Trials and observational studies: strengths and weaknesses

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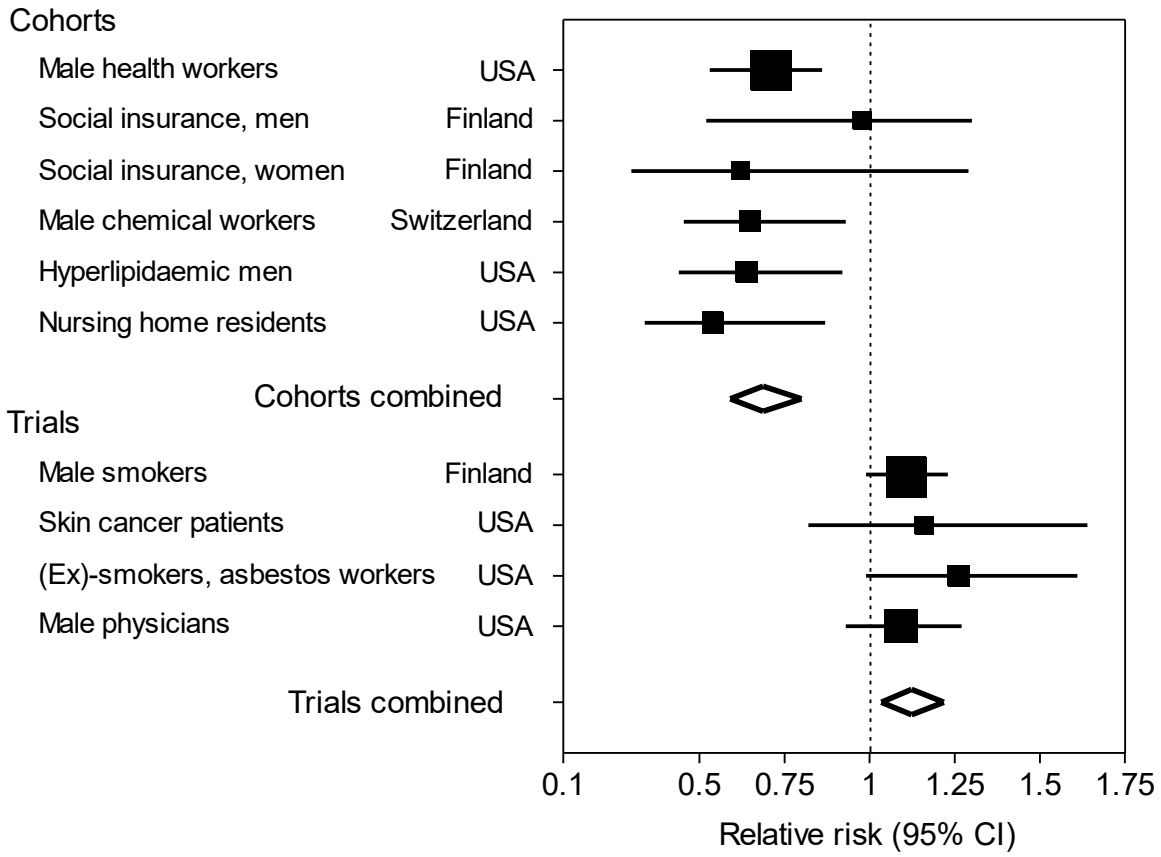
Methodological variation



Beta carotene and cardiovascular disease

Egger et al. *BMJ* 1998;316:140-4

Why do we get methodological variation?

- Let’s consider two hypothetical studies on masking for prevention of ARI
- Let one be a RCT
- And the other be an observational study

RCT vs observational study

- RCT
  - Strict eligibility criteria
  - Intervention randomly assigned
  - Participants may not comply with assigned intervention
  - Outcome could range from objective to subjective
  - Other interventions should be balanced across groups

