Target Trial Emulation in a DARWIN EU® Vaccine Effectiveness study

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Research question

What is the effectiveness of HPV vaccination in the prevention of severe disease outcomes in women, including invasive cervical cancer and CIN2+ for the different licensed HPV vaccines in Europe (Spain, UK, Norway) ?

Objectives

Main – Vaccine Effectiveness against:

1- Invasive cancer

2- CIN 2/3

3- Conisation

Potential pitfall: different % of vax according to outcome risk -> low baseline exchangeability?

Secondary - Comparative Effectiveness:

1- Between valency/brands

2- Between dose schedules

Estimand Framework (EF) & Target Trial Emulation (TTE)

EF	TTE
Population	Elegibility Criteria
Treatment conditions	Treatment Strategies
	Assignment procedures
Endpoints	Outcome
	Follow-up period
Handling of Intercurrent events	Casual contrast
Summary measure	Analysis plan
Statistical analysis plan	

EF / TTE: Population/Eligibility criteria

Population:

Women eligible for HPV vaccine/s

Females eligible (9 years or older - as per drug approval) any date after the launch of the HPV vaccine in the contributing data partners

National Schedules

UK Schedule			
Date	**Brand**	**N doses before 15 yo**	**First dose**
01 **September 2008**	Cervarix	3	12-13 yo
01 September 2012	Gardasil	3	12-13 yo
01 September 2014	Gardasil	2	12-13 yo
01 April 2018	Gardasil	2	12-13 yo
01 September 2019	Gardasil	2	12-13 yo
01 April 2022	Gardasil	2	12-13 yo
01 July 2022	Gardasil 9	2	12-13 yo
01 September 2023	Gardasil 9	1	12-13 yo

Catalonia schedule			
Date	**Brand**	**N doses before 15 yo**	**First dose**
01 **September 2008**	Gardasil	3	11-13 yo
01 September 2010	Cervarix /Gardasil in Barcelona (20%)	3	11-13 yo
01 September 2011	Gardasil / Some Cervarix surplus	3	11-13 yo
01 September 2014	Gardasil	2	11-13 yo
01 September 2017	Gardasil 9	2	11-13 yo
01 May 2018	Gardasil 9	2	11-13 yo
01 September 2022	Gardasil 9	2	11-13 yo

Norwegian schedule			
Date	**Brand**	**N doses before 15 yo**	**First dose**
01 **September 2009**	Cervarix	3	12-13 yo

EF / TTE: Population/Eligibility criteria

Decision 1 - to maximise baseline exchangeability:

To restrict to those eligible for 'universal' vaccination programmes / campaigns

- Females eligible for the vaccination programme in each country (e.g. born on or after 1995-6), and in observation and alive in the database between 9 to 15 years old

EF / TTE: Population/Eligibility criteria (2)

Decision 2 - to maximise [conditional] exchangeability:

-Match on database, year of birth, GP practice

-Match on propensity scores (conditional probability of vaccination based on baseline characteristics)

EF / TTE: Treatment conditions / strategies

Treatments :

Vaccinated with Gardasil/Silgard

Vaccinated with Cervarix

Vaccinated with Gardasil-9

Unvaccinated

TTE: Time zero and follow up

Start of follow up (time zero):

-Vaccinated: The moment they receive the first dose of HPV vaccine (before age 15)

-Unvaccinated: Moment matched pair receives the vaccine

End of follow up:

-Death

-Loss to follow-up (migration, end of study)

-Outcome

EF / TTE: Endpoints / Outcomes

Endpoints / Outcomes at 5/10/15 years :

Invasive cervical cancer

CIN 2+

Conisation

Potential pitfall: Differential screening in vaccinated vs unvax -> loss of exchangeability over time (survival bias)

TTE : Causal contrast

‘Per protocol’

Unvaccinated censored if they receive the vaccine

Vaccinated censored in further vaccination only for dose analyses

EF : Handling of intercurrent events

Treatment-related

-Unvaccinated: vaccination, dealt with a hypothetical strategy

-Vaccinated: Incomplete dosing dealt with a treatment policy strategy

EF/TTE : Analysis plan

Matched cohort

Exact on year of birth, year of first dose and geographic region or GP practice

Further matching by nearest neighbour with PS

EF/TTE: Summary Measure

At 5, 10, 15 years:

Incidence Rates and Incidence rate ratios

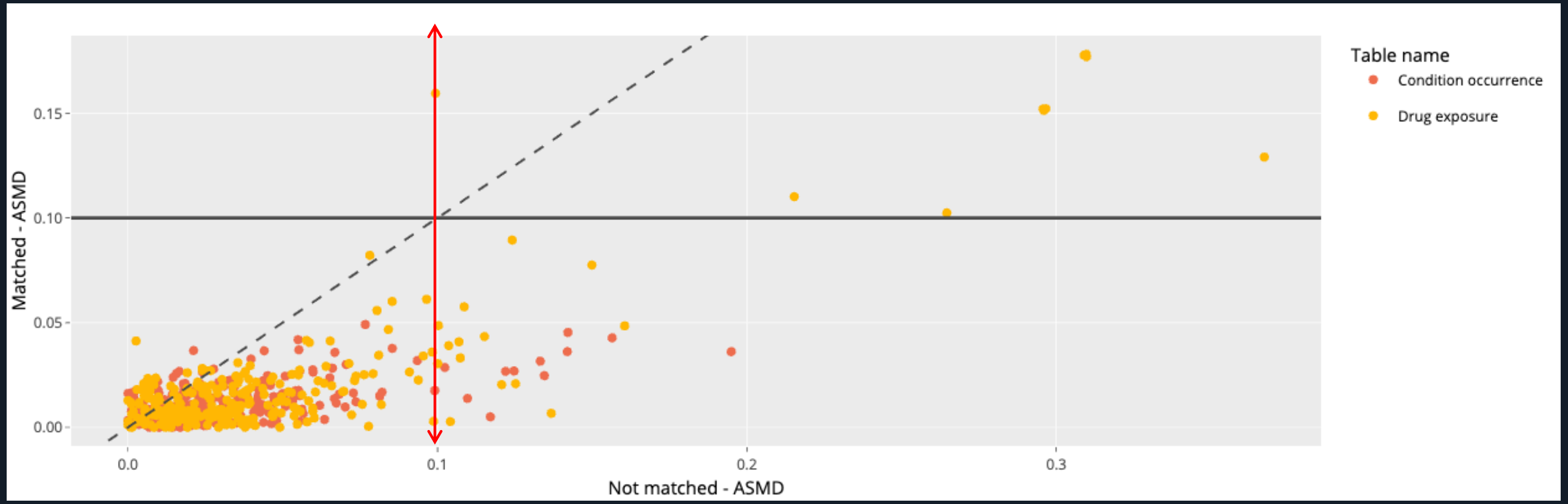
Cumulative Rates and Risk Ratios

Time to event

Hazard Ratios

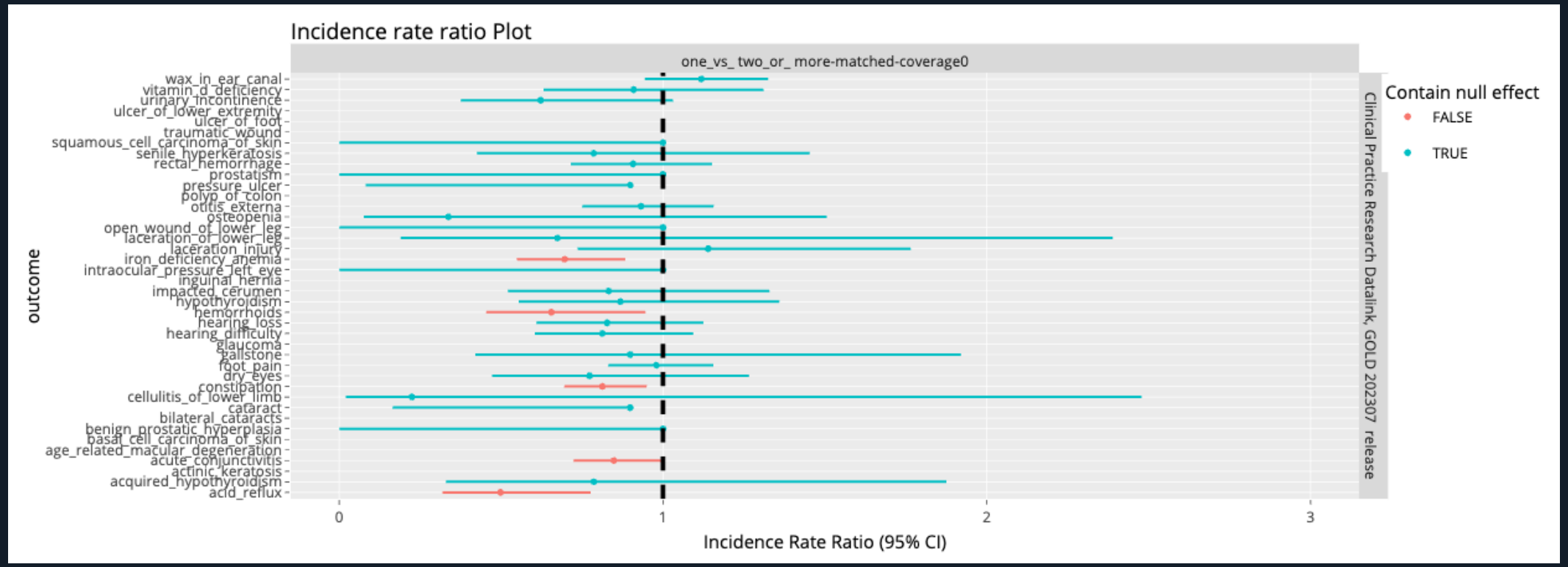
Diagnostic (1): Impact of PS matching on baseline conditional exchangeability: Vaccinated vs unvaccinated

