UK Health Security Agency

Real world measurement of COVID-19 vaccine effectiveness through the pandemic and beyond

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With many thanks to Nurin Abdul Aziz, Nick Andrews and Julia Stowe

The COVID-19 pandemic

- Unprecedented vaccine development
  - Including the use of a new platform – mRNA
- Highly unpredictable virus with high genetic variability
  - Rapid development new variants / lineages
  - New variants and lineages become dominant in the matter of months
- Need for rapid assessment where the standard phase III / RCT trails will not be practical

History of the COVID-19 vaccine programmme in the UK

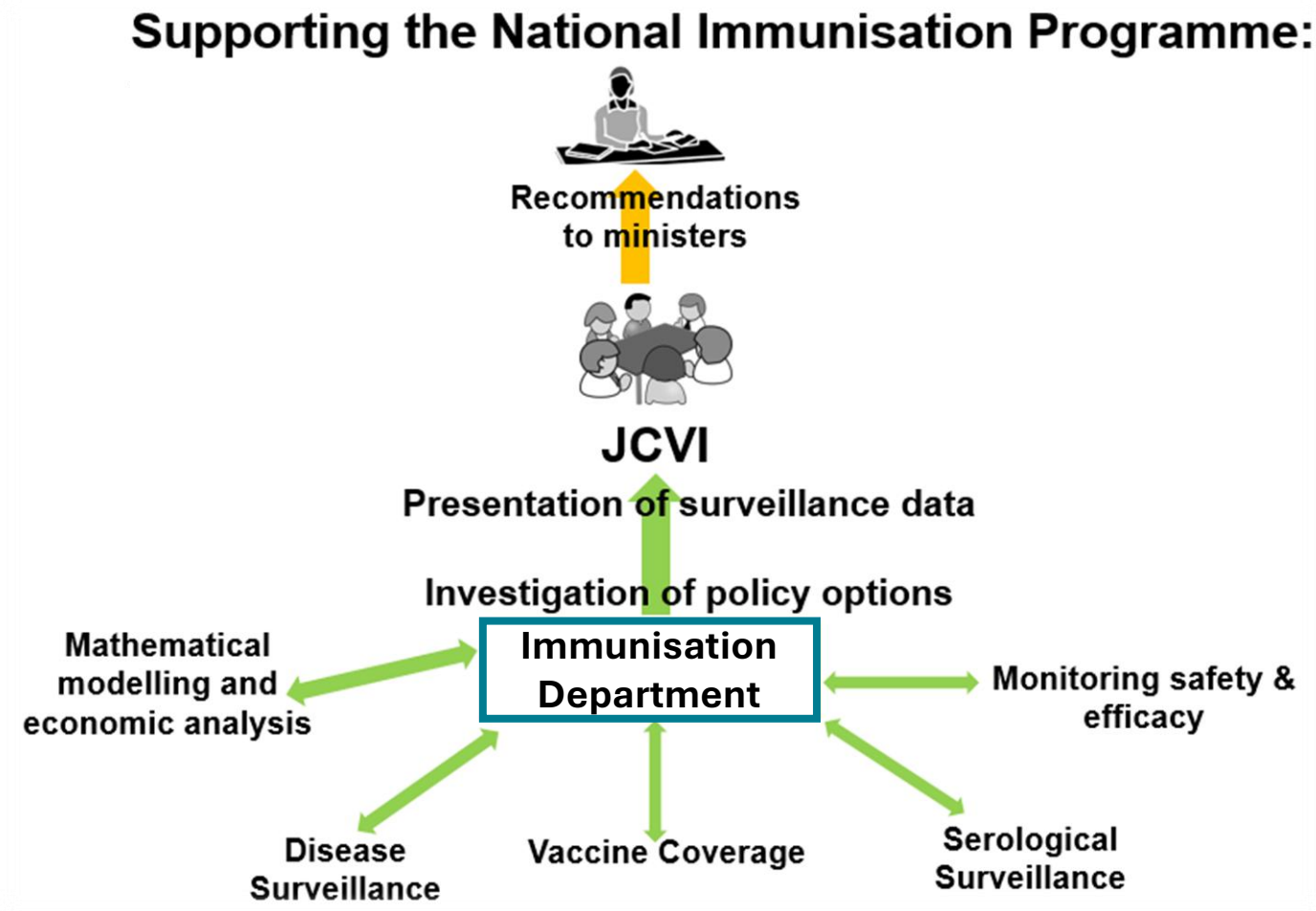
- Initial use of the Oxford-AstraZenca (ChAdOx1) and Pfizer mRNA vaccine (Comirnaty) for a population based programme

December 2020 – June 2021

  - Phased approach by risk groups (age, clinical risk factos, key workers)
  - Initial 2 dose primary schedule
  - 3rd booster dose also recommended for whole populations

- On-going programme has developed into a twice per year campaign (spring and autumn) focused on groups at higher risk of severe disease
  - Initially ages >65, care home residents, health and social care workers and a broad range of clinical risk groups
  - Now ages >75, care home residents and those with suppressed immune systems

Vaccine policy in the UK

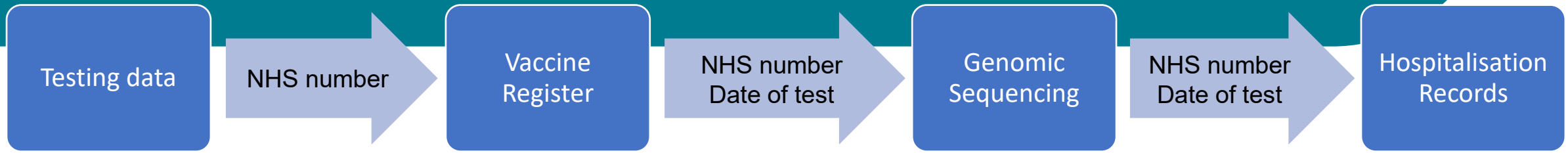


JCVI provides advice and recommendations used by Government to inform, develop and make policy.

Real world evidence for vaccine evaluation

- Test negative case control
- Age discontinuity
- Safety monitoring – self controlled case study

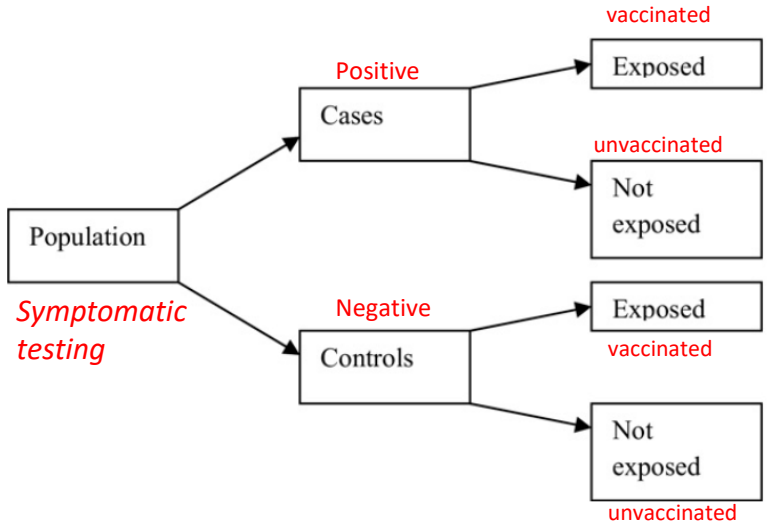
Test negative case control studies



- Case-control study but in cases and controls all pulled from symptomatic population testing for COVID-19
- Reduces bias related to reason for testing as often related to vaccination
  - Tries to reduce bias associated with health seeking behavior and health care access
- Odds of testing positive in vaccinated compared to unvaccinated
- Logistic regression with VE = 1 – *adjusted* odds ratio

