An evidence based review of the criteria for regulatory assessment of seasonal influenza vaccines

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Cochrane Vaccines Field

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Immune correlates of protection -
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Outline

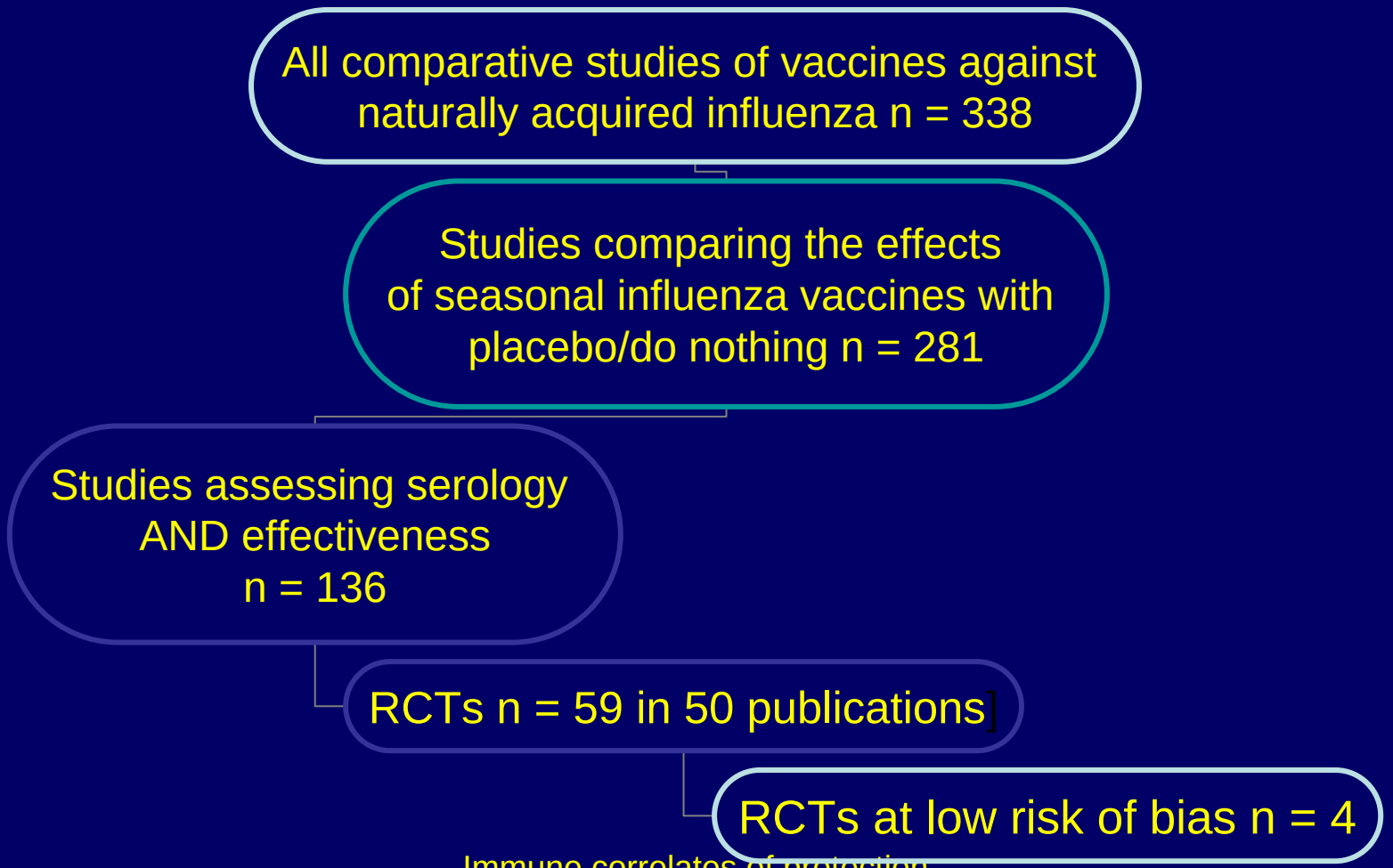
- What evidence is there that the NRA criteria make sense?
- What does the evidence show?
- What can we do to improve the situation?

What evidence is there that the NRA criteria make sense?

