002 - Motivating Examples

EPIB 607 - FALL 2020

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slides compiled on September 2, 2020

Case study 1: Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2

Case study 2: Comparison of Estimated Rates of Coronavirus Disease 2019 (COVID-19) in Border Counties in Iowa Without a Stay-at-Home Order and Border Counties in Illinois With a Stay-at-Home Order

Early phase COVID-19 vaccine trial[1]

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

Pedro M Folegatti, Katie J Ewer*, Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammerstorfer, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, Christina Dold, Saul N Faust, Adam Finn, Amy L Flaxman, Bassam Hallis, Paul Heath, Daniel Jenkin, Rajeka Lazarus, Rebecca Makinson, Angela M Minassian, Katrina M Pollock, Maheshi Ramasamy, Hannah Robinson, Matthew Snape, Richard Tarrant, Merryn Voysey, Catherine Green*, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†*

Summary

Background The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be curtailed by vaccination. We assessed the safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine that expresses the spike protein of SARS-CoV-2.

Methods We did a phase 1/2, single-blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection. A protocol amendment in two of the five sites allowed prophylactic paracetamol to be administered before vaccination. Ten participants assigned to a non-randomised, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, a muliplexed immunoassay, three live SARS-CoV-2 neutralisation assays (a 50% plaque reduction neutralisation assay [$PRNT_{50}$]; a microneutralisation assay [MNA_{50}, MNA_{80}, and MNA_{90}]; and Marburg VN), and a pseudovirus neutralisation assay. Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot assay. The co-primary outcomes are to assess efficacy, as measured by cases of symptomatic virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were done by group allocation in participants who received the vaccine. Safety was assessed over 28 days after

Published Online
July 20, 2020
https://doi.org/10.1016/
S0140-6736(20)31604-4

See Online/Comment
https://doi.org/10.1016/
S0140-6736(20)31611-1

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[1] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext

Phase 1/2 trial

- The focus in phase 1/2 trials is looking at what the vaccine does to the body and what the body does with the vaccine in *healthy* individuals
- Adults with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive **ChAdOx1 nCoV-19** or **MenACWY** (Meningococcal) as a single intramuscular injection
- Convalescent plasma samples from adults with PCR-positive SARS-CoV-2 infection were obtained from symptomatic patients admitted to the hospitals to characterize the immunological properties of COVID-19[2]
- The enzyme-linked immunosorbent assay (ELISA) technique was used to detect antibodies (i.e. levels of immunity)

[2] Convalescent plasma is collected from someone who has recovered from a virus. When a person is infected with a virus, their body starts making antibodies to fight it. It is believed these antibodies could be the key ingredient for a treatment to help others with the same virus.