In addition to vaccination status the model includes adjustments for

age (5 year bands to 90+), sex, period (week of sample), ethnicity, IMD quintile, health/social care worker (under 65s), Care home (65+), nhs region, clinically vulnerable , Severely immunosuppressed, “Risk group” (under 65s)

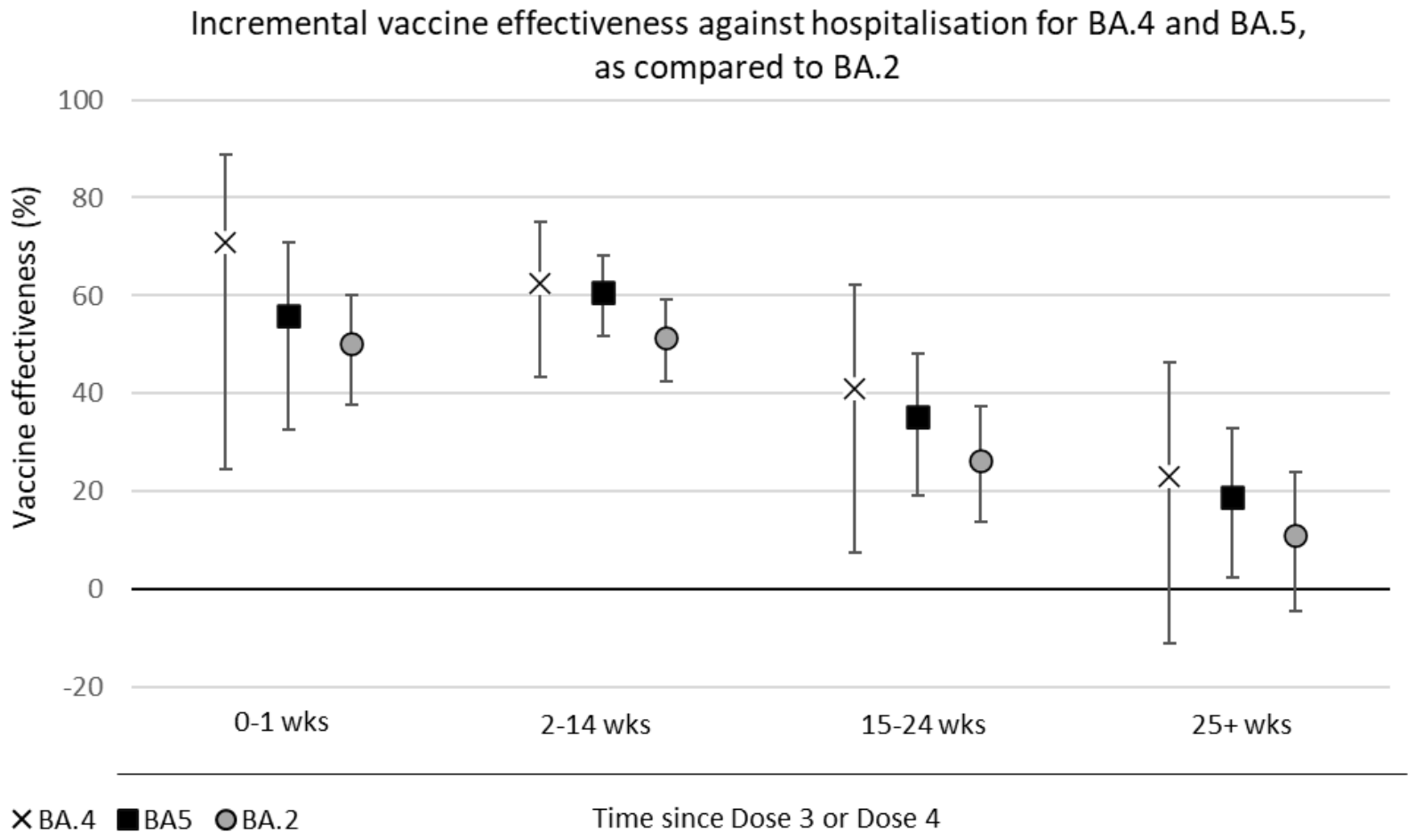


Test negative case control studies

Test-negative case-control – study population: hospitalised individuals

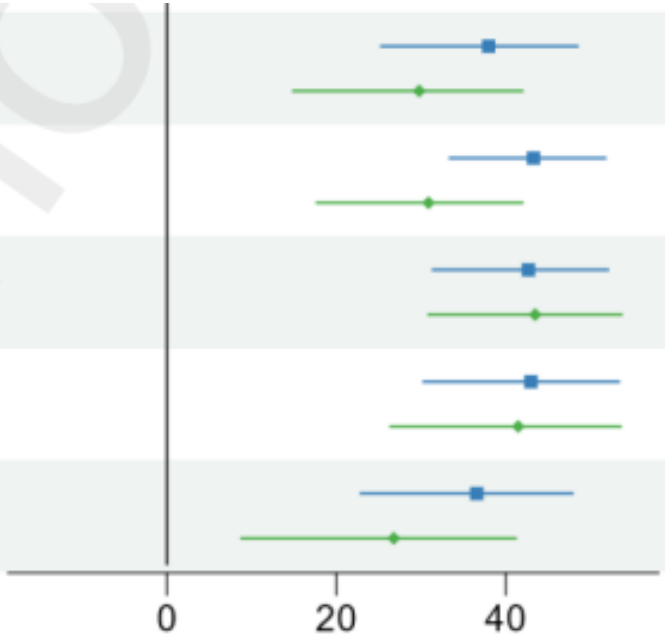
- Hospitalisation = admission where a COVID-19 PCR test was conducted and admission was associated with a respiratory ICD-10 code
- VE is compared to all not receiving a booster as long as not vaccinated within the previous 12 weeks.

Example: comparison of multiple variants



Example: comparison of multiple vaccines

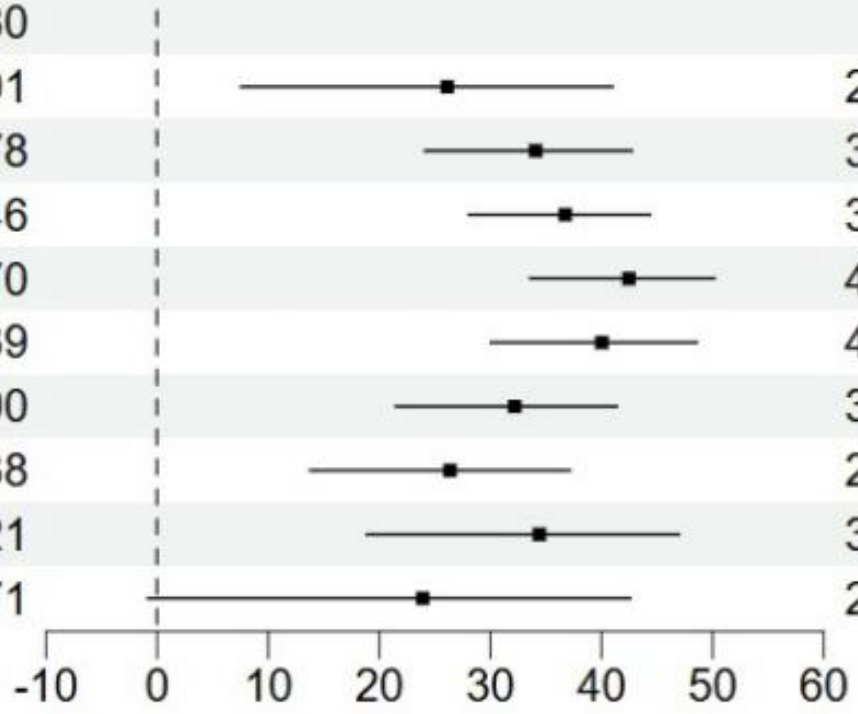
Interval since dose	Controls	Cases	VE (95% CI)
2-4 weeks	1,561	143	38 (25.3 to 48.5)
	1,393	134	29.8 (14.9 to 42)
5-9 weeks	4,777	187	43.3 (33.4 to 51.8)
	3,025	158	30.9 (17.7 to 42)
10-14 weeks	4,918	151	42.7 (31.4 to 52.1)
	3,611	114	43.5 (30.9 to 53.7)
15-19 weeks	2,910	126	43 (30.3 to 53.4)
	1,993	88	41.5 (26.4 to 53.6)
≥20 weeks	2,364	152	36.6 (22.9 to 47.9)
	1,526	112	26.8 (8.8 to 41.2)



