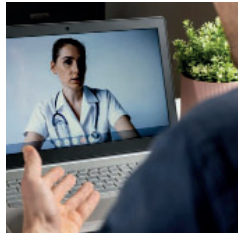
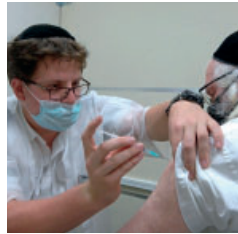


research



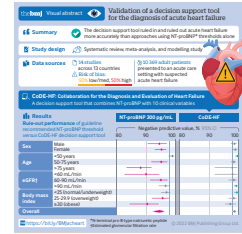
Use of internet based CBT in post-traumatic stress disorder p 395



Effectiveness of fourth BNT162b2 vaccine dose p 396



Risk of infection after vaccination with CoronaVac p 397



Decision support tool for diagnosing heart failure p 398

ORIGINAL RESEARCH Pragmatic, randomised controlled non-inferiority trial

Guided, internet based, cognitive behavioural therapy for post-traumatic stress disorder

Bisson JJ, Ariti C, Cullen K, et al

Cite this as: *BMJ* 2022;377:e069405

Find this at doi: 10.1136/bmj-2021-069405

Study question Is guided internet based cognitive behavioural therapy with a trauma focus (CBT-TF) non-inferior to individual face-to-face CBT-TF for mild to moderate post-traumatic stress disorder (PTSD) to one traumatic event?

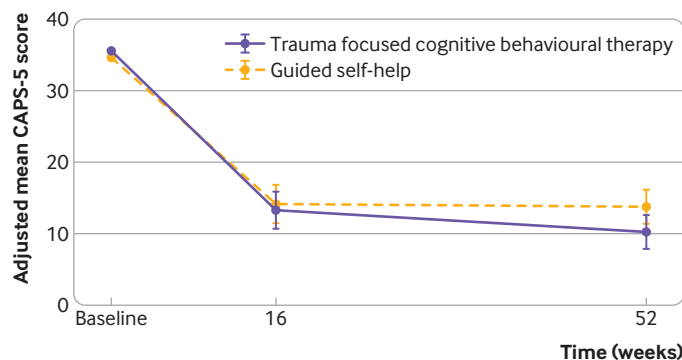
Methods This trial with an economic evaluation and nested process evaluation was conducted in 196 participants with mild to moderate PTSD, recruited from the NHS. Participants received up to 12 face-to-face, individual CBT-TF sessions, each lasting 60-90 minutes; or guided internet based CBT-TF with an eight step online programme, with up to three hours of contact with a therapist and four brief telephone calls or email contacts between sessions. The primary outcome was the score on the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) at 16 weeks after randomisation (diagnosis of PTSD based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, DSM-5).

Study answer and limitations Non-inferiority was found at 16 weeks on the CAPS-5 (mean difference 1.01, one sided 95% confidence interval $-\infty$ to 3.90, non-inferiority $P=0.01$). Improvements in CAPS-5 score of more than 60% in both groups were maintained at 52 weeks, but the non-inferiority results were inconclusive in favour of face-to-face CBT-TF at this time point (3.20, $-\infty$ to 6.00, $P=0.15$). Guided internet based CBT-TF was significantly cheaper and appeared to be acceptable and well tolerated by participants. Whether guided internet based CBT-TF was more or less helpful for people with PTSD to some precipitating events rather than others could not be determined.

What this study adds Guided internet based CBT-TF for mild to moderate PTSD to one traumatic event was non-inferior to and cheaper than individual face-to-face CBT-TF and should be considered a first line treatment for people with this condition.

Funding, competing interests, and data sharing Funded by the National Institute for Health and Care Research Health Technology Assessment programme. Full details of competing interests on bmj.com. Data available from the corresponding author.

Trial registration ISRCTN13697710.



