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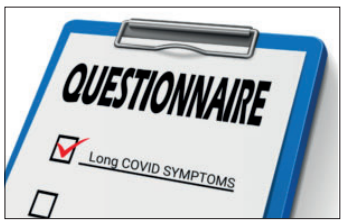

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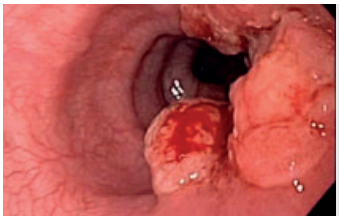
Impact of covid-19 vaccine scale-up p 144



Use of sintilimab in patients with metastatic oesophageal cancer p 146

ORIGINAL RESEARCH Rasch analysis

FAST TRACK

Development and validation of the symptom burden questionnaire for long covid (SBQ-LC)

Hughes SE, Haroon S, Subramanian A, et al

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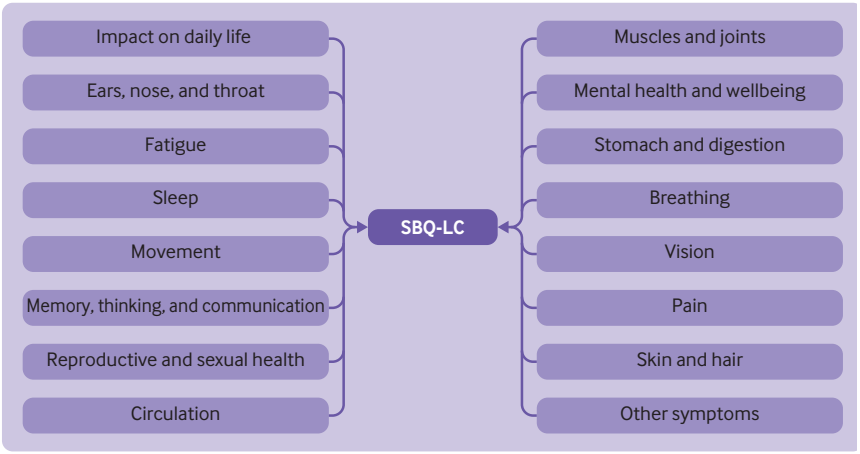
Find this at doi: 10.1136/bmj-2022-070230

Study question Is it possible to construct a linearly weighted patient reported outcome instrument that comprehensively measures the symptom burden from long covid?

Methods Published systematic reviews informed generation of the items. Cognitive debriefing with patients (n=13) and a clinician survey (n=10) established content validity, and the Therapies for Long COVID in non-hospitalised individuals: From symptoms, patient reported outcomes and immunology to targeted therapies (TLC Study) patient and public involvement group confirmed face validity of the draft instrument. 274 adults with self-reported persistent symptoms of covid-19, or long covid, participated in field testing. Rasch analysis guided refinement of the instrument and provided early evidence of the instrument's psychometric properties.

Study answer and limitations This study resulted in construction of the symptom burden questionnaire for long covid (SBQ-LC), a modular patient reported outcome instrument with promising psychometric properties. SBQ-LC comprises 17 independent scales, each covering a different symptom domain. Each scale returns a summed raw score and transformed linear score, with higher scores representing greater symptom burden. All scales met the Rasch model requirements for unidimensionality and item fit. Rating scale categories were ordered with acceptable category fit statistics (outfit mean square values <2.0 logits). 14 item pairs had evidence of local dependency (residual correlation values >0.4). Across the 17 scales, person reliability ranged from 0.34 to 0.87, person separation ranged from 0.71 to 2.56, item separation ranged from 1.34 to 13.86, and internal consistency reliability (Cronbach's alpha) ranged from 0.56 to 0.91. Sample representativeness was a study limitation.

What this study adds This study developed and validated a comprehensive, condition specific patient reported outcome instrument measuring the symptom burden from long covid. SBQ-LC is available for use in clinical trials and routine care.



Conceptual framework showing symptom domains in SBQ-LC

Funding, competing interests, and data sharing See full paper on bmj.com for funding and competing interests. Data may be released after application to the data controllers.