Group
Moderna JN.1
Pfizer JN.1

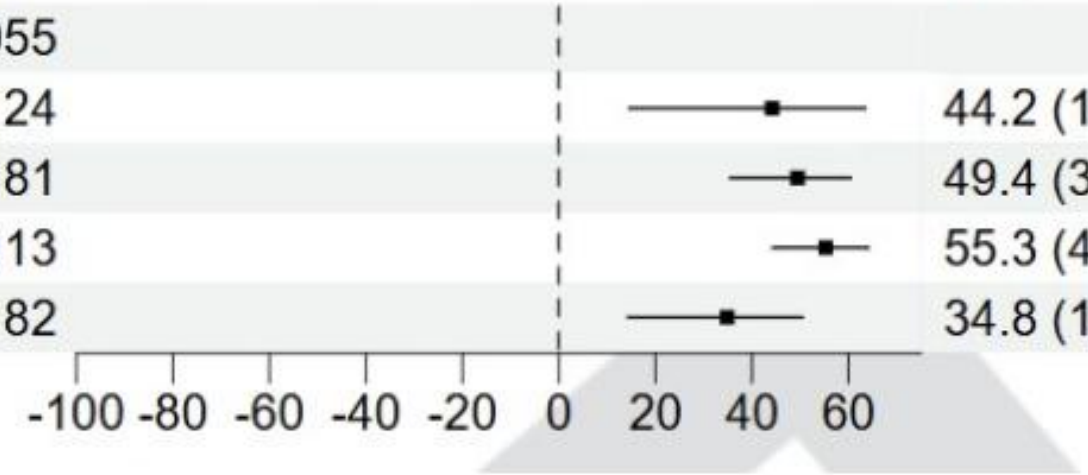
Long-term vaccine effectiveness (VE) of the COVID-19 autumn 2024 booster against hospitalisation amongst those aged 65 years and older in England

Interval since dose	Controls	Cases	VE (95% CI)
No booster received	33,101	4,080	
9-13 days	621	101	26.1 (7.6 to 40.9)
2-4 weeks	3,006	278	34.1 (24.2 to 42.7)
5-9 weeks	7,915	346	36.7 (28.1 to 44.4)
10-14 weeks	8,751	270	42.5 (33.6 to 50.2)
15-19 weeks	5,330	239	40.0 (30.1 to 48.6)
20-24 weeks	4,419	290	32.2 (21.6 to 41.4)
25-29 weeks	2,684	238	26.4 (13.8 to 37.1)
30-34 weeks	1,192	121	34.4 (18.9 to 47.0)
≥35 weeks	556	71	23.9 (-0.8 to 42.6)

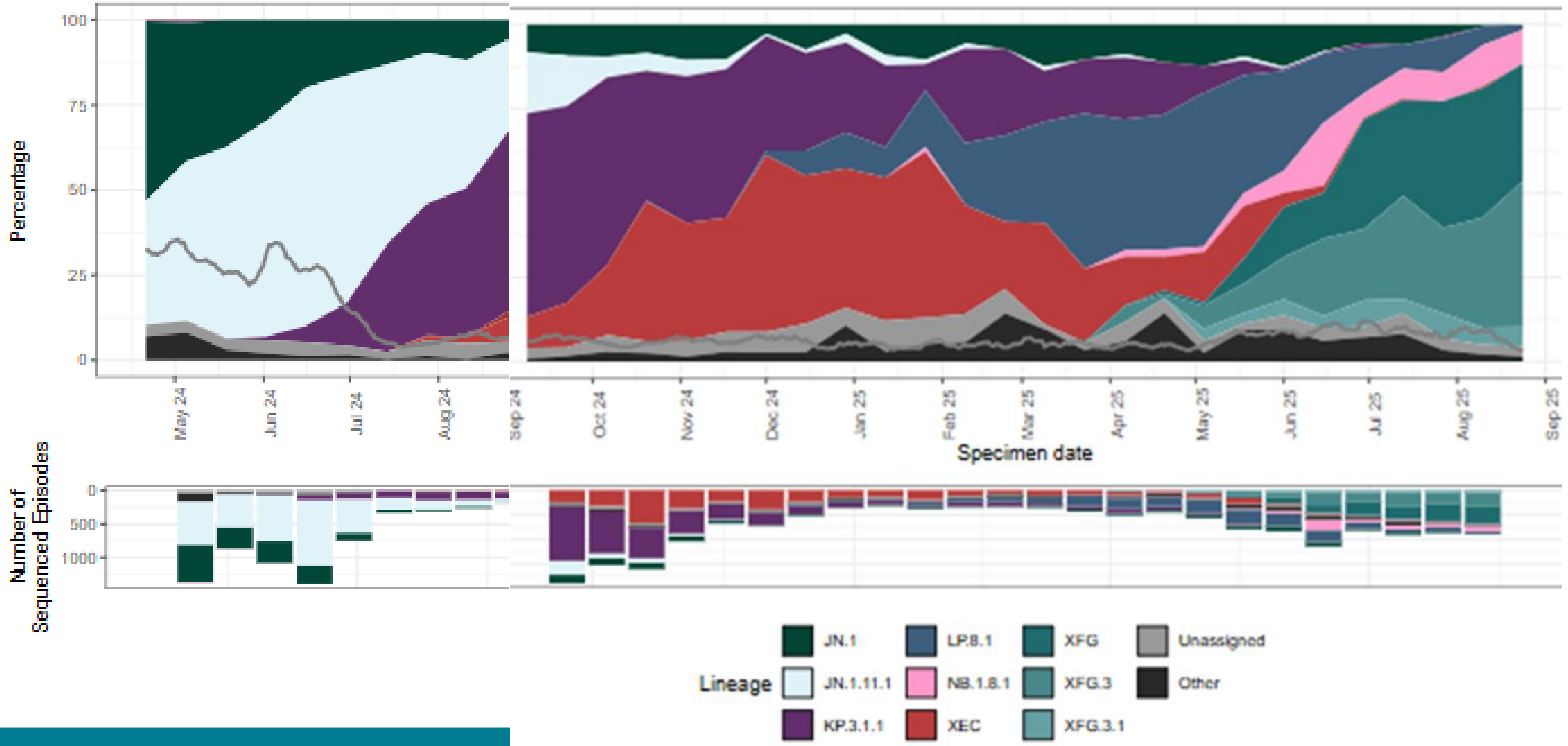


Vaccine effectiveness (VE) of the COVID-19 spring 2025 booster against hospitalisation amongst those aged 75 years and older in England

Interval since dose	Controls	Cases	VE (95% CI)
No booster received	8,969	1,055	
9-13 days	372	24	44.2 (14.7 to 63.4)
2-4 weeks	1,340	81	49.4 (35.6 to 60.3)
5-9 weeks	1,656	113	55.3 (44.4 to 64.1)
10-14 weeks	746	82	34.8 (14.3 to 50.4)



