research

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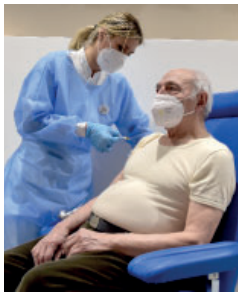

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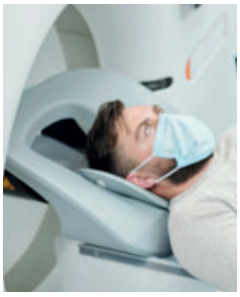

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ORIGINAL RESEARCH Systematic review and meta-analysis

Survival for waitlisted patients with kidney failure receiving transplantation versus remaining on waiting list

Chaudhry D, Chaudhry A, Peracha J, Sharif A

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Study question For waitlisted patients with kidney failure, does kidney transplantation afford better survival than remaining on dialysis?

Methods A systematic review and meta-analysis of studies compared all cause mortality rates after kidney transplantation versus dialysis for waitlisted patients with kidney failure. Online databases Medline, Ovid Embase, Web of Science, Cochrane Collection, and ClinicalTrials.gov were searched between inception and 1 March 2021. Two independent reviewers extracted the data and assessed the risk of bias of included studies. Meta-analysis was done using the DerSimonian-Laird random effects model, with heterogeneity investigated by subgroup analyses, sensitivity analyses, and meta-regression.

Study answer and limitations The search identified 48 observational studies with no randomised controlled trials (n=1 245 850 patients). In total, 92% (n=44/48) of studies reported a long term (at least one year) survival benefit associated with transplantation compared with dialysis. However, 11 of those studies identified stratums in which transplantation offered no statistically significant benefit over remaining on dialysis. In 18 studies suitable for meta-analysis, kidney transplantation showed a survival benefit (hazard ratio 0.45, 95% confidence interval 0.39 to 0.54; P<0.001), with significant heterogeneity even after subgroup/sensitivity analyses or meta-regression analysis. The substantial heterogeneity in the published literature, which could not be accounted for despite these measures, limits translation of population level data to individual circumstances.

What this study adds These findings confirm improved mortality afforded by transplantation for waitlisted patients with kidney failure, but no clear survival benefit exists for various subgroups. Significant heterogeneity also means that population level data should be cautiously translated to individual patients for personalised decision making.

Funding, competing interests, and data sharing DC was supported by a Royal College of Surgeons (England) grant. No competing interests declared. Extracted data available from the corresponding author on request.

Systematic review registration PROSPERO CRD42021247247.

Hazard ratios for transplantation versus waitlisted dialysis

Subgroup	No of studies	Hazard ratio (95% CI)
Overall	18	0.45 (0.39 to 0.54)
Geographical region:		
Europe	13	0.49 (0.40 to 0.60)
North America	2	0.34 (0.22 to 0.53)
South America	2	0.67 (0.33 to 1.35)
Oceania	1	0.19 (0.17 to 022)
Donor type:		
Deceased donor transplantation	14	0.45 (0.38 to 0.55)
Living donor transplantation	1	0.30 (0.23 to 0.39)
Population type:		
Aged ≥60 years	5	0.42 (0.34 to 0.53)
General population	13	0.47 (0.38 to 0.59)

CI=confidence interval.