I am a physician and am interested in knowing whether if I assign some folk to an influenza vaccine and a **comparable** sample to standard care or placebo I have some beneficial effects in the first group vs the second. These must outweigh harms and/or costs. So I look for evidence from RCTs in which serology and clinical effects are followed up and correlated on the same population

Flow of studies into the review

[from the Cochrane Vaccines Field Register]



What does the evidence show?

4 low risk of bias RCTs correlating serology to clinical outcomes:

- 374 school-age children in 67-68 (follow up problems)
- 697 asthmatic children aged 6-18 in 99-01
- 793 children aged 6-24 months in 99-01
- 55 COPD aged 19-75 in 60-61 (bivalent whole-virion)

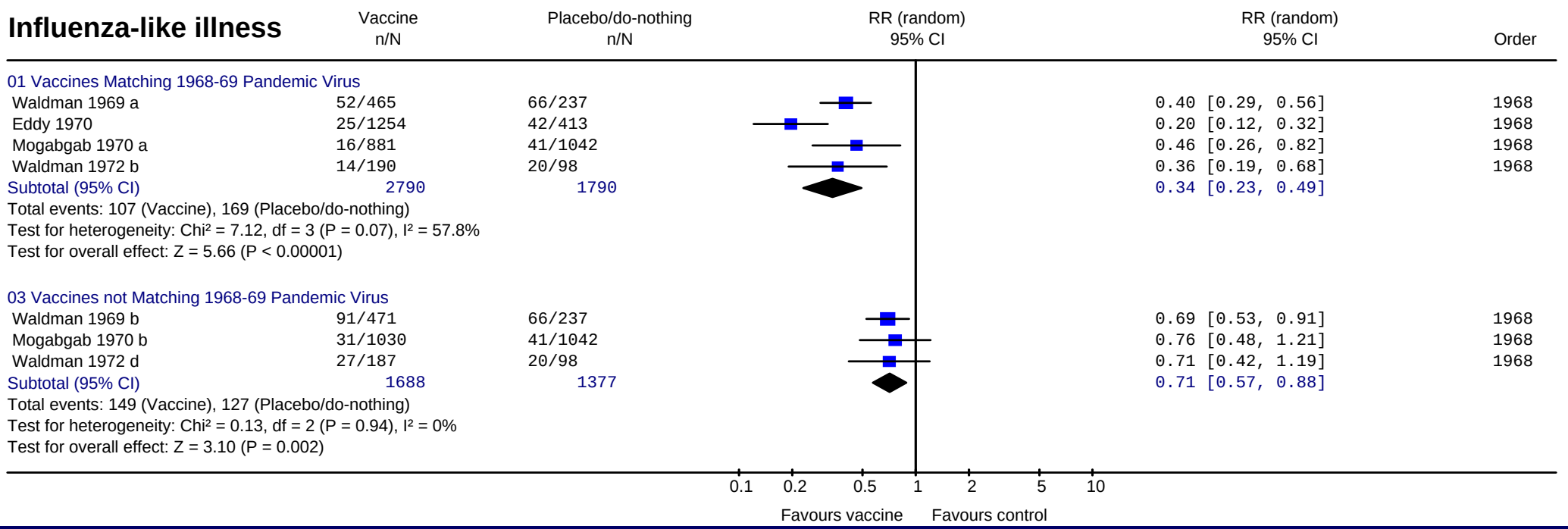
- Antibody responses were not correlated to protection in 2, one had follow-up problems, and the last (small) showed correlation (but CF test)

