Emulating the GRADE trial using real world data

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Study question What is the comparative effectiveness of four glucose lowering drugs among adults with moderately uncontrolled type 2 diabetes when using real world data to emulate an unpublished randomized clinical trial?

Methods The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) trial criteria were applied to claims and laboratory data from the US nationwide OptumLabs Data Warehouse database. The study compared the effectiveness of glimepiride (sulfonylurea), sitagliptin (dipeptidyl-peptidase 4 inhibitor), liraglutide (glucagon-like peptide-1 receptor agonist), and insulin glargine (basal analog insulin) for achieving glycemic control (time to HbA1c ≥7.0%) in people who were receiving metformin monotherapy.

Study answer and limitations 8252 people were identified (19.7% of adults starting the study drugs in the database) who met eligibility criteria for the GRADE trial (glimepiride arm=4318, liraglutide arm=690, sitagliptin arm=2993, glargine arm=251). Median times (days) to HbA1c ≥7.0% were 442 (95% CI 394 to 480) for glimepiride, 764 (741 to not calculable) for liraglutide, and 427 (380 to 483) for sitagliptin. Liraglutide was associated with lower risk of reaching HbA1c ≥7.0% compared with glimepiride (hazard ratio 0.57, 95% CI 0.43 to 0.75) and sitagliptin (0.55, 0.41 to 0.73). The glargine arm was excluded from analyses owing to small sample size. The study population was comprised of adults with private and Medicare Advantage health plans and may not generalize to those with public health plans or without health insurance.

What this study adds In this emulation of the GRADE trial, liraglutide was significantly more effective at maintaining glycemic control than glimepiride or sitagliptin when added to metformin monotherapy. This study suggests that advanced causal inference analytic methods applied to observational data can be used to emulate clinical trials.

Funding, competing interests, and data sharing This study was funded by the US Food and Drug Administration and the National Institute of Diabetes and Digestive and Kidney Diseases. See full paper on bmj.com for competing interests. The study protocol has been published online, but raw deidentified claims data are not publicly available.
Test negative, case-control study

Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network

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Study question How effective are mRNA vaccines for prevention of moderate and severe covid-19 and how does that protection vary with the number of doses and time since vaccination by age group, immunocompromised status, and vaccine product?

Methods Using Centers for Disease Control’s VISION Network and a test negative, case-control design, effectiveness of the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines was examined among US adults for prevention of covid-19 related hospital admissions and emergency department and urgent care visits. Data were collected for 893,461 patients from 261 hospitals, 272 emergency departments, and 119 urgent care clinics in 10 states. Vaccination status was categorized by number of doses received and number of months between the most recent vaccine dose and medical encounter. Multivariate logistic regression was used to estimate vaccine effectiveness controlling for confounding effects, such as level of local viral circulation and likelihood of vaccination.

Study answer and limitations During the omicron period, mRNA vaccine protection against severe covid-19 was initially high (73% (95% confidence interval 63% to 80%)) but waned after primary vaccination, increased markedly after a third dose (89% (88% to 90%)), and waned again by four to five months after a third dose (66% (63% to 68%)). A similar pattern was noted in emergency departments and urgent care clinics: vaccine effectiveness of three doses was 83% (82% to 84%) initially but waned to 46% (44% to 49%) by four to five months. Waning was evident in all subgroups, including younger adults (18-44 years) and individuals without immunocompromising conditions, although waning was most noticeable in individuals who were immunocompromised. A fourth dose was associated with increased vaccine effectiveness among most groups for whom this dose was recommended. Residual confounding potentially limits this study.

What this study adds Vaccine effectiveness of mRNA vaccines against moderate and severe covid-19 wanes with time since vaccination. Although booster doses improve vaccine protection, their effectiveness also wanes over time.

Funding, competing interests, and data sharing Funded by the US Centers for Disease Control and Prevention. Several authors report receiving funding (unrelated to this work) from Pfizer, Merck, GlaxoSmithKline, Sanofi Pasteur, AstraZeneca, and Biofire diagnostics. CDC will share aggregate study data once study objectives are complete, consistent with data use agreements with partner institutions.

![Image](https://example.com/image.jpg)

<table>
<thead>
<tr>
<th>Hospital sample</th>
<th>No</th>
<th>Covid-like illness controls (col %)</th>
<th>Covid-19 cases (col %)</th>
<th>Row %</th>
<th>Vaccine effectiveness (95% CI)</th>
<th>Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-dose vaccinated &lt;2 months</td>
<td>405</td>
<td>350 (0.4)</td>
<td>55 (0.3)</td>
<td>13.6</td>
<td>73 (63 to 80)</td>
<td>57 (51 to 62)</td>
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<tr>
<td>2-dose vaccinated 4 to &lt;6 months</td>
<td>1768</td>
<td>1434 (1.1)</td>
<td>334 (1.9)</td>
<td>18.9</td>
<td>89 (88 to 90)</td>
<td>86 (83 to 89)</td>
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<tr>
<td>3-dose vaccinated &lt;2 months</td>
<td>5516</td>
<td>5049 (6.4)</td>
<td>467 (2.7)</td>
<td>8.5</td>
<td>66 (63 to 68)</td>
<td>66 (63 to 68)</td>
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<tr>
<td>3-dose vaccinated 4 to &lt;6 months</td>
<td>12152</td>
<td>11289 (14.4)</td>
<td>863 (5.0)</td>
<td>7.1</td>
<td>63 (57 to 68)</td>
<td>63 (57 to 68)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Emergency department and urgent care sample</th>
<th>No</th>
<th>Covid-like illness controls (col %)</th>
<th>Covid-19 cases (col %)</th>
<th>Row %</th>
<th>Vaccine effectiveness (95% CI)</th>
<th>Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-dose vaccinated &lt;2 months</td>
<td>1703</td>
<td>1424 (0.7)</td>
<td>279 (0.5)</td>
<td>16.4</td>
<td>63 (57 to 68)</td>
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<tr>
<td>2-dose vaccinated 4 to &lt;6 months</td>
<td>7403</td>
<td>5539 (2.6)</td>
<td>1864 (3.3)</td>
<td>25.2</td>
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<tr>
<td>3-dose vaccinated &lt;2 months</td>
<td>14673</td>
<td>14758 (7.0)</td>
<td>1715 (3.0)</td>
<td>10.4</td>
<td>83 (82 to 84)</td>
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<tr>
<td>3-dose vaccinated 4 to &lt;6 months</td>
<td>27925</td>
<td>25297 (11.9)</td>
<td>2628 (4.6)</td>
<td>9.4</td>
<td>46 (44 to 49)</td>
<td>46 (44 to 49)</td>
</tr>
</tbody>
</table>