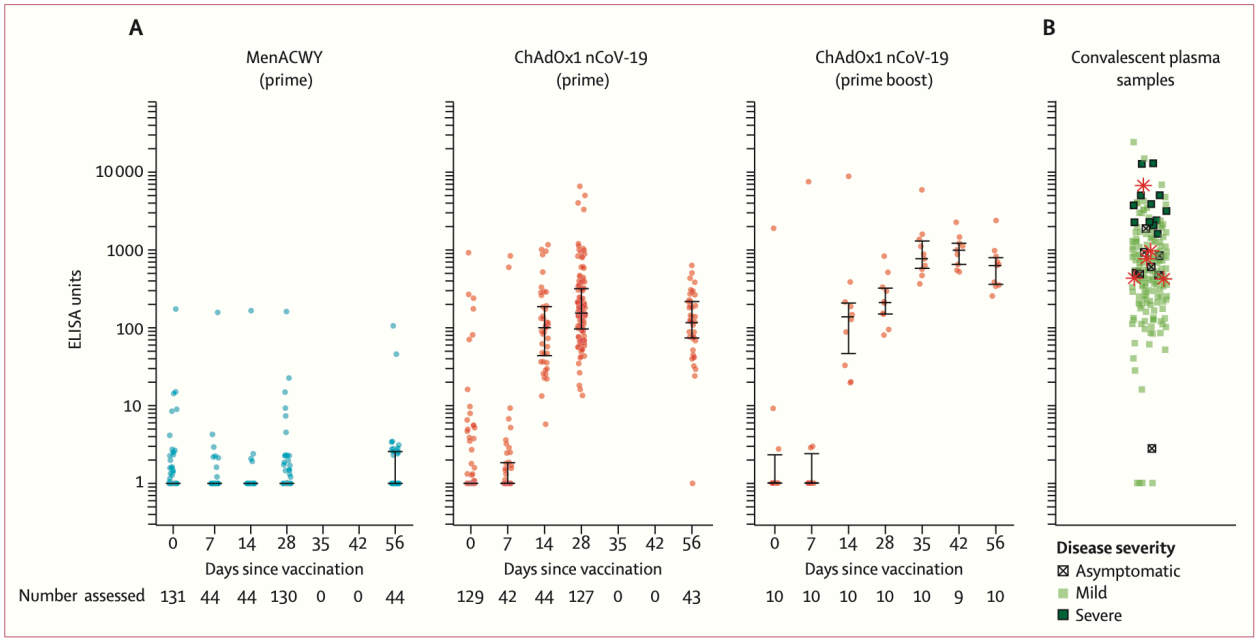


Figure 3: **SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)**

Error bars show median (IQR). Participants in the prime boost group received their second dose at day 28. Lower limit of quantification is 1 ELISA unit. Red stars in panel B show five samples also tested on the Marburg VN assay (see figure 4). MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

www.thelancet.com **Published online July 20, 2020 https://doi.org/10.1016/S0140-6736(20)31604-4**

1. What levels of immunity are found in patients who have recovered from COVID-19? (panel B)
2. Relative to these what levels of immunity are found in persons who have received the ChAdOx1 nCoV-19 vaccine? Compare panel A (prime, 28 days) vs panel B.

What levels of immunity are found in patients who have recovered from COVID-19?[3]

```
path <-
  "http://www.biostat.mcgill.ca/hanley/statbook/immunogenicityChAdOx1.nCoV-19vaccine.txt"
ds <- read.table(path)
head(ds)
```

```
##   RefIndexCategory IgGResponse.log10.ElisaUnits
## 1     Convalescent                         2.56
## 2     Convalescent                         2.74
## 3     Convalescent                         2.79
## 4     Convalescent                         3.32
## 5     Convalescent                         3.15
## 6     Convalescent                         2.35
```

```
str(ds)
```

```
## 'data.frame':^^I307 obs. of  2 variables:
##  $ RefIndexCategory           : Factor w/ 2 levels "Convalescent",..: 1 1 1 1 1 1 1 1 1 1 ...
##  $ IgGResponse.log10.ElisaUnits: num  2.56 2.74 2.79 3.32 3.15 2.35 2.72 2.95 2.42 2.64 ...
```