SARS-CoV-2 antigen lateral flow tests for detecting infectious people

Deeks JJ, Singanayagam AJ, Houston H, et al

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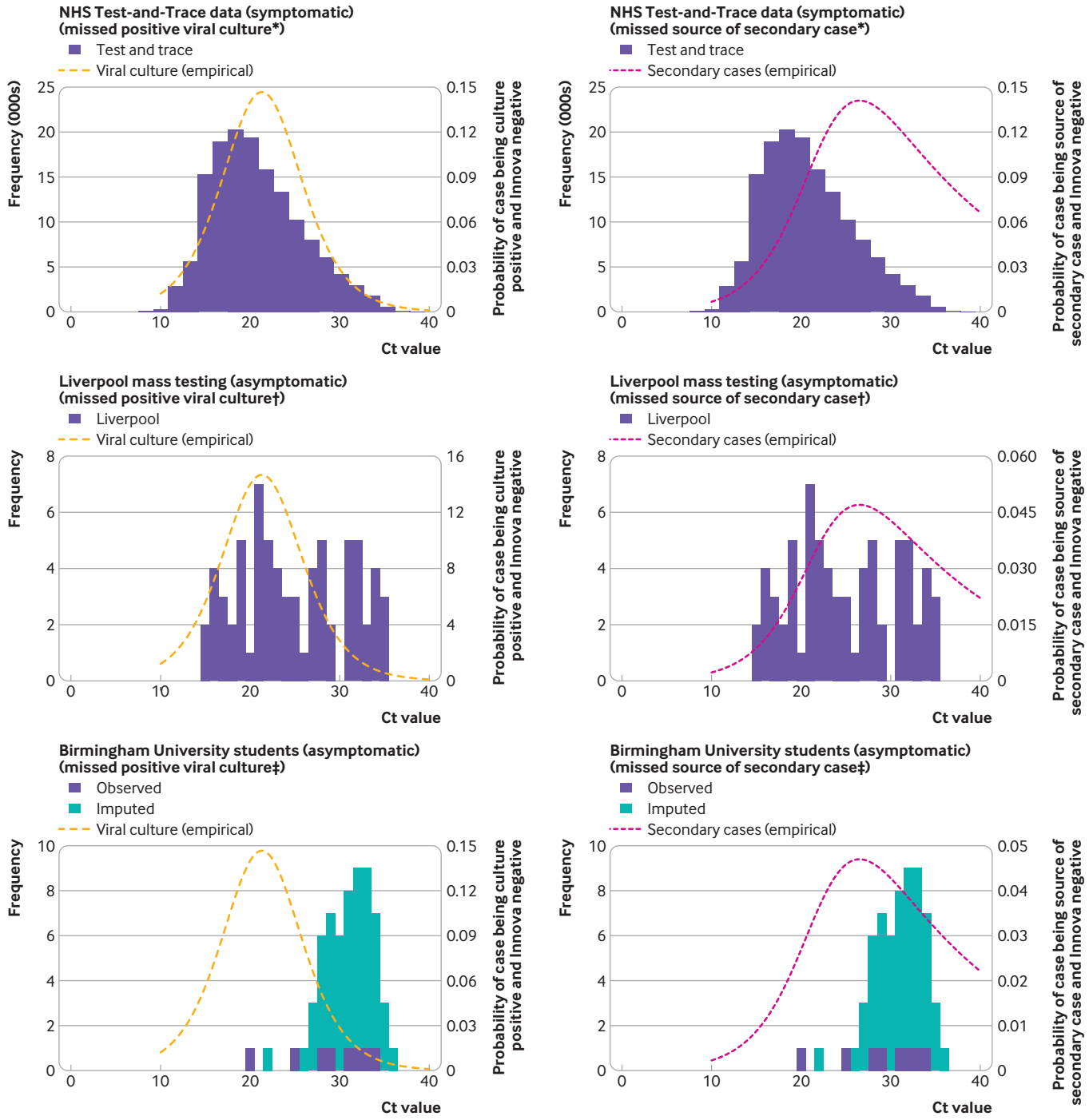
Study question What proportion of lateral flow tests (LFTs) produce negative results in those with a high risk of infectiousness from SARS-CoV-2 and what is the impact of the stage and severity of disease across test settings?

Methods This linked data analysis combined empirical evidence on the accuracy of lateral flow antigen tests, the probability of positive viral culture or transmission to secondary cases, and the distribution of viral loads of SARS-CoV-2 in people across settings to estimate the ability of LFTs to detect infectiousness. Predictions, based on empirical data, were compared with those



Distributions of cycle threshold (Ct) values of individuals positive for SARS-CoV-2 in different settings. Birmingham used imputation owing to proportional sampling design. *Distribution from Lee et al 2021.[15] †Distribution from García-Fiñana et al 2021.[28] ‡Distribution from Ferguson et al 2021.[29] See reference details in full paper on bmj.com

made by influential mathematical models. Evidence for the sensitivity of the Innova LFT, was based on 70 individuals with SARS-CoV-2. Evidence of infectiousness was based on viral culture rates on 246 samples (176 people with SARS-CoV-2) and secondary cases among 2 474 066 contacts. Distributions of cycle threshold (Ct) values from three settings were used: 231 497 index individuals attending NHS Test-and-Trace centres; 70 people with SARS-CoV-2 detected in Liverpool; and 62 students with SARS-CoV-2 at Birmingham University (54 imputed).

Study answer and limitations The analysis predicted that, of those with a viral culture positive result, Innova would miss 20% attending an NHS Test-and-Trace centre, 29% without symptoms attending municipal mass testing, and 81% attending university without symptoms, along with 38%, 47%, and 90% of sources of secondary cases. In comparison, two mathematical models underestimated the numbers of missed infectious individuals (8%, 10%, and 32% in the three settings for one model, whereas the assumptions from the second model made it impossible to miss an infectious individual). Owing to the paucity of usable data, the inputs to the analyses were from limited sources.