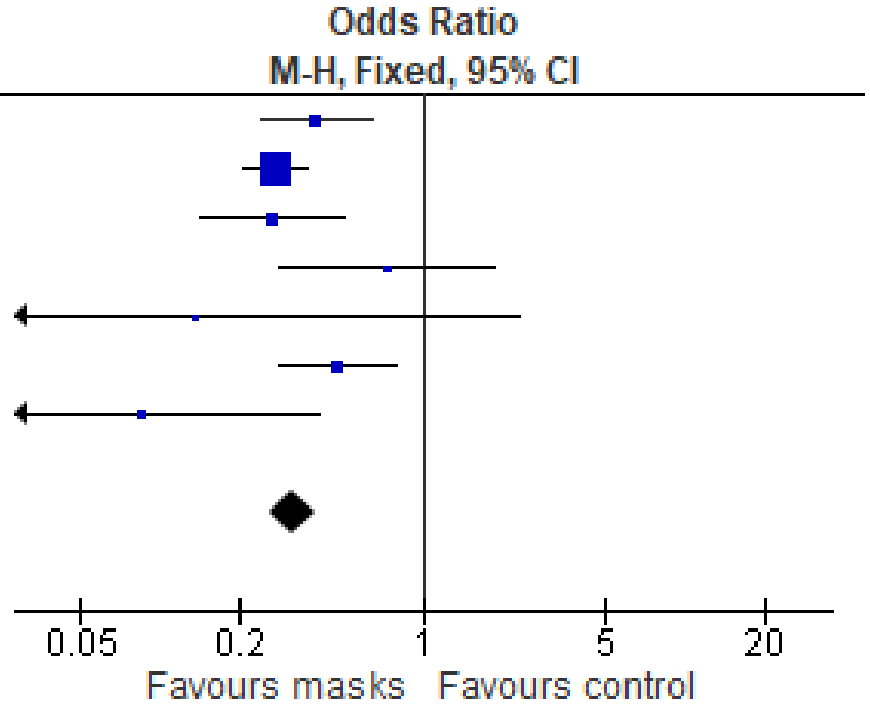
- Case-control study
  - People with outcome selected as cases
  - Cases matched with controls
  - Exposures based on retrospective self-report
  - Outcome could range from objective to subjective
  - Mask wearers may be more likely to use other prevention measures e.g. hand washing, social distancing

Case control studies of masks for ARI

Study or Subgroup	Cases Events	Cases Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen 2009	59	91	541	657	13.5%	0.40 [0.25, 0.64]
Lau 2004a	93	330	388	660	54.0%	0.28 [0.21, 0.37]
Liu 2009	15	51	259	426	11.4%	0.27 [0.14, 0.51]
Nishiura 2005	8	25	35	90	3.0%	0.74 [0.29, 1.90]
Seto 2003	0	13	51	241	1.6%	0.14 [0.01, 2.34]
Wu 2004	25	94	121	281	12.9%	0.48 [0.29, 0.80]
Yin 2004	68	77	178	180	3.6%	0.08 [0.02, 0.40]
Total (95% CI)		**681**		**2535**	**100.0%**	**0.32 [0.26, 0.39]**
Total events	268		1573			

Heterogeneity: $Chi^2 = 10.65$, $df = 6$ ($P = 0.10$); $I^2 = 44\%$

Test for overall effect: $Z = 11.07$ ($P < 0.00001$)



Jefferson, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses; Cochrane Database of Systematic Reviews, 6 JUL 2011; DOI: 10.1002/14651858.CD006207.pub4

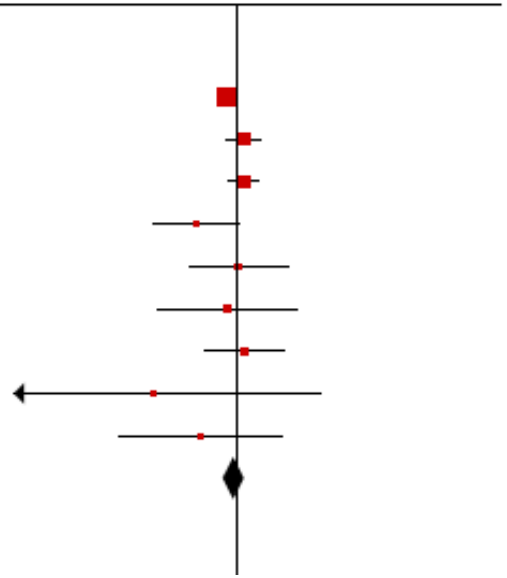
RCTs of masks for ARI

Analysis 1.1. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 1: Viral illness