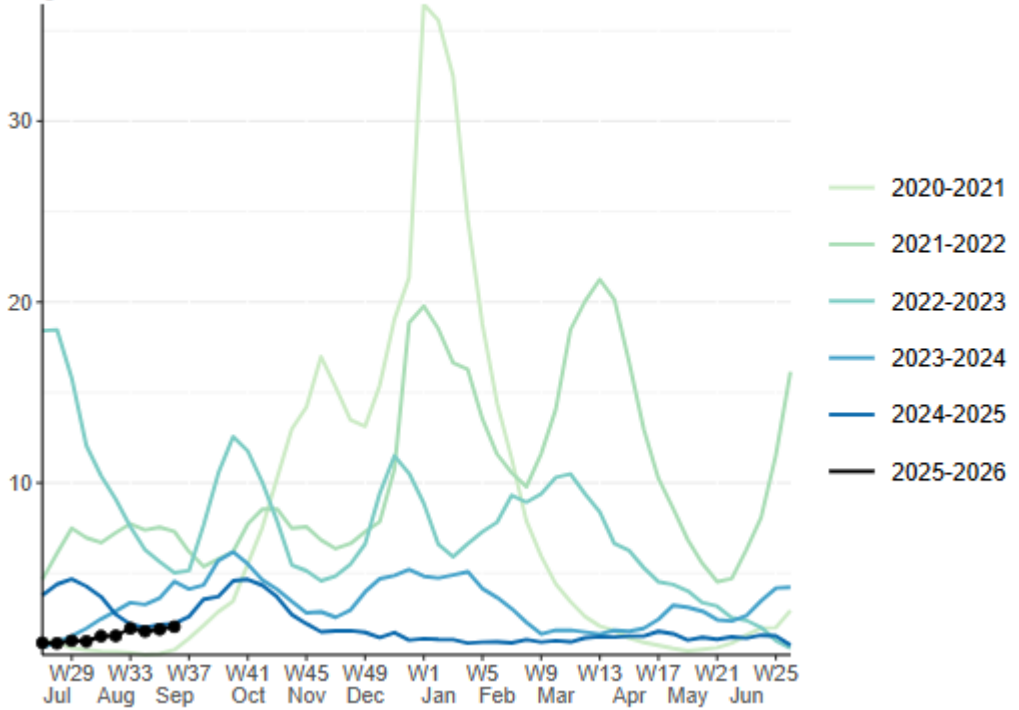
Variant distribution May 2024-Aug 2025



Epidemological context

- Evidence that the full waning by 6m we have seen for booster doses (such as spring 2024) did not happen for the autumn 2024 dose.
- Despite this we still got good VE for the spring 2025 dose even in those who had an autumn dose - too early to check waning for that dose.
- Perhaps better vaccine match for autumn 2024/spring 2025?
- These VE estimates have been in a period of low incidence / hospitalisations.

Figure 6. Weekly overall COVID-19 hospital admission rates per 100,000 trust catchment population reported through SARI Watch mandatory surveillance, England



UK Health Security Agency

Age discontinuity analysis – mortality surveillance

Rationale

- At and above the age cut off for the COVID-19 vaccine, we would expected a massive increase in coverage
- We expect the population just above and just below this cut off to be extremely similar is terms of other contributory factors
- Provides a natural experiment, ideally controlling for confounding in a manner similar to randomisation (it is effectively random whether someone is just above or just below the cut-off)
- Therefore the difference in outcomes (death) should be primarily due to the intervention (the COVID-19 vaccine)

- We aimed to assess the impact of spring boosters given in England in the spring periods of 2022,2023 and 2024.
- An age discontinuity approach is used because a large coverage difference is expected at age 75 within those without an immunosuppression flags (since those at highest risk were also eligible below age 75).
- A discontinuity may therefore be expected at age 75 when looking at the period after vaccine introduction.
- The main analysis will use COVID-19 rates in the period 8 weeks before introduction as a “control” and so model the ratio of post:pre by age in years. This was done using hospitalised COVID-19 for 2022 and 2023 (Andrews et al, 2024).
- An alternative is just to use post vaccination rates of covid-19 by age.

Methods – deaths and risk flags

- ONS deaths with Covid-19 mention anywhere on the death certificate were extracted by week for the period from week 1 2022 to week 40 2024.
- For the deaths in week 1 to week 52 of each year (2022,2023,2024 (to week 40) age in years was calculated based on age on April 1st of each year.
- Risk group was assigned as below:
  - Clinically extremely vulnerable and severely immunosuppressed flags from August 2022 for deaths from Week 1 2022 to Week 34 2022,
  - IIS risk flags from Autumn 2022 for deaths from Week 35 2022 to Week 34 2023
  - IIS risk flags from Autumn 2023 for deaths from Week 35 2023 to Week 40 2024
- Note that for the risk flag Immunosuppression was better defined for the autumn 2022 and 2023.
- Those aged 65+ and without an immunosuppression risk flag retained for analysis

Periods

- The pre and post periods used were as in the table below:

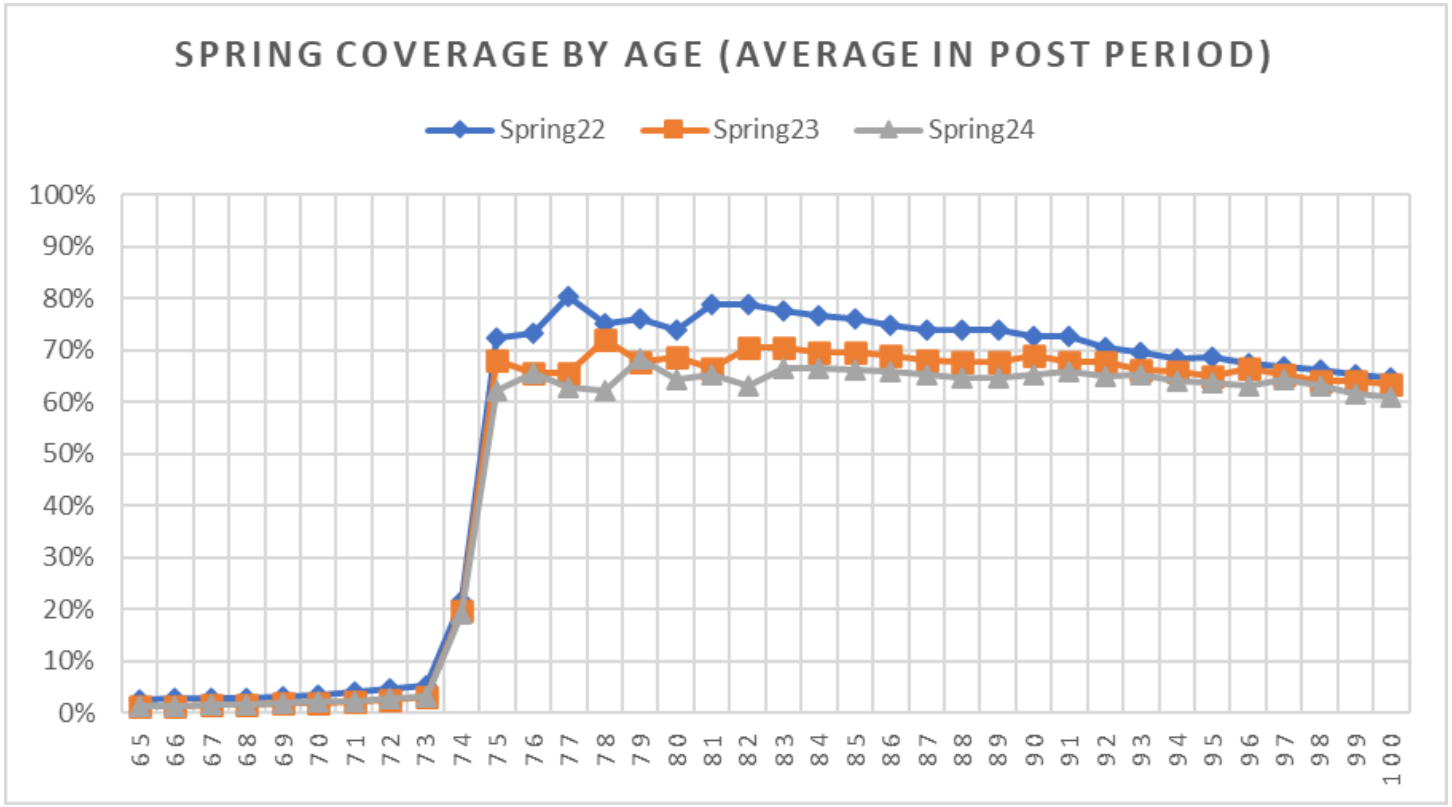
Year	Pre	Post
2022	Weeks 5-12	Weeks 17-33
2023	Weeks 8-15	Weeks 20-35
2024	Weeks 9-16	Weeks 21-36