The benefits of large scale covid-19 vaccination

ORIGINAL RESEARCH Observational study

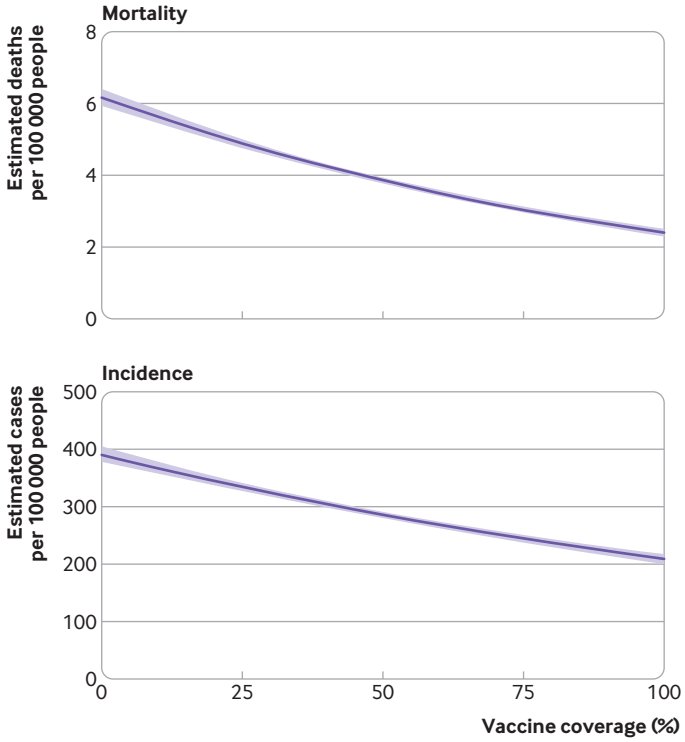
Public health impact of covid-19 vaccines in the US

Suthar AB, Wang J, Seffren V, Wiegand RE, Griffing S, Zell E

Cite this as: *BMJ* 2022;377:e069317
Find this at doi: 10.1136/bmj-2021-069317

Study question What was the impact of vaccine scale-up on population level mortality and incidence in the United States?

Methods This US observational study included county level case surveillance and vaccine related data reported from 14 December 2020 to 18 December 2021. The study estimated the impact of a 10% improvement in county vaccination coverage (defined as at least one dose of a covid-19 vaccine in adults aged ≥18 years) on mortality and incidence rates during the first year of vaccine scale-up. County mortality rates (deaths/100 000 population/county week) were calculated as the primary outcome, and incidence (cases/100 000 population/county week) was the secondary outcome. Incidence rate ratios were used to compare rates across vaccination coverage levels. For impact estimates during the eras of alpha and delta variant predominance, the effect of very low (0-9%), low (10-39%), medium (40-69%), and high (≥70%) vaccination coverage levels on mortality and incidence rates were compared.



COMMENTARY New evidence confirms that fewer people die in better vaccinated communities

Another confidence booster for covid-19 vaccines

The first covid-19 vaccines were administered under emergency use authorisation in December 2020, just one year into the pandemic, a "miracle" of pharmaceutical innovation that has saved an estimated million lives or more in the US alone.[1 2] The authorisation was given on the basis of safety and efficacy in randomised controlled trials, which found that immunisation with Pfizer-BioNTech and Moderna mRNA vaccines protected a remarkably high percentage (>90%) of recipients from developing symptomatic infection and, to a lesser extent, from asymptomatic infection too. In other words, when tested against the SARS-CoV-2 variants prevailing in 2020 and early 2021, these novel covid-19 vaccines could stop the great majority of infections from causing illness and help to prevent transmission of SARS-CoV-2. But could vaccination prevent infection and illness on a large scale, outside the controlled environment of clinical trials? The study by Suthar and colleagues in this issue adds to the evidence that it can, across the US.[3]