Adjusted mean Clinician Administered Post-Traumatic Stress Disorder Scale for DSM-5 (CAPS-5) scores over time in the two groups (diagnosis of PTSD based on criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, DSM-5)

Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel

Gazit S, Saciuk Y, Perez G, Peretz A, Pitzer VE, Patalon T

Cite this as: *BMJ* 2022;377:e071113

Find this at doi: 10.1136/bmj-2022-071113

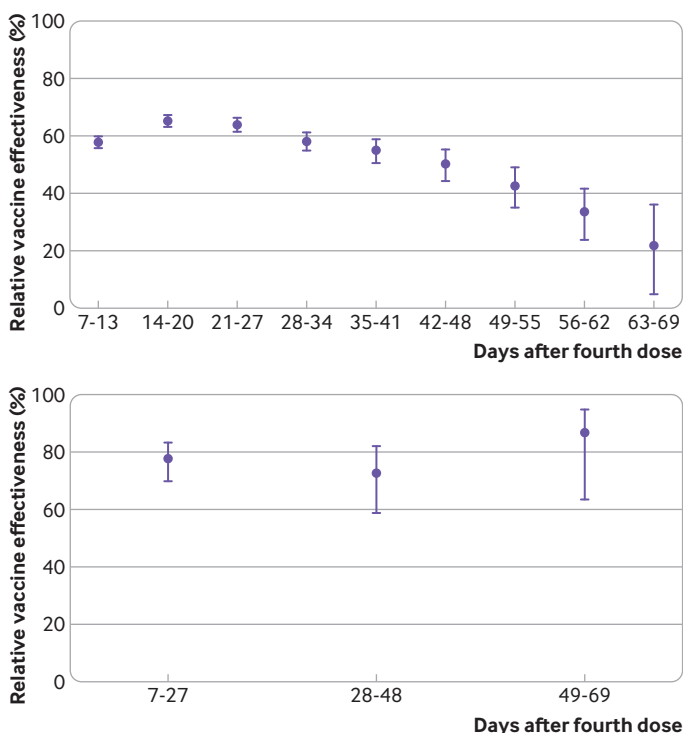
Study question What is the relative effectiveness of a fourth dose of the Pfizer-BioNTech mRNA (BNT162b2) vaccine against SARS-CoV-2 compared with three doses?

Methods The study population included 97 499 members of the Maccabi Healthcare Service, an Israeli national health fund for 2.5 million people. Participants were aged ≥ 60 years who were eligible to receive a fourth vaccine dose and received at least one polymerase chain reaction (PCR) test between 10 January and 13 March 2022, an omicron dominant period in Israel. The study included a matched analysis and unmatched multiple tests analysis. Main outcomes were breakthrough SARS-CoV-2 infection (defined as a positive result from a PCR test performed seven or more days after inoculation with the BNT162b2 vaccine) and breakthrough SARS-CoV-2 infection resulting in severe covid-19 disease (defined as hospital admission or death related to covid-19).

Study answer and limitations 27 876 participants received four BNT162b2 vaccine doses and 69 623 received three doses only. Of 106 participants who died during the follow-up period, 77 had third doses only and 23 had fourth doses during the first three weeks after inoculation. In the first three weeks, a fourth dose provided additional protection against SARS-CoV-2 infection and severe disease relative to three doses. However, relative vaccine effectiveness against SARS-CoV-2 infection quickly decreased over time, peaking during the third week at 65.1% (95% confidence interval 63.0% to 67.1%) and falling to 22.0% (4.9% to 36.1%) by the end of the 10 week follow-up period. The relative effectiveness of a fourth dose against severe covid-19 stayed above 72% throughout follow-up, but severe disease was a relatively rare event, occurring in $<1\%$ of study participants who received four doses or three doses only. To provide timely evidence of the relative vaccine effectiveness of a fourth dose, only 10 weeks of data were included.

What this study adds Relative vaccine effectiveness of the fourth BNT162b2 dose against severe covid-19 stayed at a high level throughout the 10 week follow-up; by week 5, relative effectiveness against infection dropped back to levels similar to those observed during the first week after vaccination, indicating a faster waning of protection for the fourth dose than for previous doses.

Funding, competing interests, and data sharing Research supported by the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health. Details of competing interests are available on bmj.com. According to the Israel Ministry of Health regulations, individual level data cannot be shared openly. Specific requests for access to deidentified data should be referred to Kahn Sagol Maccabi Research and Innovation Centre, Maccabi Healthcare Services.