- So 8 weeks before roll out, then a 4 week washout period as vaccine uptake increases, then a 16-17 week post period (2022 was 17 weeks although the intention was 16 weeks I think)

Methods / Analysis

- The main analysis planned was a negative binomial regression model on the counts post vaccination with an offset for the pre-counts.
- To optimise power all three years initially modelled together with a factor for year, a common age trend and an indicator variable for age<74 and >=75 (with age 74 excluded by allowing it to have a separate level on the indicator variable).
- Models allowing the age trend to vary by year, and vary pre and post age 75 were assessed. Also models with a different vaccine impact by year and with each year modelled separately.
- A model was also assessed with coverage by age used instead of the indicator variable.
- Models of just the post vaccine rates with an offset for population denominator will also be assessed.

Results – uptake by age

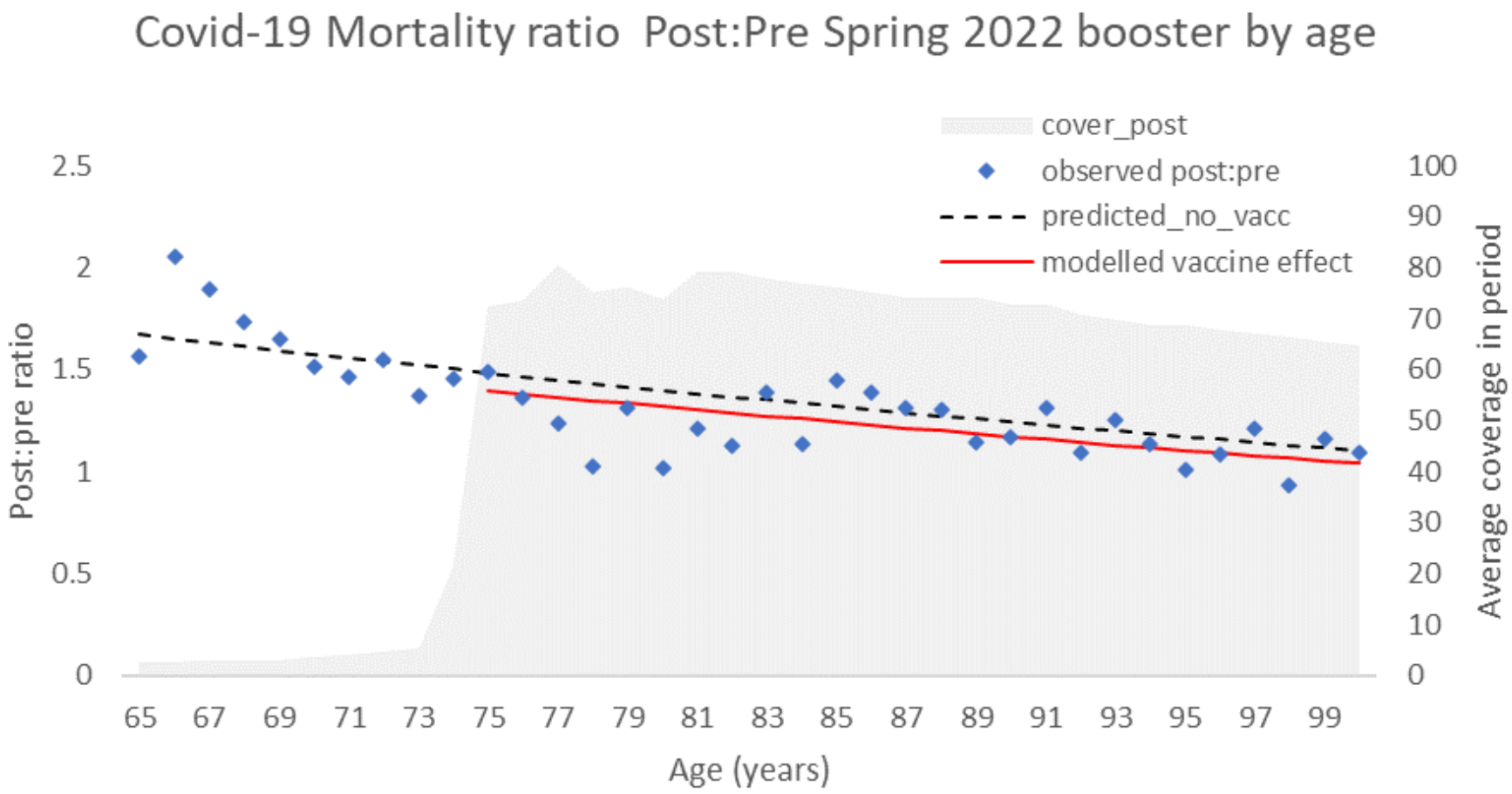


Uptake is not the final coverage but the average across the post vaccination period assessed.