Study or Subgroup	log[Risk Ratio]	SE	Medical/surgical masks Total	No masks Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Influenza/COVID-like illness						
Abaluck 2022 (1)	-0.135	0.036	111525	155268	41.4%	0.87 [0.81 , 0.94]
Aiello 2012	0.095	0.115	392	370	19.8%	1.10 [0.88 , 1.38]
Alfelali 2020	0.095	0.105	3864	3823	21.9%	1.10 [0.90 , 1.35]
Barasheed 2014	-0.55	0.3	75	89	4.6%	0.58 [0.32 , 1.04]
Canini 2010	0.025	0.342	148	158	3.6%	1.03 [0.52 , 2.00]
Cowling 2008	-0.128	0.483	61	205	1.9%	0.88 [0.34 , 2.27]
MacIntyre 2009	0.1	0.28	186	100	5.2%	1.11 [0.64 , 1.91]
MacIntyre 2016	-1.139	1.16	302	295	0.3%	0.32 [0.03 , 3.11]
Suess 2012	-0.494	0.571	26	30	1.4%	0.61 [0.20 , 1.87]
Subtotal (95% CI)			**116579**	**160338**	**100.0%**	**0.95 [0.84 , 1.09]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.44$, df = 8 (P = 0.18); $I^2 = 30\%$

Test for overall effect: Z = 0.71 (P = 0.48)



Jefferson, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev. 2023 Jan 30;1(1):CD006207; doi: 10.1002/14651858.CD006207.pub6.

Are observational studies useless?

- Not necessarily
- They are more difficult to get right compared to RCTs
- Trial emulation and other causal observational designs
- Need to be aware of potential for specific biases

The NEW ENGLAND JOURNAL of MEDICINE

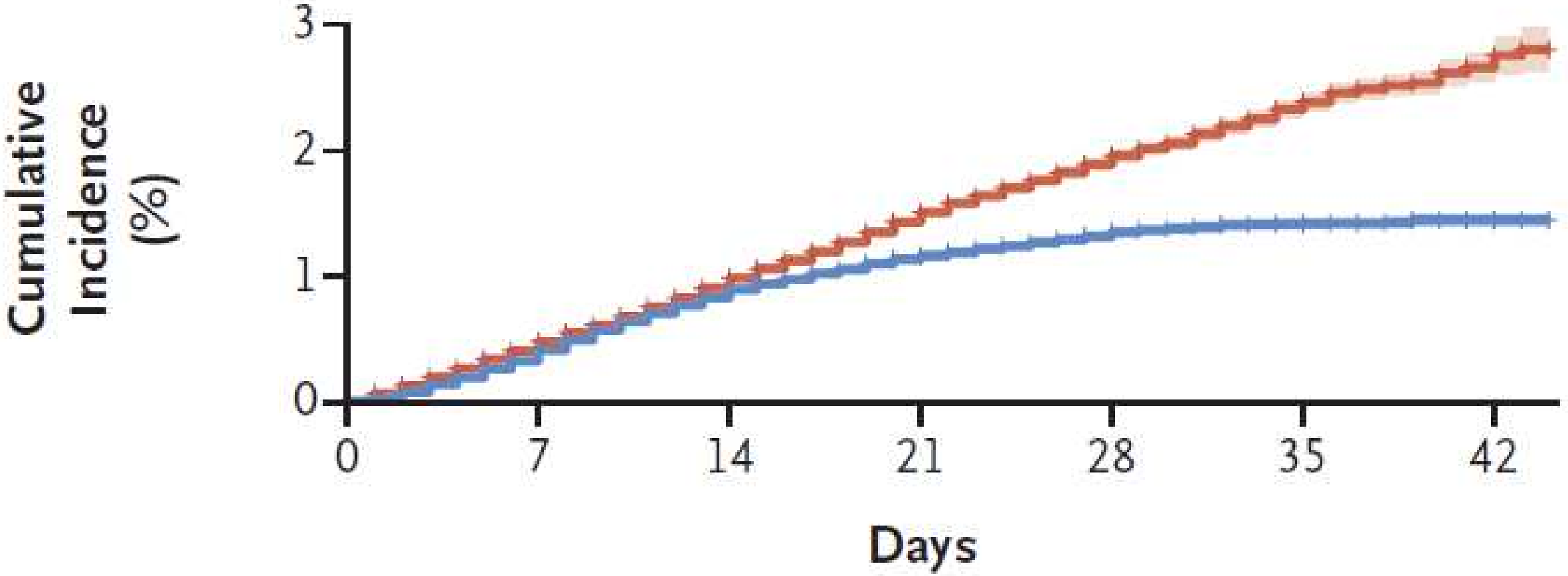
ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

