from those with linked data to PHE to tackle 11% dropout	0.98 (95% CI: 0.86 to 1.11)
Follow-up window was changed from day of booster vaccination to 8th day after booster vaccination to account for antibody production Not primary analysis due to survival biases; also ignoring infections between day 1 and 7 may induce immortal time bias	1.01 (95% CI: 0.89 to 1.14)
Exact date matching instead of staggered cohorts* - 3000-ish participants	1.01 (95% CI: 0.75 to 1.35)

Discussion, Limitation, Strengths

Findings

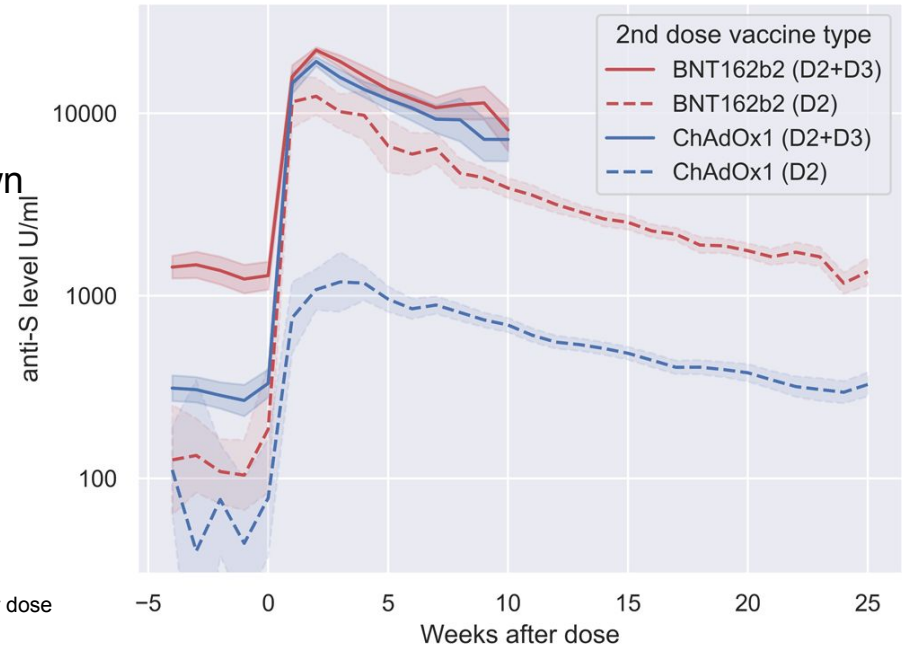
- Short term follow-up estimated no differential in mRNA-boosted individuals based upon differential primary courses (mRNA vs Chimpanzee Adenovirus)
- Analyses of vaccination should consider the time-varying confounding-by-indication induced by the priority distribution of vaccines based upon age and clinical vulnerability and new variants - often known as Cohort effects in social sciences
- If you do see this effect, consider staggering your cohorts and find the right balance between your window and statistical power

Limitations

- Staggering reduces sample size/covariate adjustment set for each local cohort (e.g. ethnicity was binary, could not measure geography)
- Full case analysis - further Virus Watch work has reduced missingness in certain known sociodemographic variables
- Outcome was SARs-CoV-2 infection, not COVID-19 but most tests were symptomatic

Strengths

- Reduction of time-varying confounding by indication based upon booster prioritisation
- Reduced time-zero biases based upon changes in SARs-CoV-2 variant
- Triangulates very well with Spike-antibody levels



Yavlinsky A, Beale S, Nguyen V *et al.* Anti-spike antibody trajectories in individuals previously immunised with BNT162b2 or ChAdOx1 following a BNT162b2 booster dose [version 1; peer review: awaiting peer review]. Wellcome Open Res 2022, **7**:181 (https://doi.org/10.12688/wellcomeopenres.17914.1)

Further Reading Material on Trial Emulation

Resources on the Target Trial Emulation Framework - Epidemiology methods based upon conditional regression

- Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. *JAMA.* 2022;328(24):2446–2447. doi:https://doi.org/10.1001/jama.2022.21383
- Miguel A. Hernán , James M. Robins, Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available, *American Journal of Epidemiology*, Volume 183, Issue 8, 15 April 2016, Pages 758–764, https://doi.org/10.1093/aje/kwv254
- Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008 Nov;19(6):766-79. doi: https://doi.org/10.1097/EDE.0b013e3181875e61. PMID: 18854702; PMCID: PMC3731075.

Resources on Causal Inference using Observational data: Statistic Methods to estimate potential outcomes

- Hernán MA. The hazards of hazard ratios. Epidemiology. 2010 Jan;21(1):13-5. doi: https://doi.org/10.1097/EDE.0b013e3181c1ea43. Erratum in: Epidemiology. 2011 Jan;22(1):134. PMID: 20010207; PMCID: PMC3653612.
- Smith, MJ, Mansournia, MA, Maringe, C, et al. Introduction to computational causal inference using reproducible Stata, R, and Python code: A tutorial. *Statistics in Medicine*. 2022; 41(2): 407– 432. doi: https://doi.org/10.1002/sim.9234
- Megan S. Schuler , Sherri Rose, Targeted Maximum Likelihood Estimation for Causal Inference in Observational Studies, *American Journal of Epidemiology*, Volume 185, Issue 1, 1 January 2017, Pages 65–73, https://doi.org/10.1093/aje/kww165

Comprehensive Resources on Target Trial Emulation and Potential Outcomes Framework

- “Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.”: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/