Measurable imbalances reduced in before (X axis) vs after PS matching (Y axis)



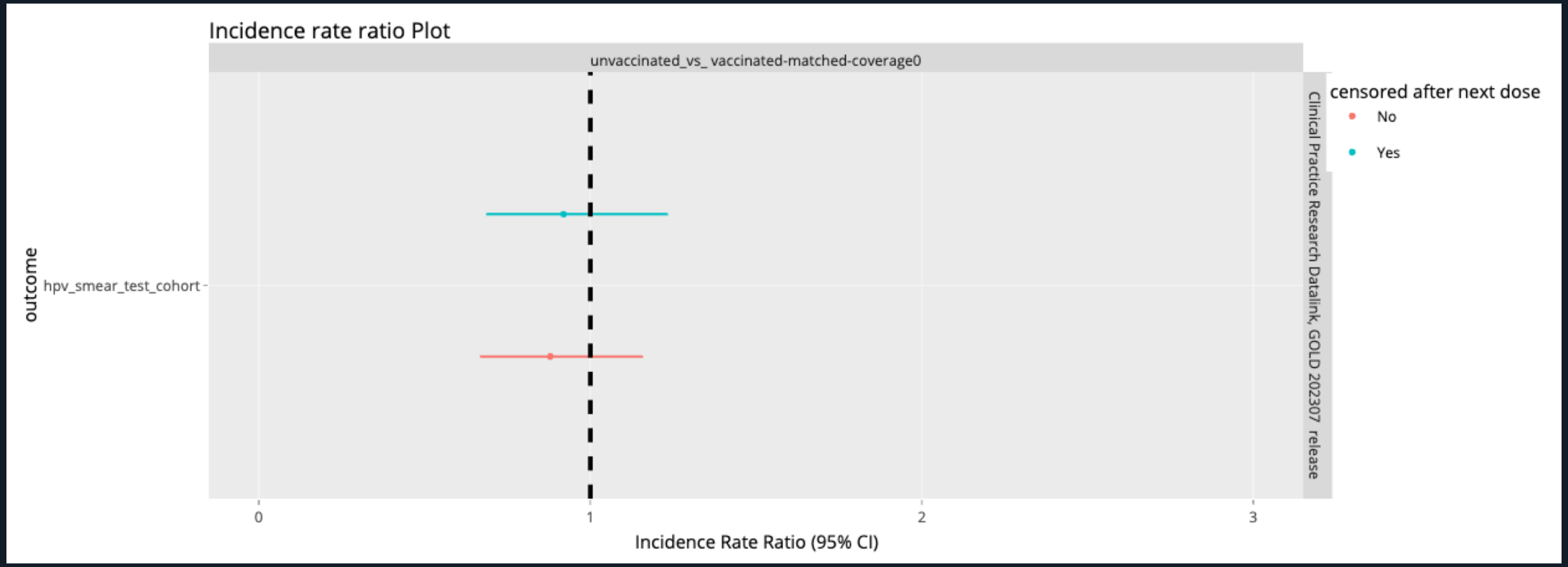
Diagnostic (2): negative control outcomes to detect unobserved or residual confounding

Incidence Rate Ratio of NCOs ~15y follow-up according to vaccination status in PS-matched cohorts



Diagnostic (3): potential loss of conditional exchangeability over time due to differential testing

Incidence Rate Ratio of smear tests during ~15y follow-up according to vaccination status in PS-matched cohorts



Conclusions

Both EF and TTE frameworks are useful and complementary to better specify analyses.

EF: Especially useful to focus the research question and how decisions, especially on intercurrent events, affect it.

Conclusions

TTE: Especially useful for better define timing decisions, more unique to observational research, like randomisation time vs ascertainment of treatment and start and end of follow-up times

Study design and analyses improved (conditional) exchangeability, at baseline and over time

Use of diagnostics to detect departures from causal inference assumptions