We matched vaccine recipients and controls on variables associated with the probability of both vaccination and infection or severity of Covid-19: age, sex, sector (general Jewish, Arab, or ultra-Orthodox Jewish), neighborhood of residence (since disease activity and vaccination uptake vary greatly across defined geostatistical areas), history of influenza vaccination during the preceding 5 years (0, 1 or 2, 3 or 4, or ≥5 vaccinations), pregnancy (a potential risk factor for severe Covid-19[5] and associated with the rate of vaccination owing to evolving vaccination guidelines for pregnant women), and the total number of coexisting conditions that had been identified by the Centers for Disease Control and Prevention (CDC) as risk factors for severe Covid-19 as of December 20, 2020.[6,7] (See Supple-

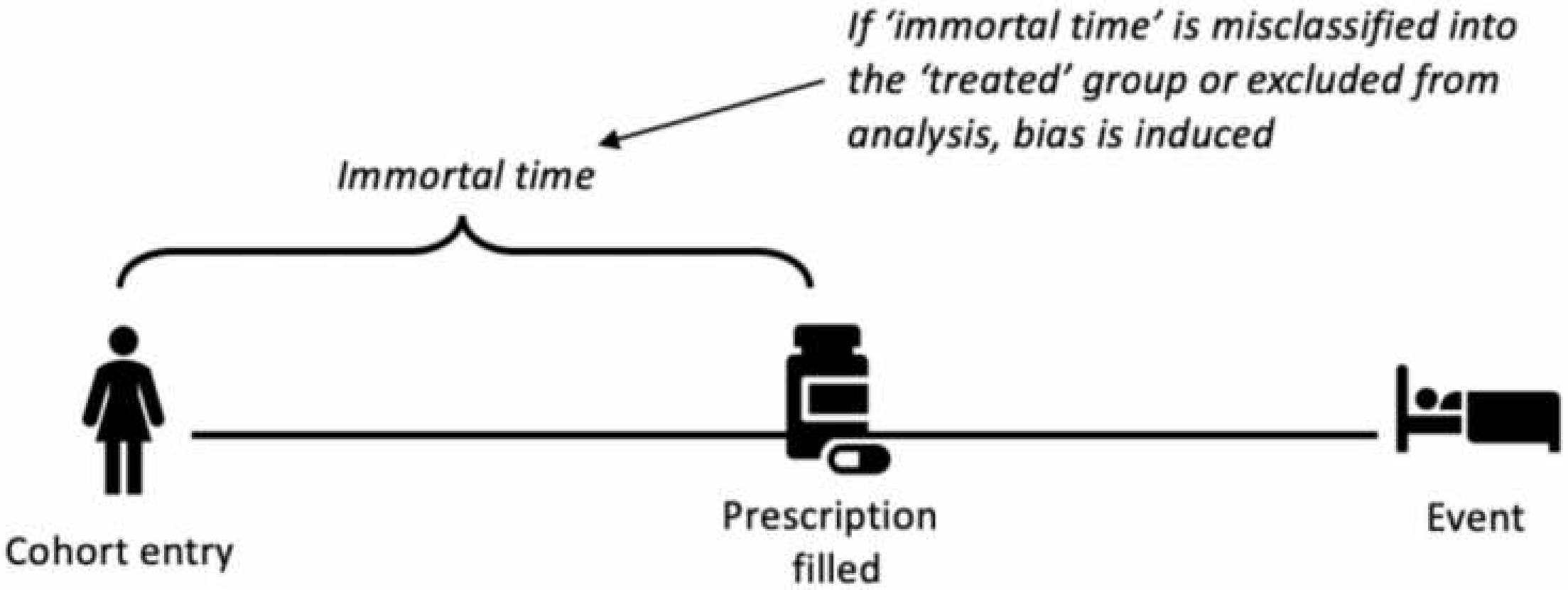
A Documented SARS-CoV-2 Infection

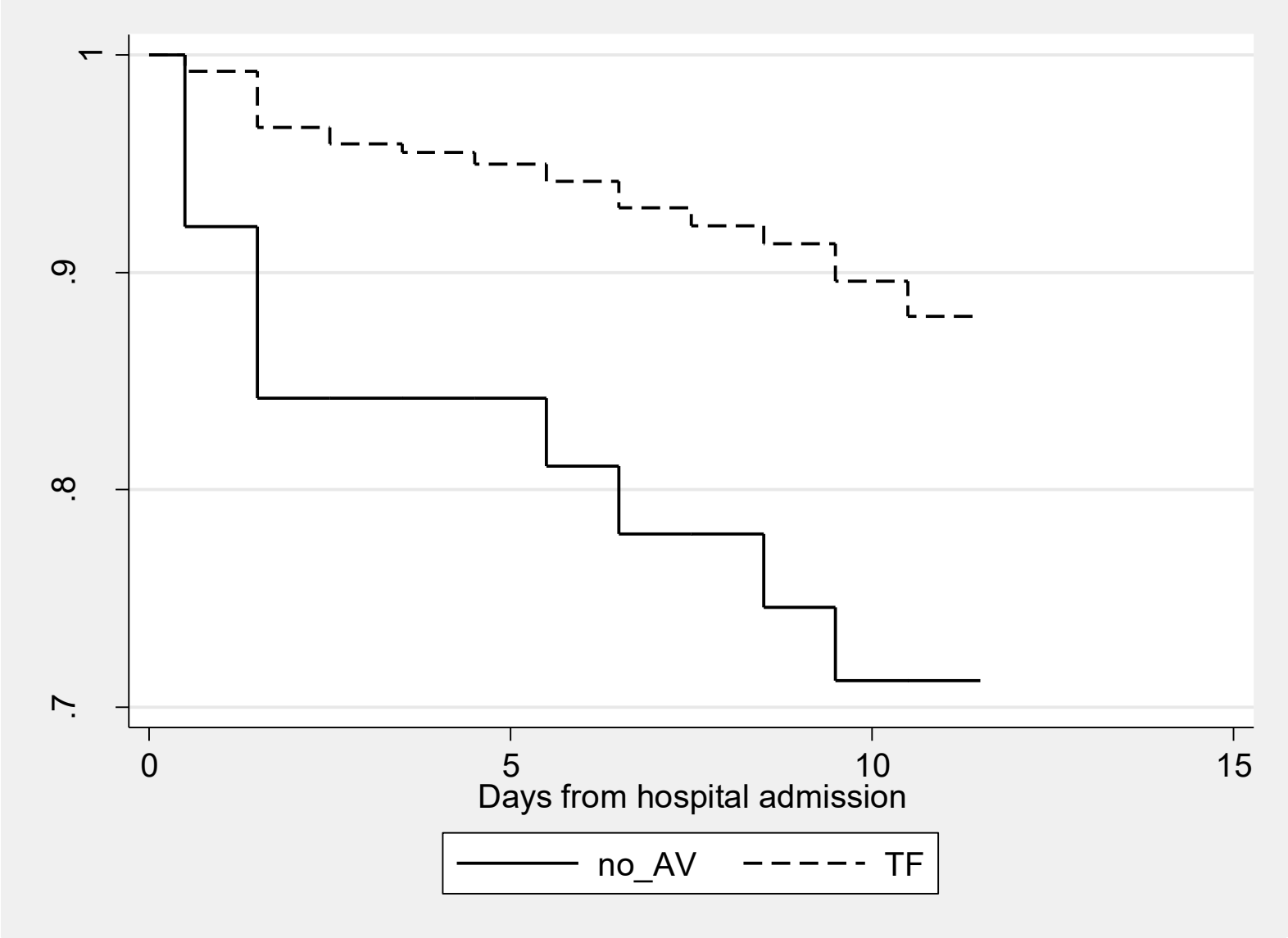


No. at Risk

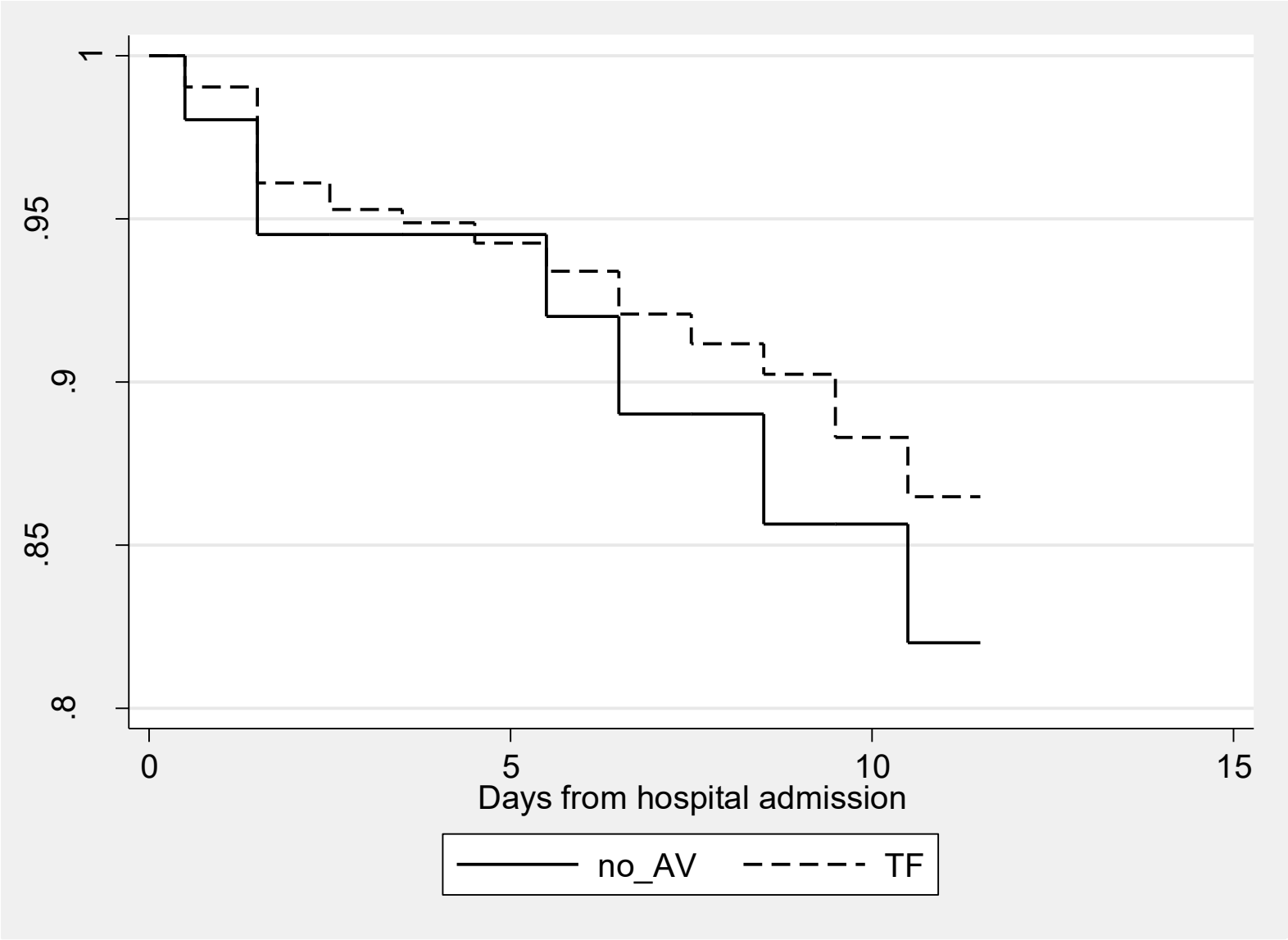
Unvaccinated	596,618	413,052	261,625	186,553	107,209	37,164	4132
Vaccinated	596,618	413,527	262,180	187,702	108,529	38,029	4262

