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Supporting Information

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.

Appendix to: Hemming K, Taljaard M. Why proper understanding of confidence intervals and statistical significance is important. *Med J Aust* 2021; doi: 10.5694/mja2.50926.

Appendix

Case study 1: The N95 respirators for health care professional's trial (ResPECT trial)
Background
The ResPECT trial is a pragmatic, unblinded multicentre two arm cluster randomized trial of N95 respirators versus medical masks for the prevention of respiratory infections in health care workers. The trial enrolled 4,051 health care professionals working across multiple in-patient and out-patient settings across more than 190 sites across

seven US hospitals between 2011 and 2015.
Design
The primary outcome was laboratory-confirmed influenza. The trial was designed to detect a target effect size of a 25% relative risk reduction (i.e. from 7.5% to 5.6%, or approximately a 2 percentage point reduction in risk) at 80% power and 5% significance. However, like most studies, this was a target effect size (i.e. the effect the trial was powered to detect) rather than being the minimally important difference.
Primary outcome result
The authors state that: "There were 207 laboratory-confirmed influenza infection events (8.2%) in the N95 respirator group and 193 (7.2%) in the medical mask group (difference, 1.0%, [95%CI, −0.5% to 2.5%]; P = .18) (adjusted odds ratio [OR], 1.18 [95%CI, 0.95-1.45])."
Results on absolute scale
Percentage point difference: 1% (95% CI: -0.5% to 2.5%); NNH 100 (95% CI: NNH 200, NNT 40)
Investigators conclusions
"Among outpatient health care personnel, N95 respirators vs medical masks as worn by participants in this trial resulted in no significant difference in the incidence of laboratory-confirmed influenza."
Suggested clinically important differences
In the ResPECT trial the event rate (laboratory confirmed infection) is about 7% under the medical mask group. Subject expertise will help in considering that might constitute a meaningful change in this event rate. We might say that differences of up to 1.5% might be clinically non-important. Whilst setting this value might be considered arbitrary, note that in our interpretation we interpret this value with considerable caution.
Interpretation of the confidence interval
The results for the primary outcome tell us that the true effect of N95 respirators might be to increase risk of laboratory confirmed influenza by up to 2.5% (i.e. a result consistent with clinically important harm) or to decrease the risk of influenza by up to 0.5% (i.e. small but clinically unimportant benefit). Whilst this trial is therefore compatible with an effect which might be beneficial or harmful the majority of the confidence interval supports small and unimportant effects. Because values at the tails of the confidence intervals are less likely, this trial is finds little support for any benefit or harm of the N95 respirator over and above the medical mask.
Suggested Interpretation
The ResPECT trial supports a conclusion that wearing N95 respirators has minimal impact or might even slightly increase the risk of influenza. This counter intuitive finding might be a consequence of risk compensation that can occur in the real world. However, because secondary outcomes do not support any increased risk it might well be due to random chance. Moreover, this trial suggests there is no beneficial effect of N95 respirators over medical masks.
Notes
Values taken are those reported in trial reports, except the NNH, NNH confidence intervals were estimated using 1/reported absolute risk difference. NNT: Number Needed to Treat for benefit; NNH: Number Needed to treat for Harm; CI: Confidence Interval.
Reference
Radonovich LJ Jr, Simberkoff MS, Bessesen MT, Brown AC, Cummings DAT, Gaydos CA, Los JG, Krosche AE, Gibert CL, Gorse GJ, Nyquist AC, Reich NG, Rodriguez-Barradas MC, Price CS, Perl TM; ResPECT investigators. N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel: A Randomized Clinical Trial. JAMA. 2019 Sep 3;322(9):824-833.

Case study 2: A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19
Background
The Lopinavir-Ritonavir trial is an unblinded single centre two arm individually randomized trial of Lopinavir-Ritonavir treatment for 14 days versus standard care for the treatment severe illness in patients with laboratory confirmed SARS-CoV-2. The trial enrolled 199 patients between 18th January and 3rd February 2020.
Design
The primary outcome was time to clinical improvement on a 7-point ordinal scale, but this is a difficult outcome to interpret. Moreover, in hospitalised patients with confirmed SARS-CoV-2 infection mortality is clearly an important outcome. We therefore focus on mortality here. Under the control arm around 20% of patients died. A trial with 200 patients has 90% power to detect a 15% absolute risk reduction (i.e. invention mortality rate of 5%).
Results
The trial observed a median time to clinical improvement of 16 days (IQR: 13.0 to 17.0) in the intervention arm and 16 days (IQR 15 to 18) in the control arm. For the primary outcome the hazard ratio for clinical improvement was 1.24 (95% CI: 0.90 to 1.72). Mortality at 28 days was 19.2% in Lopinavir–Ritonavir group and 25% in the standard-care group (risk difference, −5.8 percentage points 95% CI: −17.3 to 5.7).
Result on absolute scale
Percentage point difference (mortality): -5% (95% CI: -17.3% to 5.7%); NNT 20 (95% CI: NNT 6, NNH 18)
Investigators conclusions
“In hospitalized adult patients with severe Covid-19, no benefit was observed with Lopinavir–Ritonavir treatment beyond standard care.”
Suggested minimally important differences
The trial had power to detect a 15% absolute risk reduction in mortality. This is a very large effect size that, whilst clearly of clinical importance, is arguably not likely to be achieved by many drug interventions. Smaller effect sizes would also be clinically important. Reducing mortality even by 1 percentage point is likely to be considered important, provided there are no major adverse side effects.
Interpretation of the confidence interval
The results for the outcome mortality tell us that the true effect of Lopinavir–Ritonavir treatment might be to increase risk of mortality by up to 5.7% (i.e. a result consistent with clinically important harm) or to decrease the risk of mortality by up to 17.3% (i.e. large clinically unimportant benefit). This trial is therefore compatible with an effect which might be beneficial or harmful, and the range of these effects so large that the result is uncertain.
Suggested Interpretation
Mortality, despite not being pre-specified as the primary outcome is arguably the more important outcome in this trial. The trial findings are mostly supportive of positive effects but the trial does not rule out small to moderate harm. Secondary outcomes are mostly also inconclusive. There is insufficient evidence to support whether treatment with Lopinavir–Ritonavir can improve mortality in patients with severe Covid-19. More research is needed.
Notes
Values taken are those reported in trial reports, except the NNT, NNT confidence intervals were estimated using 1/reported absolute risk difference. NNT: Number Needed to Treat for benefit; NNH: Number Needed to treat for Harm; CI: Confidence Interval.
Reference
Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2001282.