Given the practical challenges of scaling up immunisation programmes—maintaining cold chains, carrying out mass inoculation in busy or makeshift clinics, and accurately reporting both numbers vaccinated and health outcomes—real world vaccine effectiveness is typically less than the efficacy achieved in clinical trials. Following reports that effectiveness has remained high for a variety of outcomes (infection, symptomatic illness, visits to emergency departments, hospital admissions, severe illness, and death) in diverse settings,[4-10] Suthar and colleagues have now investigated the impact of covid-19 vaccination, largely with Pfizer-BioNTech and Moderna vaccines, across 2558 counties in 48 US states, covering nearly 80% of the US population. Their evaluation is based on more than 30 million cases of covid-19 and more than 400 000 deaths linked to covid-19, which were reported during the second year of the pandemic, between December 2020 and December 2021.[3]

During the first half of 2021, when the alpha variant of SARS-CoV-2 was dominant, the covid-19 mortality rate was reduced by 60%, 75%, and 81% in counties with low, medium, and high vaccination coverage, compared with counties that had very low coverage. The corresponding figures for the reduction in case incidence were 57%, 70%, and 80%. The impact on mortality was similar during the second half of 2021 when the delta variant became dominant in the US, with smaller effects on incidence.[3]

Disproportionately large effect

Clearly, counties with higher vaccination coverage had fewer covid-19 cases and deaths per head of population, and the measured effectiveness in counties with high vaccine coverage was reassuringly large. More than this, vaccination had a disproportionately large effect in counties with low and medium coverage. For instance, an incremental increase in coverage of only 20% (from very low to low) and 50% (from very

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Effect of vaccination coverage on county covid-19 related mortality and incidence during first year of vaccine roll-out. Analyses are from 2558 counties in 48 US jurisdictions. Model controlled for county population size, social vulnerability index, and mobility changes

Study answer and limitations In total, 30 643 878 cases of covid-19 and 439 682 deaths associated with covid-19 occurred over 132 791 county weeks. A 10% improvement in vaccination coverage was associated with an 8% (95% confidence interval 8% to 9%) reduction in mortality rates and a 7% (6% to 8%) reduction in incidence. Higher vaccination coverage levels were associated with reduced mortality and incidence rates during the eras of alpha and delta variant predominance. Residual and temporal confounding may affect estimated effect sizes.

What this study adds In this observational study, including nearly 80% of US counties and 300 million people, higher vaccination coverage was associated with lower rates of population level covid-19 mortality and incidence. This community level benefit complements the large body of evidence indicating individual level benefits of covid-19 vaccination.

Funding, competing interests, and data sharing No funding was received. The authors report no competing interests. Data are available at https://data.cdc.gov/.

low to medium) led to reductions in mortality of 60% and 75%, respectively.

Suthar and colleagues argue that vaccination benefits whole communities, and indeed it does when coverage is high.[3] But they did not seek, and their data do not show, any extra effect of herd immunity, whereby vaccinated people prevented the transmission of infection to others in their communities.[11] A more likely explanation for the disproportionately beneficial effect in counties with low and medium coverage is that vaccination campaigns first targeted older people who are at greatest risk of severe illness and death from covid-19. Vaccine rollout in most countries began with older and otherwise vulnerable people and progressively included younger and less vulnerable people. In states that have achieved relatively low vaccination coverage overall, the percentage of older people vaccinated is invariably higher than the population average.[13] Suthar and colleagues did not investigate the effect of vaccination by age, but doing this should be possible with existing data available to the US Centers for Disease Control and Prevention.

The findings of this study also make clear that many more lives could have been saved, and will be saved, by encouraging people to keep up to date with vaccination in the face of waning immunity and new SARS-CoV-2 variants and by achieving even higher population coverage. How many lives is a matter for others to explore. Meanwhile, this new study is another confidence booster for covid-19 vaccines.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.o867

PAUL CHRISTIAN GORDON/ALAMY

Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15)