Vaccine effectiveness (%) against covid-19 associated hospital admissions and emergency department and urgent care visits by time since vaccination, restricted to omicron period. Vaccine effectiveness estimates are adjusted for geographical area, calendar week, age, race, ethnicity, presence of respiratory and non-respiratory comorbidities, immunocompromise status, local viral circulation, and propensity to be vaccinated score. CI=confidence interval; col=column.
Study question Do covid-19 booster vaccine doses provide additional benefit beyond a primary vaccine series alone against severe omicron related covid-19?

Methods This observational vaccine effectiveness study used a test negative design among 4760 adults admitted to hospital in the United States with acute respiratory symptoms between 26 December 2021 and 30 June 2022, a period when the omicron variant was dominant. Participants included 2385 (50%) patients with laboratory confirmed covid-19 (cases) and 2375 (50%) patients who tested negative for SARS-CoV-2 (controls). Vaccine effectiveness for the prevention of covid-19 associated admission to hospital was calculated by comparing the odds of antecedent vaccination versus no vaccination between case patients and control patients.

Study answer and limitations Overall, median age of participants was 64 years (interquartile range 52-75 years), 994 (20.8%) were immunocompromised, 85 (1.8%) were vaccinated with a primary series plus two boosters, 1367 (28.7%) with a primary series plus one booster, and 1875 (39.3%) with a primary series alone, and 1433 (30.1%) were unvaccinated. Among immunocompetent patients, vaccine effectiveness for prevention of hospital admission with omicron related covid-19 was higher with two booster doses (63%, 95% confidence interval 37% to 78%) or one booster dose (65%, 58% to 71%) compared with a primary series alone (37%, 25% to 47%) (P<0.001 for the pooled boosted regimens compared with a primary series alone). A similar pattern was observed for immunocompromised adults. This study was limited to a period when omicron lineages BA.1, BA.2, and BA.5 were dominant, and further surveillance will be needed as other variants emerge.

What this study adds During the first six months of 2022 in the US, booster doses of a covid-19 vaccine provided additional benefit beyond a primary vaccine series alone for preventing hospital admissions with omicron related covid-19.

Funding, competing interests, and data sharing Funded by the US Centers for Disease Control and Prevention. Scientists from CDC participated in this work. No additional data available.

Vaccine effectiveness using multivariable logistic regression models (see variables in full paper on bmj.com) among immunocompetent and immunocompromised individuals for prevention of hospital admission with covid-19 in the United States during an omicron dominant period, 26 December 2021 to 30 June 2022.
**Study question** What are the most important symptom clusters of post-covid syndrome six to 12 months after acute infection?

**Methods** Adults aged 18-65 years with confirmed SARS-CoV-2 infection in four geographically defined regions in southern Germany between October 2020 and March 2021 were invited to participate. Symptom frequencies (six to 12 months after versus before acute infection), symptom severity and clustering, risk factors, and associations with general health recovery and working capacity were analysed.

**Study answer and limitations** Analyses included 11 710 participants (58.8% (n=6881) women; mean age 44.1 years; 3.6% (412/11 602) previously admitted with covid-19; mean follow-up time 8.5 months). The symptom clusters fatigue (in 37.2% (4213/11 312) of participants) and neurocognitive impairment (in 31.3% (3561/11 361) of participants) contributed most to reduced health recovery and working capacity, but chest symptoms, anxiety/depression, headache/dizziness, and pain syndromes were also prevalent and relevant for working capacity, with some differences according to sex and age. The response rate of 24% was low, with the possibility of selection bias (for example, potential for overestimation of prevalence measures).

**What this study adds** This study provides evidence of persistence of new symptom clusters (not present before acute infection) such as fatigue, neurocognitive impairment, chest symptoms, smell or taste disorder, and anxiety/depression beyond six to 12 months after acute SARS-CoV-2 infection. The three most frequent clusters (fatigue, neurocognitive impairment, chest symptoms) often interfere with daily life and activities and often co-occur, and fatigue and neurocognitive impairment have the largest impact on working capacity. Long term smell and taste disorders were also prevalent and relevant for working capacity, with some differences according to sex and age. The response rate of 24% was low, with the possibility of selection bias (for example, potential for overestimation of prevalence measures).

**Co-occurrence network of symptom clusters 6-12 months after acute infection.** Outer circles represent individual symptoms. Circle area represents proportion of patients with that symptom. These are linked to inner circles, which represent symptom clusters. Width of link lines again represents proportion of patients with that symptom. Circle area for clusters represents proportion of patients with at least one symptom from that cluster. Central links between symptom clusters represent co-occurrence of symptom clusters. Link width represents degree of co-occurrence. Based on data from 11 536 participants. Only symptoms not present before acute SARS-CoV-2 infection were considered.