Adjusted vaccine effectiveness of fourth BNT162b2 dose against SARS-CoV-2 infection (top) and against severe covid-19 (bottom), relative to three doses only. Data based on results from primary matched analysis. Relative vaccine effectiveness = $100\% \times (1 - \text{odds ratio})$ for each week since vaccination; error bars = 95% confidence intervals



EDDIE GERALD/LAMMY

Change in covid-19 risk over time following vaccination with CoronaVac

Hitchings MDT, Ranzani OT, Lind ML, et al

Cite this as: *BMJ* 2022;377:e070102

Find this at doi: 10.1136/bmj-2022-070102

Study question What is the change in odds of covid-19 over time following primary series completion of the inactivated whole virus vaccine, CoronaVac (Sinovac Biotech), in São Paulo State, Brazil?

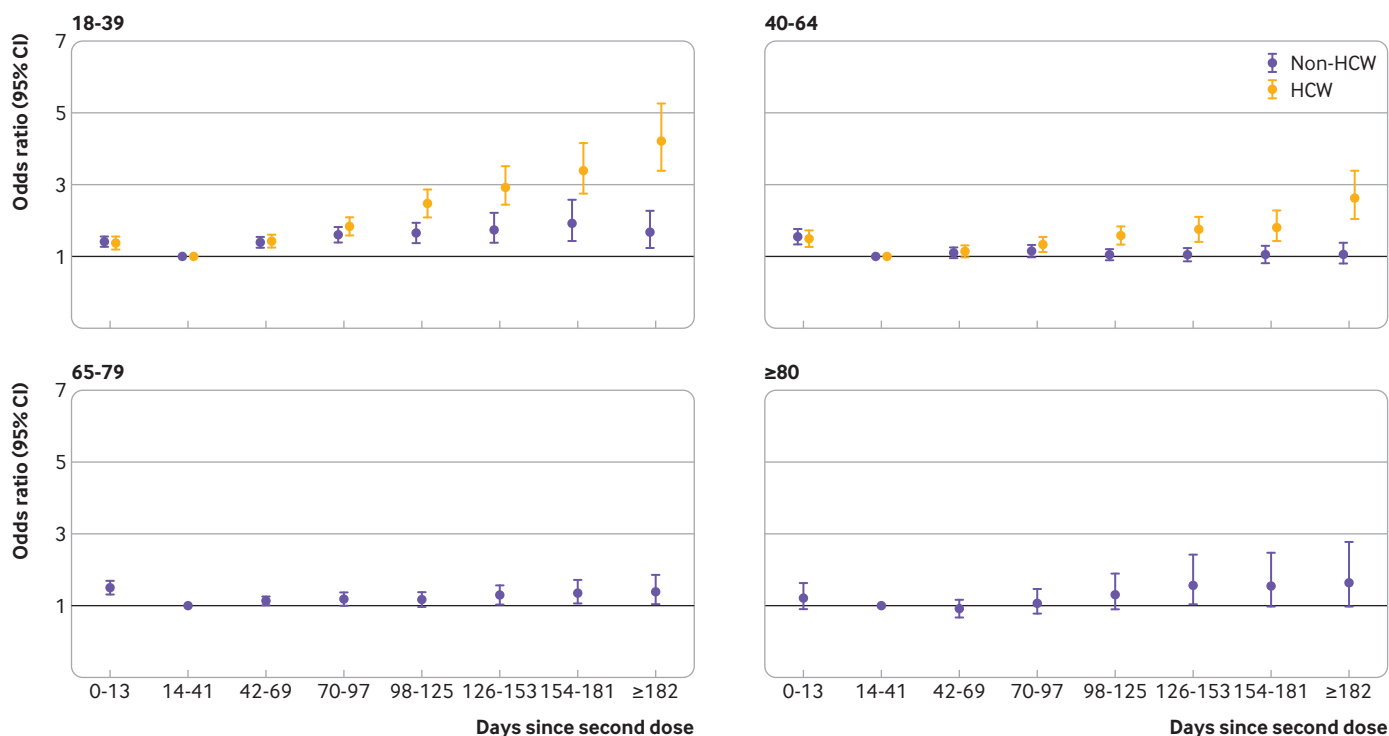
Methods This test negative case-control study included people aged ≥ 18 years who received two doses of CoronaVac, did not have a laboratory confirmed SARS-CoV-2 infection before vaccination, had an acute respiratory illness, and underwent reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 from 17 January to 14 December 2021. Cases were matched to test negative controls by age, municipality of residence, healthcare worker status, and week of RT-PCR test (43 257 matched sets). Conditional logistic regression was used to estimate change in odds of covid-19 and severe covid-19 over time since primary series completion, adjusting for sex, number of covid-19 associated comorbidities, race, and previous acute respiratory illness.