Lu Z, Wang J, Shu Y, et al; on behalf of the ORIENT-15 study group

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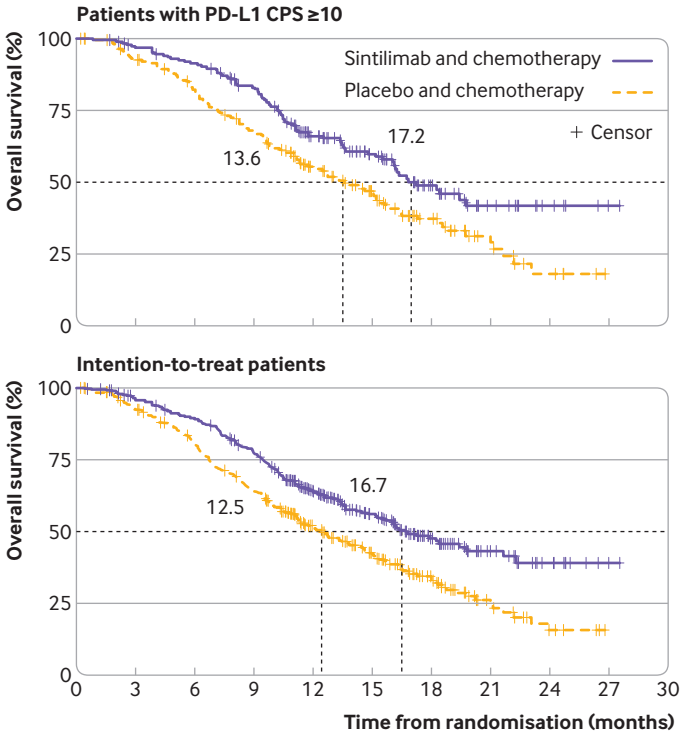
Find this at doi: 10.1136/bmj-2021-068714

Study question Is sintilimab in combination with chemotherapy for first line treatment of unresectable locally advanced, recurrent, or metastatic oesophageal squamous cell carcinoma better than placebo with chemotherapy?

Methods In this multicentre, double blind, randomised, phase 3 trial (ORIENT-15), patients with untreated advanced or metastatic oesophageal squamous cell carcinoma were enrolled from 66 sites in China and 13 sites outside of China. Patients were randomised 1:1 to receive sintilimab or placebo (3 mg/kg in patients weighing <60 kg, or 200 mg in patients weighing ≥60 kg) with cisplatin 75 mg/m^2 plus paclitaxel 175 mg/m^2 every three weeks. The trial was amended to allow investigators to choose the chemotherapy regimen: cisplatin plus paclitaxel or cisplatin plus 5-flourouracil (800 mg/m^2 continuous on days 1-5). The primary end points were overall survival in all patients and in patients with combined positive scores of ≥10 for expression of programmed cell death ligand 1.

Study answer and limitations At the interim analysis, sintilimab with chemotherapy showed better overall survival than placebo with chemotherapy in all patients (median 16.7 *v* 12.5 months, hazard ratio 0.63, 95% confidence interval 0.51 to 0.78, P<0.001) and in patients with combined positive scores of ≥10 (17.2 *v* 13.6 months, 0.64, 0.48 to 0.85, P=0.002). Sintilimab and chemotherapy significantly improved progression-free survival compared with placebo and chemotherapy in all patients (7.2 *v* 5.7 months, 0.56, 0.46 to 0.68, P<0.001) and in patients with combined positive scores of ≥10 (8.3 *v* 6.4 months, 0.58, 0.45 to 0.75, P<0.001). Rates of adverse events related to treatment, grade ≥3, were 60% (196/327) and 55% (181/332) in the sintilimab-chemotherapy and placebo-chemotherapy groups, respectively. The main limitation was the small number of patients enrolled in the study from outside of China and the small number of patients who received the cisplatin plus 5-flourouracil chemotherapy regimen.



Overall survival in patients who received sintilimab or placebo in combination with chemotherapy. Kaplan-Meier plot of overall survival in all patients and in patients with combined positive scores of ≥10 for expression of programmed cell death ligand 1 (PD-L1 CPS ≥10)

What this study adds Compared with placebo and chemotherapy, sintilimab and chemotherapy as first line treatment for unresectable locally advanced, recurrent, or metastatic oesophageal squamous cell carcinoma significantly prolonged median overall survival by more than four months, with a 37% reduction in the risk of death.

Funding, competing interests, and data sharing Funded by Innovent Biologics and Eli Lilly. Full details of competing interests on bmj.com. Data access and sharing policy of the Human Genetic Resource Administration of China and other participating sites will be followed.

Trial registration ClinicalTrials.gov NCT03748134.