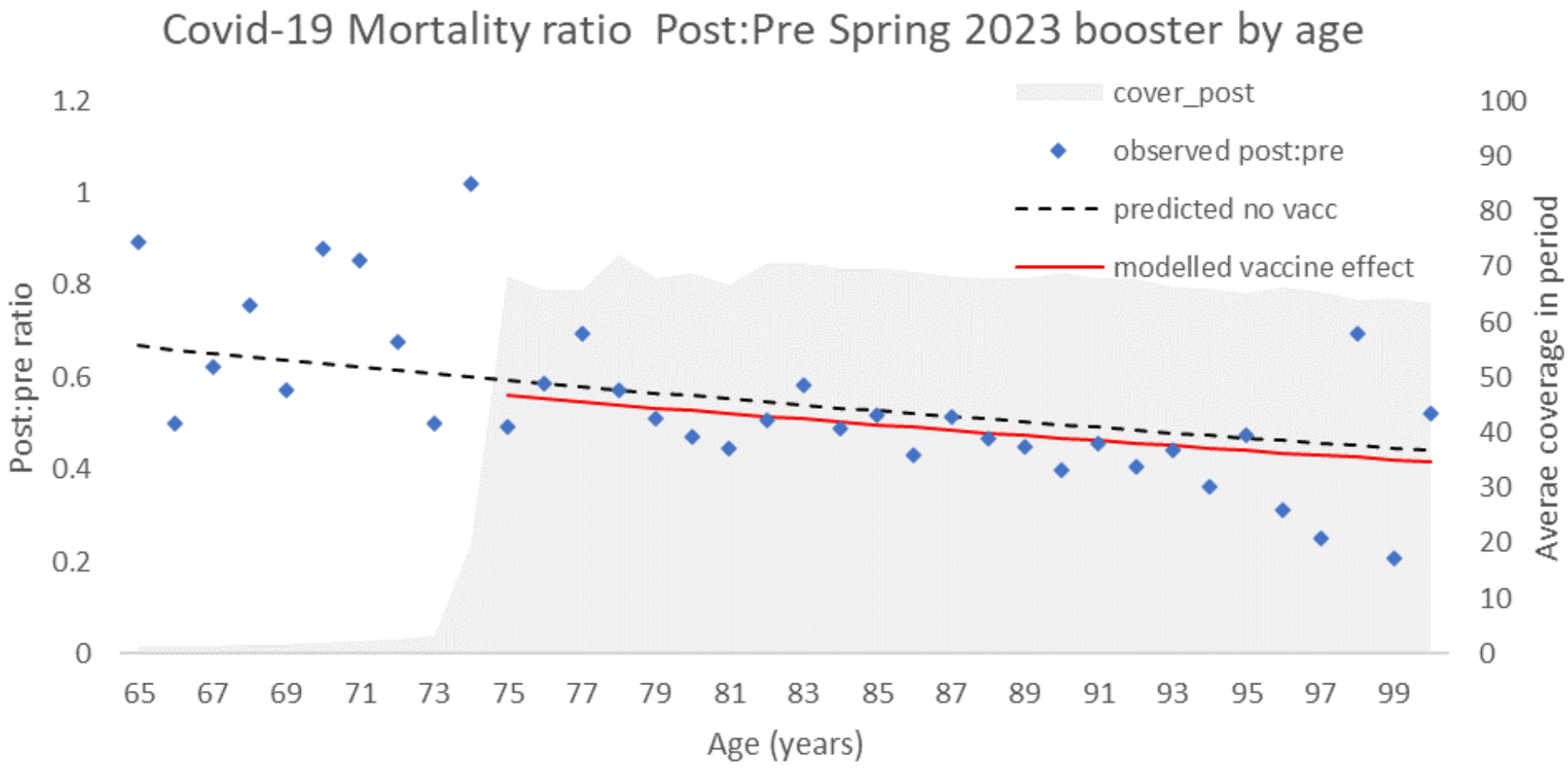
Fairly large discontinuity of about 60-70%

Some 74 years olds as of April each year were vaccinated (probably as they turned 75)

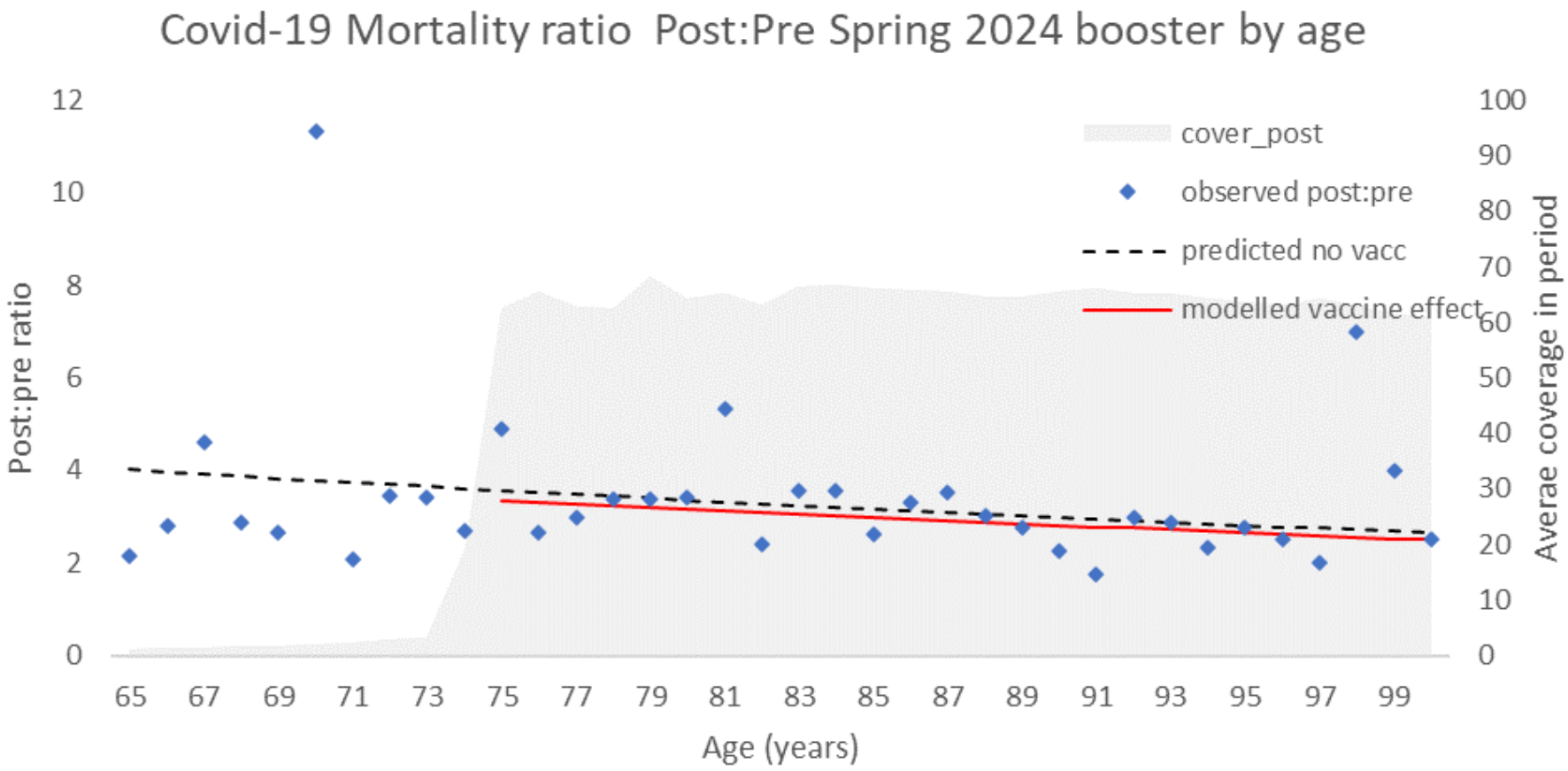
Final model on the post:pre ratio 2022



Final model on the post:pre ratio 2023



Final model on the post:pre ratio 2024



How impact compares to what we may have expected

- With average post vaccination coverage difference of about 65% then if the average VE post vacc were truly about 30% (allows waning) then an impact of 0.3*0.65 = 19.5% would be expected.

- So we seem to have less impact than expected – appears about 10% discontinuity

Why don’t we see a clear impact?

Possible reason 1: Many ONS COVID-19 deaths that are not actually caused by COVID-19

- Non-differential misclassification leading bias towards the null hypothesis.
- Could perhaps be the case as we use COVID-19 anywhere on the death certificate – how much is COVID-19 contributing?
- Going against this is fact we get 50-70% VE by case coverage **on this end point**. BUT we also know this could be biased by healthy vaccinee effects
- Could a more accurate measure be found. Hospital deaths with positive testing could be better – but numbers much smaller (or ONS coded deaths with also a positive test).

Why don’t we see a clear impact?

Possible reason2: Those getting vaccinated are skewed toward the healthy – so we see less impact.

- Certainly, we see few vaccinations given just prior to a Covid-19 death in a period we know the vaccine doesn’t work. Cohort studies also have shown VE as high as 50% against non-COVID-19 death.