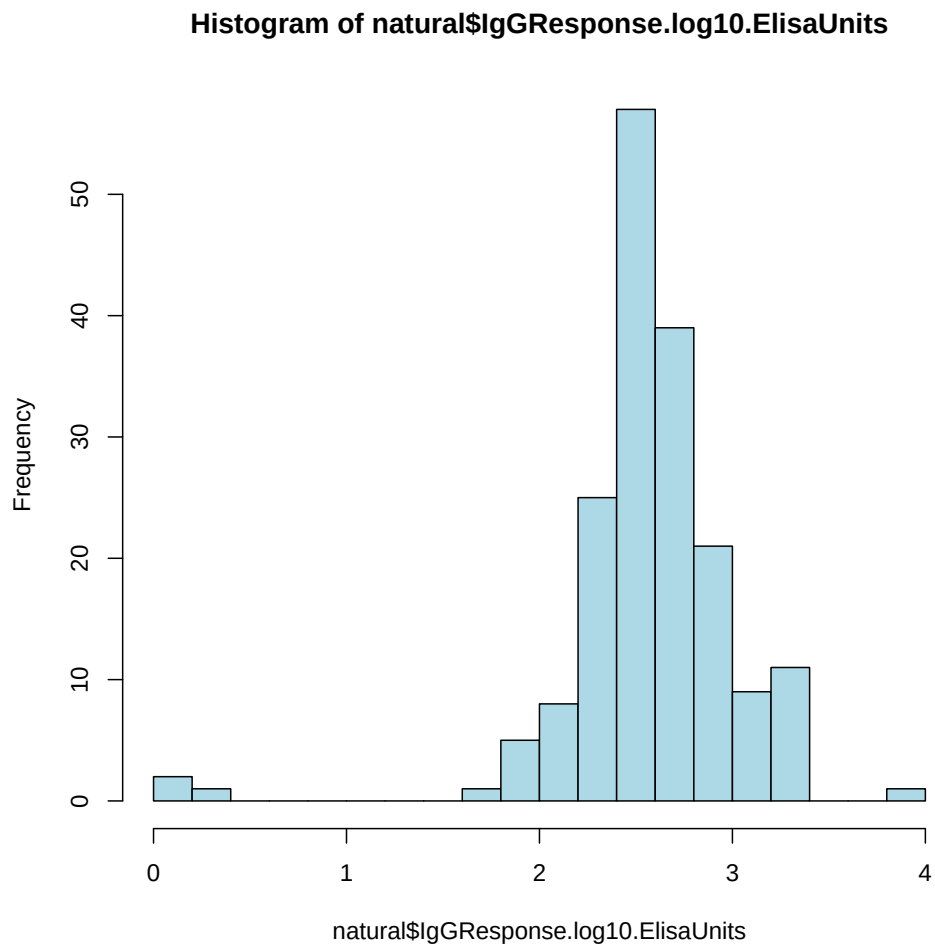
```
levels(ds$RefIndexCategory)
```

```
## [1] "Convalescent"             "Day28PostChAdOx1 nCoV-19"
```

[3] Data were (imperfectly) scraped from the Postscript file "behind" the pdf file by Dr. Hanley

What levels of immunity are found in patients who have recovered from COVID-19?

```
natural <- ds[ds$RefIndexCategory=="Convalescent",]
hist(natural$IgGResponse.log10.ElisaUnits,
     breaks = 20, col = "lightblue")
```

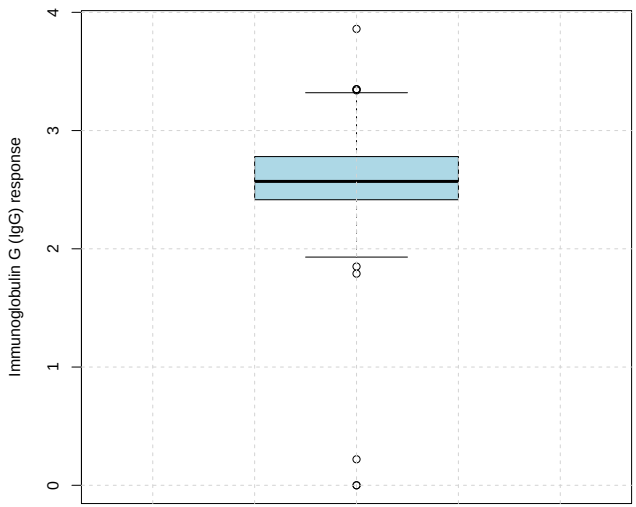


Three different methods of calculating the mean

```r
summary(natural$IgGResponse.log10.ElisaUnits)
```

```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   0.000   2.417   2.570   2.577   2.780   3.860
```

```r
boxplot(natural$IgGResponse.log10.ElisaUnits,
        col = "lightblue",
        ylab = "Immunoglobulin G (IgG) response")
grid(lty = "dashed")
```




```r
t.test(natural$IgGResponse.log10.ElisaUnits)
```

```
## One Sample t-test with natural$IgGResponse.log10.ElisaUnits
## t = 75.0898, df = 179, p-value < 2.2e-16
## alternative hypothesis: true mean is not equal to 0
## 95 percent confidence interval:
##  2.509603 2.645064
## sample estimates:
## mean of x
##  2.577333
```

```r
fit1 <- glm(IgGResponse.log10.ElisaUnits ~ 1, data = natural)
summary(fit1)
```