Credit: Catalog of Bias





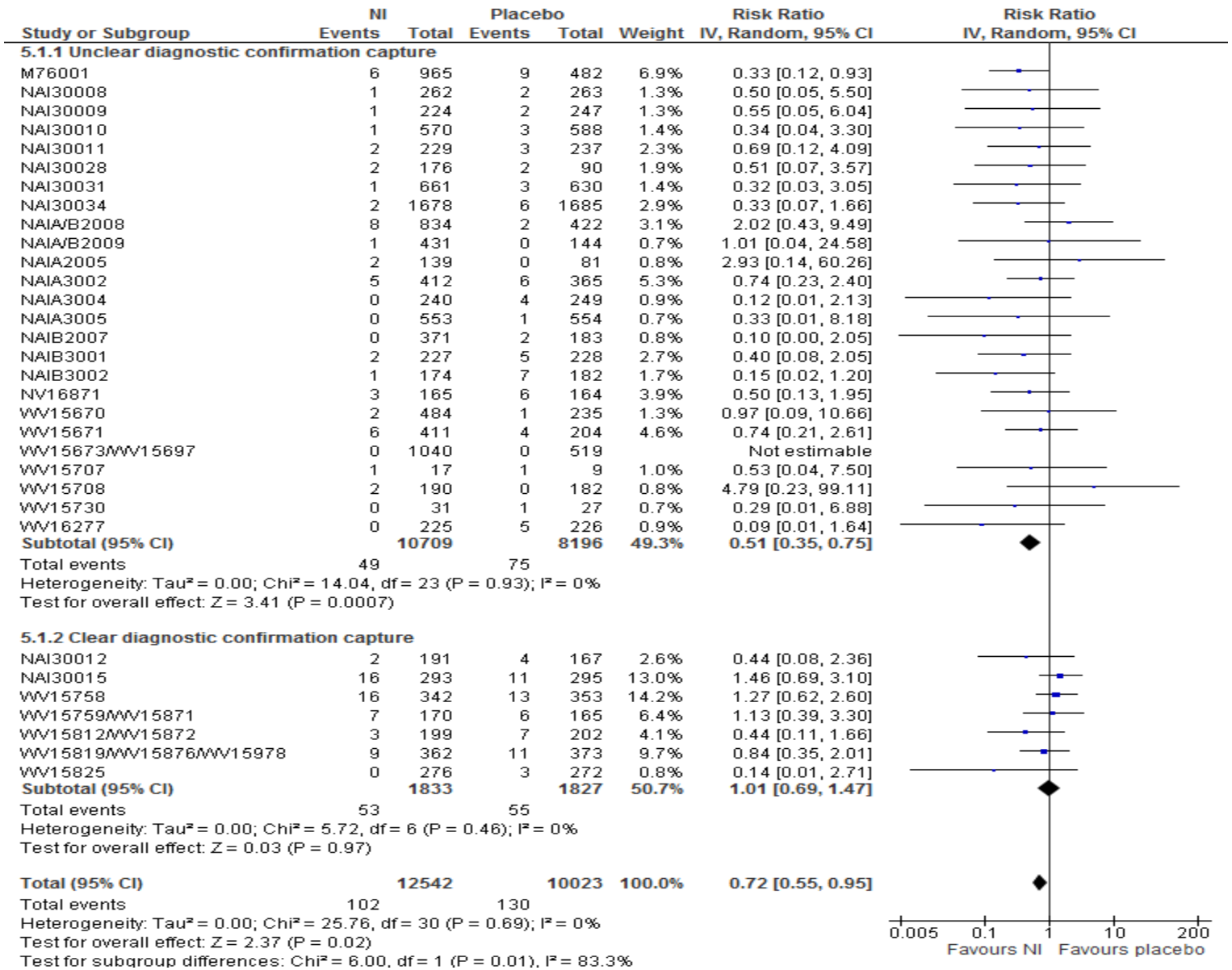
Jones & Fowler. Fitting time dependent exposures in survival analysis to avoid immortal time bias. Journal of Critical Care, 2016, 36, 195-199.



Jones & Fowler. Fitting time dependent exposures in survival analysis to avoid immortal time bias. Journal of Critical Care, 2016, 36, 195-199.