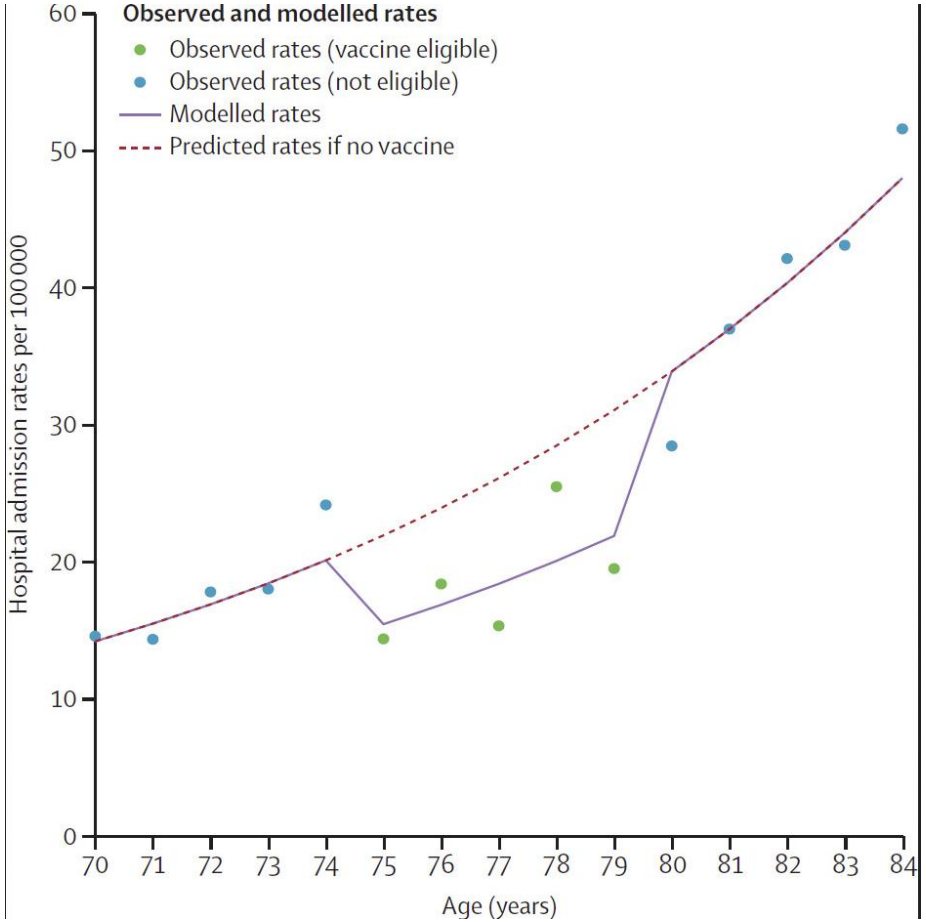
- Healthy vaccinee seems likely and can partly explain the high 50-70% VE by case coverage (and perhaps other cohort studies) compared to TNCC. If there was, for example, a 50% healthy vaccinee bias then 70% VE would drop to (1- (1-0.7)x2) = 40%

- **Possible reason 3: VE against death is truly low**

- If true it would be odd that we have good evidence of VE and Impact on hospitalised COVID-19.

- More plausible that a combination of reasons 1 and 2 is at play along with perhaps the uncertainly in the analysis.

Age discontinuity in RSV hospitalisations



Vaccine Safety

Vaccine safety is considered throughout a vaccines journey to licensure and beyond…..

Vaccine Trials

Reactogenicity
Serious adverse events
Common adverse events

Licensure

Pharmacovigilance for signal detection

Yellow Card
MHRA

Medical examiners

UKHSA: Large linked electronic data

Full epidemiological studies
(hypothesis testing)

MHRA EWG

JCVI

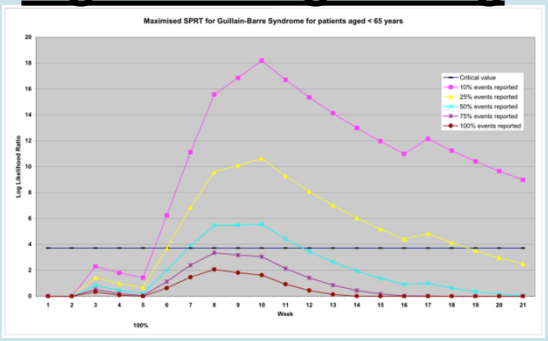

BMJ

RESEARCH

Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis


MMR vaccination and pervasive developmental disorders: a case-control study

Signal Strengthening



Plausibility, observed vs. expected, descriptive epi, experts, interval from vaccine and hypothesis generation

New era of anti-vaccine propaganda

NHS VACCINES

CONSENT CHECKLIST
FOR COVID-19 VACCINATION

If you choose to have a vaccine for yourself or your child, you should take this form to your appointment and ensure it is signed by both you and the clinician.

"Informed consent" means agreeing to something once you have been given the full information surrounding it. Informed consent is legally required in the UK *before* you undergo a medical procedure, such as COVID-19 vaccination.

Both patient/carer and clinician should tick the box for each statement they understand. See overleaf for verifications.

Statement	Patient	Clinician
1. Unlike traditional vaccines, the vaccines being used for COVID-19 ("the COVID-19 vaccines") instruct the body cells to create the SARS-CoV-2 spike protein.	☐	☐
2. The COVID-19 vaccines may reduce severity of symptoms if the patient gets COVID-19, but may not prevent them from getting COVID-19 nor from passing it on.	☐	☐
3. Although alternative treatments are available, the COVID-19 vaccines have been granted Emergency Use Authorisation, so require less comprehensive clinical data.	☐	☐
4. By 8 Sep 2021, of the 48,344,566 people that had received at least one jab, there had been 1,645 deaths (†**1 in 29,389 chance of dying from vaccine**) and 1,196,813 adverse reactions *officially reported*. The *actual* figures may be ten times higher. Adverse reactions were reported more often in younger people than in older adults.	☐	☐
5. Adverse reactions to the COVID-19 vaccines include, but are not limited to: strokes, blindness, deafness, clotting, miscarriages, anaphylaxis and cardiovascular disorders.	☐	☐
6. We will not know what the possible long term effects of the COVID-19 vaccines may be (e.g., infertility) until after the studies of the clinical trials conclude in 2023. For this reason, the COVID-19 vaccines may be considered experimental.	☐	☐
7. The manufacturers of the COVID-19 vaccines are immune from civil liability.	☐	☐
8. As of 11 Jan 2021, the average age of death in the UK with COVID-19 was 83.	☐	☐
9. Crude mortality rates from 29 Jun 2020 to 12 May 2021 show under-30's *may* be more likely to die from taking a COVID-19 vaccine† than from dying with COVID-19: • **Under fives: 1 in 500,000 chance of dying with COVID-19** • **5 to 9 years-old: 1 in 1,000,000 chance of dying with COVID-19** • **10 to 19 years-old: 1 in 166,667 chance of dying *with* COVID-19** • **20 to 29 years-old: 1 in 43,478 chance of dying with COVID-19** • 30 to 39 years-old: 1 in 12,500 chance of dying with COVID-19 • 40 to 49 years-old: 1 in 4,065 chance of dying with COVID-19 • 50 to 59 years-old: 1 in 1,399 chance of dying with COVID-19 • 60 to 69 years-old: 1 in 500 chance of dying with COVID-19 • 70 to 79 years-old: 1 in 189 chance of dying with COVID-19 • 80 years-old and above: 1 in 44 chance of dying with COVID-19	☐	☐
10. *The patient/carer does not feel coerced and is free to refuse a COVID-19 vaccine.*	☐	☐

Patient/carer:

I accept each of the above statements, and hereby give my informed consent to receive an experimental COVID-19 vaccine, for which the long-term effects are unknown.