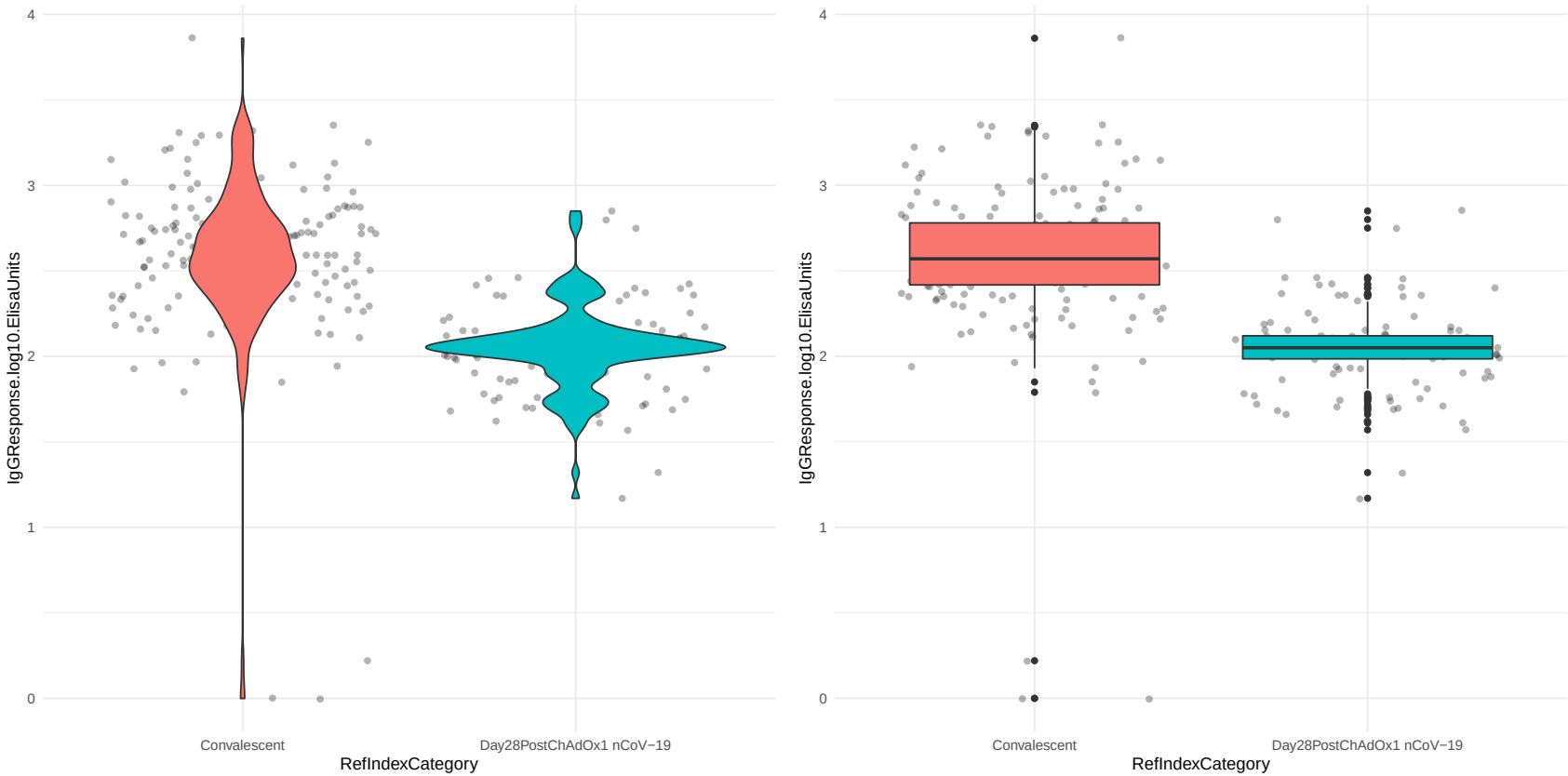
```
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  2.57733    0.03432   75.09   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for gaussian family taken to be 0.2120565)
##
##     Null deviance: 37.958  on 179  degrees of freedom
## Residual deviance: 37.958  on 179  degrees of freedom
## AIC: 234.65
##
## Number of Fisher Scoring iterations: 2
```

```r
confint(fit1)
```

```
##    2.5 %   97.5 %
## 2.510061 2.644606
```