But RCTs can have problems too

Antivirals for influenza - pneumonia



Study or Subgroup	NI Events	NI Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 Unclear diagnostic confirmation capture						
M76001	6	965	9	482	6.9%	0.33 [0.12, 0.93]
NAI30008	1	262	2	263	1.3%	0.50 [0.05, 5.50]
NAI30009	1	224	2	247	1.3%	0.55 [0.05, 6.04]
NAI30010	1	570	3	588	1.4%	0.34 [0.04, 3.30]
NAI30011	2	229	3	237	2.3%	0.69 [0.12, 4.09]
NAI30028	2	176	2	90	1.9%	0.51 [0.07, 3.57]
NAI30031	1	661	3	630	1.4%	0.32 [0.03, 3.05]
NAI30034	2	1678	6	1685	2.9%	0.33 [0.07, 1.66]
NAIA/B2008	8	834	2	422	3.1%	2.02 [0.43, 9.49]
NAIA/B2009	1	431	0	144	0.7%	1.01 [0.04, 24.58]
NAIA2005	2	139	0	81	0.8%	2.93 [0.14, 60.26]
NAIA3002	5	412	6	365	5.3%	0.74 [0.23, 2.40]
NAIA3004	0	240	4	249	0.9%	0.12 [0.01, 2.13]
NAIA3005	0	553	1	554	0.7%	0.33 [0.01, 8.18]
NAIB2007	0	371	2	183	0.8%	0.10 [0.00, 2.05]
NAIB3001	2	227	5	228	2.7%	0.40 [0.08, 2.05]
NAIB3002	1	174	7	182	1.7%	0.15 [0.02, 1.20]
NV16871	3	165	6	164	3.9%	0.50 [0.13, 1.95]
WV15670	2	484	1	235	1.3%	0.97 [0.09, 10.66]
WV15671	6	411	4	204	4.6%	0.74 [0.21, 2.61]
WV15673/WV15697	0	1040	0	519		Not estimable
WV15707	1	17	1	9	1.0%	0.53 [0.04, 7.50]
WV15708	2	190	0	182	0.8%	4.79 [0.23, 99.11]
WV15730	0	31	1	27	0.7%	0.29 [0.01, 6.88]
WV16277	0	225	5	226	0.9%	0.09 [0.01, 1.64]
Subtotal (95% CI)		**10709**		**8196**	**49.3%**	**0.51 [0.35, 0.75]**
Total events	49		75			
Heterogeneity: Tau² = 0.00; Chi² = 14.04, df = 23 (P = 0.93); I² = 0%						
Test for overall effect: Z = 3.41 (P = 0.0007)						
5.1.2 Clear diagnostic confirmation capture						
NAI30012	2	191	4	167	2.6%	0.44 [0.08, 2.36]
NAI30015	16	293	11	295	13.0%	1.46 [0.69, 3.10]
WV15758	16	342	13	353	14.2%	1.27 [0.62, 2.60]
WV15759/WV15871	7	170	6	165	6.4%	1.13 [0.39, 3.30]
WV15812/WV15872	3	199	7	202	4.1%	0.44 [0.11, 1.66]
WV15819/WV15876/WV15978	9	362	11	373	9.7%	0.84 [0.35, 2.01]
WV15825	0	276	3	272	0.8%	0.14 [0.01, 2.71]
Subtotal (95% CI)		**1833**		**1827**	**50.7%**	**1.01 [0.69, 1.47]**
Total events	53		55			
Heterogeneity: Tau² = 0.00; Chi² = 5.72, df = 6 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Total (95% CI)		**12542**		**10023**	**100.0%**	**0.72 [0.55, 0.95]**
Total events	102		130			
Heterogeneity: Tau² = 0.00; Chi² = 25.76, df = 30 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: Chi² = 6.00, df = 1 (P = 0.01), I² = 83.3%						

Jefferson, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database of Systematic Reviews, 2014 Apr 10;4:CD008965.

TABLE 4 Characteristics of clinically identified and unrecognised radiographic pneumonias

Clinical characteristics	Clinically identified radiographic pneumonia	Clinically unrecognised radiographic pneumonia	p-value
Patients n	41	99	
Symptoms and signs			
Runny nose	44	64	0.031
Fever	90	41	<0.001
Chest pain	68	52	0.068
Comorbidity (pulmonary, cardiac or DM)[#]	20	23	0.629
Abnormal auscultation lungs	83	50	<0.001
Diminished vesicular breathing	15	20	0.441
Crackles	66	16	<0.001
Rhonchi	27	23	0.652
Heart rate >100 beats·min^{-1}	24	7	0.004
Breathing frequency >24 breaths·min^{-1}	10	2	0.040
Blood pressure <90/60 mmHg	12	4	0.073
Gradation of illness[¶]			
Severe cough	30	43	0.143
Severe breathlessness	26	13	0.133
Severe fever	31	7	0.002
Severe chest pain	23	8	0.045
Severe general unwellness	25	26	0.912
Severe interference with daily activities	23	27	0.697

S.F. VAN VUGT ET AL. Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography. Eur Respir J 2013; 42: 1076–1082 | DOI: 10.1183/09031936.00111012

Irrespective of study design need to be aware of conflicts of interest and investigators with strong prior beliefs