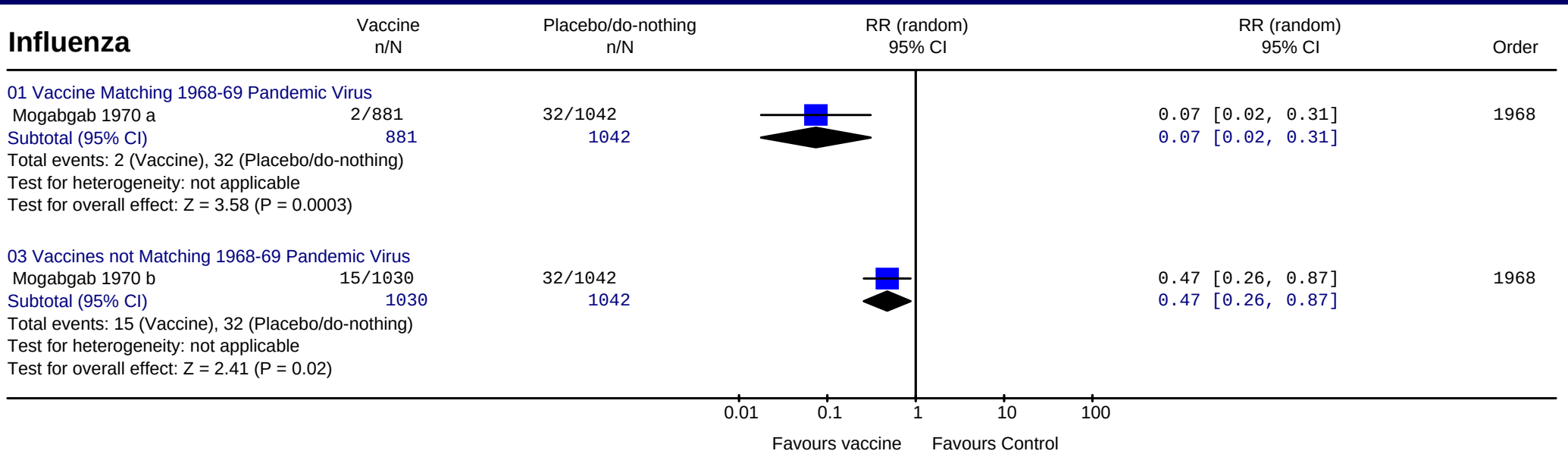
So

- Judgment made on 2 RCTs on children
- Substantial uncertainty
- Absolute requirement are good quality RCTs compared with placebo with serology / effectiveness outcomes

What can we do to improve the situation?

- More attention to design
- More attention to reporting
- More accountability
- More attention to transaparency
- Methodological research into evidence-based criteria of study quality and reporting


Influenza-like illness
Vaccine n/N
Placebo/do-nothing n/N
RR (random) 95% CI
RR (random) 95% CI
Order
01 Vaccines Matching 1968-69 Pandemic Virus
Waldman 1969 a 52/465 66/237 0.40 [0.29, 0.56] 1968
Eddy 1970 25/1254 42/413 0.20 [0.12, 0.32] 1968
Mogabgab 1970 a 16/881 41/1042 0.46 [0.26, 0.82] 1968
Waldman 1972 b 14/190 20/98 0.36 [0.19, 0.68] 1968
Subtotal (95% CI) 2790 1790 0.34 [0.23, 0.49]
Total events: 107 (Vaccine), 169 (Placebo/do-nothing)
Test for heterogeneity: Chi² = 7.12, df = 3 (P = 0.07), I² = 57.8%
Test for overall effect: Z = 5.66 (P < 0.00001)
03 Vaccines not Matching 1968-69 Pandemic Virus
Waldman 1969 b 91/471 66/237 0.69 [0.53, 0.91] 1968
Mogabgab 1970 b 31/1030 41/1042 0.76 [0.48, 1.21] 1968
Waldman 1972 d 27/187 20/98 0.71 [0.42, 1.19] 1968
Subtotal (95% CI) 1688 1377 0.71 [0.57, 0.88]
Total events: 149 (Vaccine), 127 (Placebo/do-nothing)
Test for heterogeneity: Chi² = 0.13, df = 2 (P = 0.94), I² = 0%
Test for overall effect: Z = 3.10 (P = 0.002)
0.1 0.2 0.5 1 2 5 10
Favours vaccine
Favours control


Influenza
Vaccine n/N
Placebo/do-nothing n/N
RR (random) 95% CI
RR (random) 95% CI
Order
01 Vaccine Matching 1968-69 Pandemic Virus
Mogabgab 1970 a 2/881 32/1042 0.07 [0.02, 0.31] 1968
Subtotal (95% CI) 881 1042 0.07 [0.02, 0.31]
Total events: 2 (Vaccine), 32 (Placebo/do-nothing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.58 (P = 0.0003)
03 Vaccines not Matching 1968-69 Pandemic Virus
Mogabgab 1970 b 15/1030 32/1042 0.47 [0.26, 0.87] 1968
Subtotal (95% CI) 1030 1042 0.47 [0.26, 0.87]
Total events: 15 (Vaccine), 32 (Placebo/do-nothing)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.41 (P = 0.02)
0.01 0.1 1 10 100
Favours vaccine
Favours Control

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