Naturally vs. vaccine-induced response levels

```
p1 <- ggplot(data = ds, mapping = aes(x = RefIndexCategory, y = IgGResponse.log10.ElisaUnits,
    fill = RefIndexCategory)) + geom_jitter(alpha = 0.3) + theme_minimal() + theme(legend.position = "none")
p1 + geom_violin()
p1 + geom_boxplot()
```



(a) Violin plot

(b) Boxplot

Comparing means using classic methods

1. Numerical summary

```
by(ds$IgGResponse.log10.ElisaUnits,ds$RefIndexCategory,summary)

## ds$RefIndexCategory: Convalescent
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   0.000   2.417   2.570   2.577   2.780   3.860
## ------------------------------------------------------------
## ds$RefIndexCategory: Day28PostChAdOx1 nCoV-19
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##   1.170   1.985   2.050   2.047   2.120   2.850
```

2. Another "dot" test

```
t.test(IgGResponse.log10.ElisaUnits ~ RefIndexCategory, data = ds)

## Welch Two Sample t-test with IgGResponse.log10.ElisaUnits by RefIndexCategory
## t = 13.1047, df = 284.781, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  0.4510720 0.6105238
## sample estimates:
##             mean in group Convalescent mean in group Day28PostChAdOx1 nCoV-19
##                               2.577333                               2.046535
```

Comparing means using regression

3. Regression

```
fit2 <- glm(IgGResponse.log10.ElisaUnits ~ RefIndexCategory, data = ds)
print(summary(fit2), signif.star = FALSE)
```

```
##
## Coefficients:
##                                        Estimate Std. Error t value Pr(>|t|)
## (Intercept)                             2.57733    0.02874   89.67   <2e-16
## RefIndexCategoryDay28PostChAdOx1 nCoV-19 -0.53080    0.04469  -11.88   <2e-16
##
## (Dispersion parameter for gaussian family taken to be 0.1487187)
##
##     Null deviance: 66.339  on 306  degrees of freedom
## Residual deviance: 45.359  on 305  degrees of freedom
## AIC: 290.17
##
## Number of Fisher Scoring iterations: 2
```

```
confint(fit2)
```

```
##                                           2.5 %     97.5 %
## (Intercept)                           2.5209962  2.6336704
## RefIndexCategoryDay28PostChAdOx1 nCoV-19 -0.6183894 -0.4432064
```

Fitted regression line

```
plot(ds$RefIndexCategory, ds$IgGResponse.log10.ElisaUnits, pch=19, cex=0.5)
abline(h = seq(0,4,0.5),col = "lightblue")
lines(ds$RefIndexCategory, fit2$fitted.values, col = "red", lwd = 3)
```

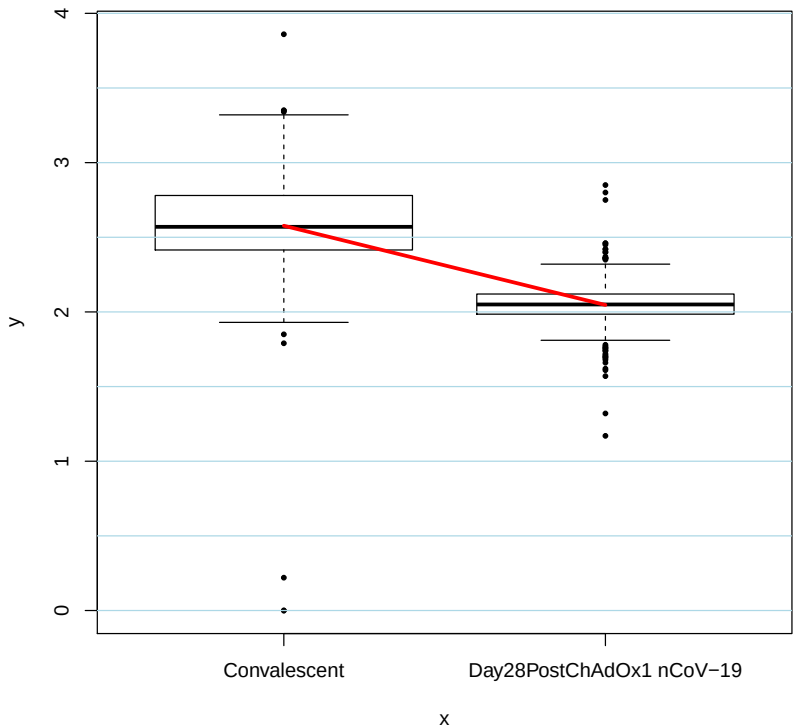


Figure: The red line is the fitted regression from the previous slide.