What this study adds The proportion of infectious people with SARS-CoV-2 missed by LFTs is substantial enough to be of clinical importance. The proportion missed varied between settings because of different viral load distributions and is likely to be highest in those without symptoms. Key models have substantially overestimated the sensitivity of LFTs compared with empirical data. An urgent need exists for additional robust well designed and reported empirical studies from intended use settings to inform evidence based policy.

Funding, competing interests, and data sharing
Authors supported by the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre and NIHR Health Protection Research Unit, Imperial College London. JJD contributed to the Birmingham University evaluation of Innova, with grant funding from The Foundation for Innovative New Diagnostics for the Cochrane reviews of the accuracy of tests for SARS-CoV-2; AJS reports NIHR/UKRI funding. Data are reported in the supplementary file on bmj.com.

ORIGINAL RESEARCH Systematic review and meta-analysis

Efficacy of covid-19 vaccines in immunocompromised patients

Lee ARYB, Wong SY, Chai LYA, et al
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Study question How efficacious are covid-19 vaccines in immunocompromised patients compared with immunocompetent people?

Methods PubMed, Embase, Central Register of Controlled Trials, and COVID-19 Open Research Dataset Challenge were searched for prospective observational studies published between 1 December 2020 and 5 November 2021 that compared the efficacy of covid-19 vaccines between immunocompromised patients and immunocompetent controls. Unpublished relevant articles were also searched through ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The primary outcomes of interest were cumulative incidence of seroconversion after a first and second dose of covid-19 vaccine. Secondary outcomes included SARS-CoV-2 antibody titres after a first and second vaccine dose. After the removal of duplicate data, a frequentist random effects meta-analysis was used to separately to pool the relative (risk ratio) and absolute risks of seroconversion.

Study answer and limitations After one vaccine dose, seroconversion was about half as likely in patients with haematological cancers (relative risk 0.40, 95% confidence interval 0.32 to 0.50, I^2=80%; absolute risk 0.29, 95% confidence interval 0.20 to 0.40, I^2=89%), immune mediated inflammatory disorders (0.53, 0.39 to 0.71, I^2=89%; 0.29, 0.11 to 0.58, I^2=97%), and solid cancers (0.55, 0.46 to 0.65, I^2=78%; 0.44, 0.36 to 0.53, I^2=84%) compared with immunocompetent controls, whereas organ transplant recipients were 16 times less likely to seroconvert (0.06, 0.04 to 0.09, I^2=0%; 0.06, 0.04 to 0.08, I^2=0%). After a second dose, seroconversion remained least likely in transplant recipients (0.39, 0.32 to 0.46, I^2=92%; 0.35; 0.26 to 0.46; I^2=92%). Seroconversion was increasingly likely in patients with haematological cancers (0.63, 0.57 to 0.69, I^2=88%; 0.62, 0.54 to 0.70, I^2=90%), immune mediated inflammatory disorders (0.75, 0.69 to 0.82, I^2=92%; 0.77, 0.66 to 0.85, I^2=93%), and solid cancers (0.90, 0.88 to 0.93, I^2=51%; 0.89, 0.86 to 0.91, I^2=49%). Seroconversion was similar between people with HIV and immunocompetent controls (1.00, 0.98 to 1.01, I^2=0%; 0.97, 0.83 to 1.00, I^2=89%). Third doses of covid-19 vaccines might induce seroconversion in those who failed to show seroconversion. Limitations of this study include seroconversion serving as a proxy for vaccine efficacy on infection rates and severity of covid-19, and heterogeneity in study design such as seroconversion definition, immunoassay type, and vaccine type.

What this study adds Seroconversion rates after covid-19 vaccination were significantly lower in immunocompromised patients, especially organ transplant recipients. A second dose was associated with improved seroconversion across all patient groups.

Funding, competing interests, and data sharing No funding received. No competing interests declared. No additional data available.

Systematic review registration PROSPERO CRD42021272088.

Seroconversion rates after doses 1 and 2 of covid-19 vaccines in immunocompromised patients compared with immunocompetent controls

	Risk estimate (95% CI)				
	Solid cancers	Haematological cancers	Organ transplant	Autoimmune conditions	HIV
First dose					
Relative risk	0.55 (0.46 to 0.65)	0.40 (0.32 to 0.50)	0.06 (0.04 to 0.09)	0.53 (0.39 to 0.71)	1.06 (0.74 to 1.54)
Absolute risk	0.44 (0.36 to 0.53)	0.29 (0.20 to 0.40)	0.06 (0.04 to 0.08)	0.29 (0.11 to 0.58)	0.69 (0.53 to 0.82)
Second dose					
Relative risk	0.90 (0.88 to 0.93)	0.63 (0.57 to 0.69)	0.39 (0.32 to 0.46)	0.75 (0.69 to 0.82)	1.00 (0.98 to 1.01)
Absolute risk	0.89 (0.86 to 0.91)	0.62 (0.54 to 0.70)	0.35 (0.26 to 0.46)	0.77 (0.66 to 0.85)	0.97 (0.83 to 1.00)

Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe covid-19 during predominant circulation of the delta variant in Italy

Fabiani M, Puopolo M, Morciano C, et al; on behalf of the Italian Integrated Surveillance of covid-19 study group and Italian covid-19 Vaccines Registry group

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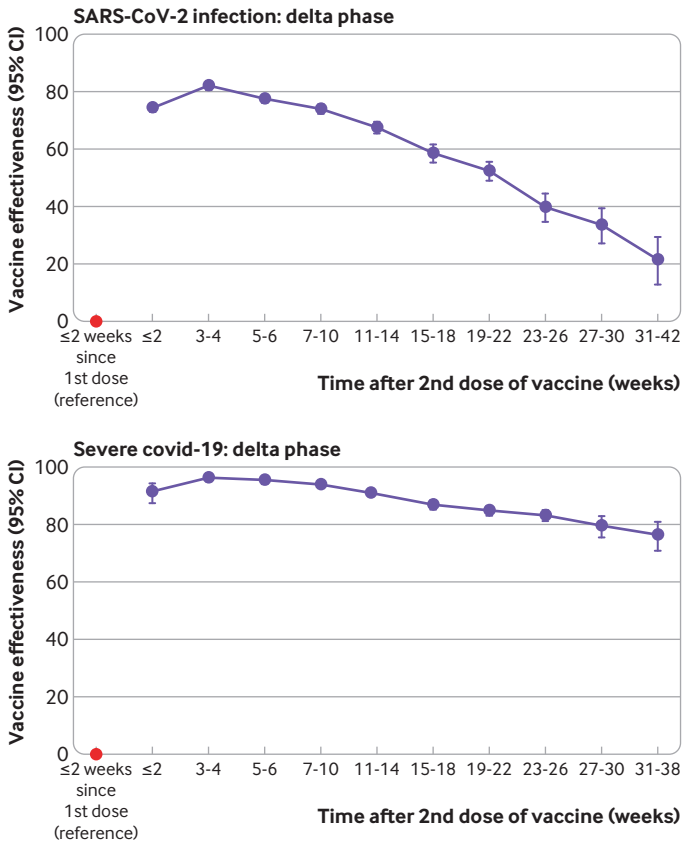
Study question Are mRNA vaccines effective against SARS-CoV-2 infection and severe covid-19 over time after vaccination?

Methods A retrospective cohort study was conducted in Italy in 33 250 344 individuals aged ≥16 years who received an mRNA vaccine (Comirnaty (Pfizer) or Spikevax (Moderna)). Outcomes included SARS-CoV-2 infection and severe covid-19 (admission to hospital or death). Incidence rate ratios at different time intervals from vaccination were estimated by negative binomial models, adjusting for sex, age group, brand of vaccine, priority risk category, regional weekly incidence in the general population, and geographical region. Adjusted vaccine effectiveness was calculated as (1−IRR)×100, where IRR=incidence rate ratio, with a time interval of 0-14 days from the first dose as the reference.

Study answer and limitations During the epidemic phase when the delta variant of the SARS-CoV-2 virus was the predominant strain, vaccine effectiveness against infection decreased significantly (P<0.001), from 82% (95% confidence interval 80% to 84%) at 3-4 weeks after the second dose of vaccine to 33% (27% to 39%) at 27-30 weeks after the second dose. In the same time intervals, vaccine effectiveness against severe covid-19 also decreased (P<0.001), although to a lesser extent, from 96% (95% to 97%) to 80% (76% to 83%). The decrease was more pronounced in high risk individuals (residents of long term care facilities, people with comorbidities, and immunocompromised people) and those aged ≥60 years, who did not appear to be protected against SARS-CoV-2 infection at 27-30 weeks after the second dose of vaccine. The available data did not allow for controlling of individual behavioural factors.

What this study adds The results support the covid-19 vaccination campaigns targeting high risk individuals and those aged ≥60 years to receive a booster dose of vaccine six months after the primary vaccination cycle. Timing the booster dose earlier than six months and extending the offer of the booster dose to the wider eligible population might also be warranted.



Effectiveness of mRNA vaccines against SARS-CoV-2 infection and severe covid-19 at different time intervals after completion of the primary vaccination cycle, when circulation of the delta variant of SARS-CoV-2 was dominant, Italy, 19 July 2020 to 7 November 2021. Vaccine effectiveness calculated as (1−IRR)×100, where IRR=incidence rate ratio

Funding, competing interests, and data sharing No funding provided. No competing interests declared. No additional data available.