Study answer and limitations Adjusted odds ratios of symptomatic covid-19 increased with time since completion of the vaccination series, except in 40-64 year old non-healthcare workers. The adjusted odds ratios of covid-19 related hospital admission or death significantly increased over time since vaccination: from 1.25 (95% confidence interval 1.04 to 1.51) at 70-97 days to 1.94 (1.41 to 2.67) from 182 days onwards, compared with the odds 14-41 days after series completion. Analyses did not correct for bias, and vaccine effectiveness over time was not estimated.

What this study adds Significant increases in the risk of moderate and severe covid-19 outcomes occurred three months after primary vaccination with CoronaVac among adults aged ≥ 65 . These findings provide supportive evidence for the implementation of vaccine boosters in these populations who received this inactivated vaccine.

Funding, competing interests, and data sharing This work was supported by grants from the National Institute for Allergy and Infectious Diseases, the Sendas Family, and Beatrice Kleinberg Neuwirth Funds.

See bmj.com for other funding and competing interests. Deidentified databases and R codes will be deposited at <https://github.com/julioCroda/VebraCOVID-19>.



Odds ratio of symptomatic polymerase chain reaction confirmed covid-19 against days since vaccination, relative to 14-41 days from vaccination, by age group and healthcare worker (HCW) status

The *BMJ* is an Open Access journal. We set no word limits on *BMJ* research articles but they are abridged for print.

The full text of each *BMJ* research article is freely available on bmj.com.

The online version is published along with signed peer and patient reviews for the paper, and a statement about how the authors will share data from their study. It also includes a description of whether and how patients were included in the design or reporting of the research.

The linked commentaries in this section appear on bmj.com as editorials. Use the citation given at the end of commentaries to cite an article or find it online.

Development and validation of decision support tool for diagnosis of acute heart failure

Lee KK, Doudesis D, Anwar M, et al; on behalf of the CoDE-HF investigators

Cite this as: *BMJ* 2022;377:e068424

Find this at doi: 10.1136/bmj-2021-068424

Study question What is the diagnostic performance of N-terminal pro-B-type natriuretic peptide (NT-proBNP) thresholds for acute heart failure, and can this be improved by a decision support tool that combines NT-proBNP concentrations with clinical characteristics?

Methods Following a systematic review, individual patient level data in 10 369 patients with suspected acute heart failure across 14 studies from 13 countries were used to evaluate diagnostic performance of NT-proBNP thresholds. A decision support tool (Collaboration for the Diagnosis and Evaluation of Heart Failure (CoDE-HF)) combining NT-proBNP with clinical variables to report the probability of acute heart failure for an individual patient was developed and validated.

Study answer and limitations Overall, 43.9% (n=4549) of patients had an adjudicated diagnosis of acute heart failure. The guideline recommended NT-proBNP thresholds for acute heart failure had relatively poor diagnostic performance in important patient subgroups. CoDE-HF ruled in and ruled out acute heart failure more accurately than any approach using NT-proBNP thresholds alone and performed consistently across all subgroups, with a negative predictive value for having acute heart failure of 98.6% and a positive predictive value of 75.0% in patients without previous heart failure. This study is limited by the retrospective analysis of data from multiple previous studies.

What this study adds A decision support tool that uses statistical modelling to combine NT-proBNP as a continuous measure and clinical variables ruled in and ruled out acute heart failure more accurately than NT-proBNP thresholds alone.

Funding, competing interests, and data sharing This study is supported by the British Heart Foundation and Medical Research Council.

Authors KKL, DD, and NLM are employed by the University of Edinburgh, which has filed a patent on the CoDE-HF score. The R code and anonymised data used to develop and validate the CoDE-HF score can be made available to researchers on request to the corresponding author.

Study registration PROSPERO CRD42019159407.