Patient name: _____

Signature: _____ Date: _____

Clinician:

I accept the above statements, and the patient/carer has given informed consent to receive a COVID-19 vaccine. I am not liable for any resulting adverse reactions.

Clinician name: _____

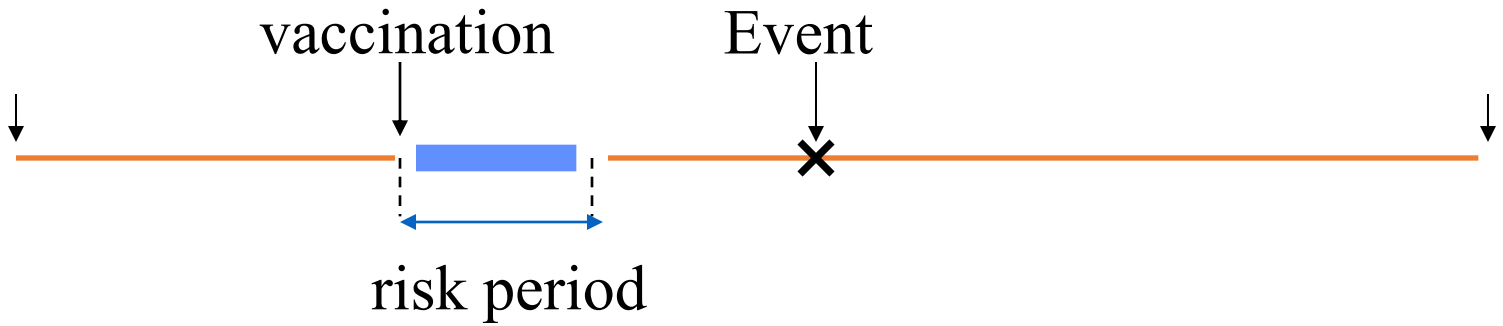
Signature: _____ Date: _____

Once signed by both parties, this form should be kept by the patient/carer.

Self Controlled Cases-Series (SCCS) method

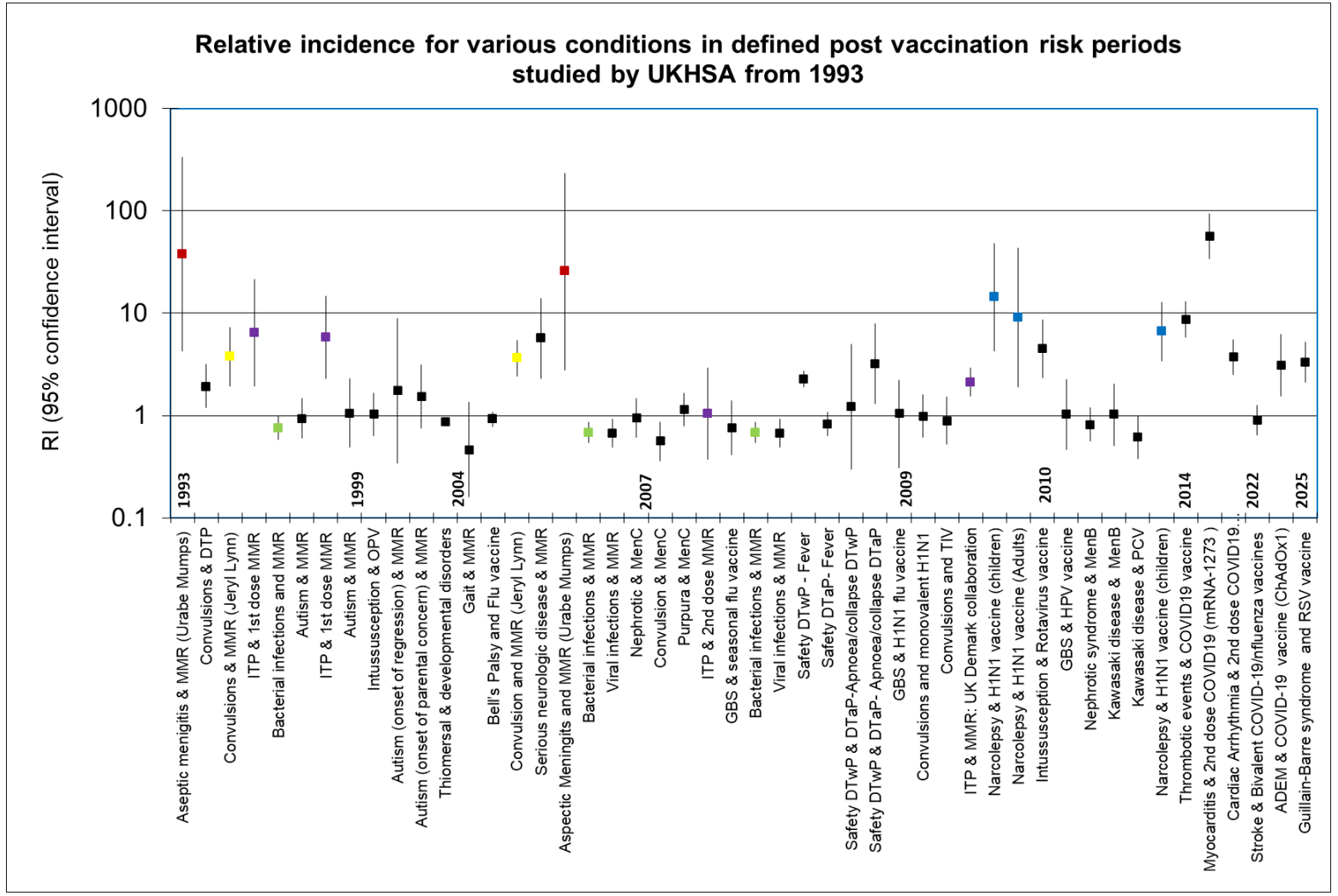
Self controlled case series for automatically linked datasets:

- Uses *cases only* with vaccination dates
- For each individual each day and event in the study period will fall inside or outside the risk period.
- Compare risk of events in risk period to background
- Automatic within subject confounder adjustment
- Unbiased ascertainment of all or a sample of cases in a given age group and study period and their vaccination details.



- Relative incidence = Events inside risk period / days inside risk period .
  Events outside risk period / days outside risk period
  - Method automatically controls for long and medium term individual level confounders
  - Same power as cohort study

Vaccine safety questions addressed using large linked datasets



- Pick up rare adverse events
- High relative incidence doesn't mean large number of cases attributable to the vaccine
- Self-limiting conditions
- Vaccine not in use anymore

References / Sources

- COVID-19 binnual report - https://www.gov.uk/government/publications/epidemiology-of-covid-19-in-england
- Weekly respiratory virus surveillance report - https://www.gov.uk/government/statistics/national-flu-and-covid-19-surveillance-reports-2025-to-2026-season
- UKHSA data dashboard - https://ukhsa-dashboard.data.gov.uk/
- RSV age discontinuity - https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)00346-0/fulltext
- Selected papers:
  - Andrews, Nick, et al. "Covid-19 vaccine effectiveness against the Omicron (B. 1.1. 529) variant." *New England Journal of Medicine* 386.16 (2022): 1532-1546.
  - Kirsebom, Freja Cordelia Møller, et al. "Vaccine effectiveness against hospitalisation estimated using a test-negative case-control study design, and comparative odds of hospital admission and severe outcomes with COVID-19 sub-lineages BQ. 1, CH. 1.1. and XBB. 1.5 in England." *The Lancet Regional Health–Europe* 35 (2023).
  - Aziz, Nurin Abdul, et al. "Effectiveness of spring 2024 (XBB. 1.5) and autumn 2024 (JN. 1) COVID-19 vaccination against hospitalisation in England." *Vaccine* 67 (2025): 127870.

Thank you!

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