Case study 1: Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2

Case study 2: Comparison of Estimated Rates of Coronavirus Disease 2019 (COVID-19) in Border Counties in Iowa Without a Stay-at-Home Order and Border Counties in Illinois With a Stay-at-Home Order

Comparing Iowa and Illinois Cases[4]

JAMA Network Open

Original Investigation | Public Health

Comparison of Estimated Rates of Coronavirus Disease 2019 (COVID-19) in Border Counties in Iowa Without a Stay-at-Home Order and Border Counties in Illinois With a Stay-at-Home Order

Wei Lyu, MS; George L. Wehby, PhD

Abstract

IMPORTANCE Iowa is 1 of 5 states in the US that have not issued a stay-at-home order during the coronavirus disease 2019 (COVID-19) pandemic. There is no empirical evidence on whether issuing a stay-at-home order in Iowa could have been associated with a reduced rate of COVID-19 infections in the state.

OBJECTIVE To compare COVID-19 cases in border counties in Iowa, which did not issue a stay-at-home order, with cases in border counties in Illinois, which did issue a stay-at-home order.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study with a difference-in-differences design compared daily changes in COVID-19 cases per 10 000 residents in 8 Iowa counties bordering Illinois with those in the 7 Illinois counties bordering Iowa before and after Illinois issued a stay-at-home order on March 21, 2020. Additional sensitivity analyses were conducted to account for differences in timing of closing schools and nonessential businesses between the 2 states and differential trends in COVID-19 cases by county population density and poverty rates.

Key Points

Question Was the stay-at-home order in Illinois associated with different rates of coronavirus disease 2019 (COVID-19) compared with Iowa, which did not issue a stay-at-home order?

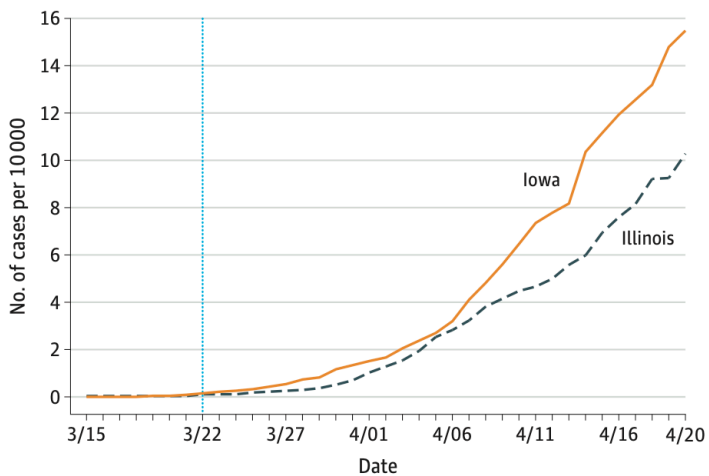
Findings This cross-sectional study of border counties in Iowa and Illinois used difference-in-differences design and found an increase in estimated rates of COVID-19 cases per 10 000 residents in the border counties in Iowa compared with the border counties in Illinois after a stay-at-home order was implemented in Illinois but not in Iowa.

[4] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766229

Are the difference in curves real? Or just random variation?

- This study compared COVID-19 cases in border counties in Iowa, which did not issue a stay-at-home order, with cases in border counties in Illinois, which did issue a stay-at-home order.

Figure 1. Cumulative Coronavirus Disease 2019 (COVID-19) Cases per 10 000 Residents in Iowa and Illinois Border Counties



The vertical line represents the date on which the stay-at-home order took effect in Illinois.

JAMA Network Open. 2020;3(5):e2011102. doi:10.1001/jamanetworkopen.2020.11102 May 15, 2020 3/7

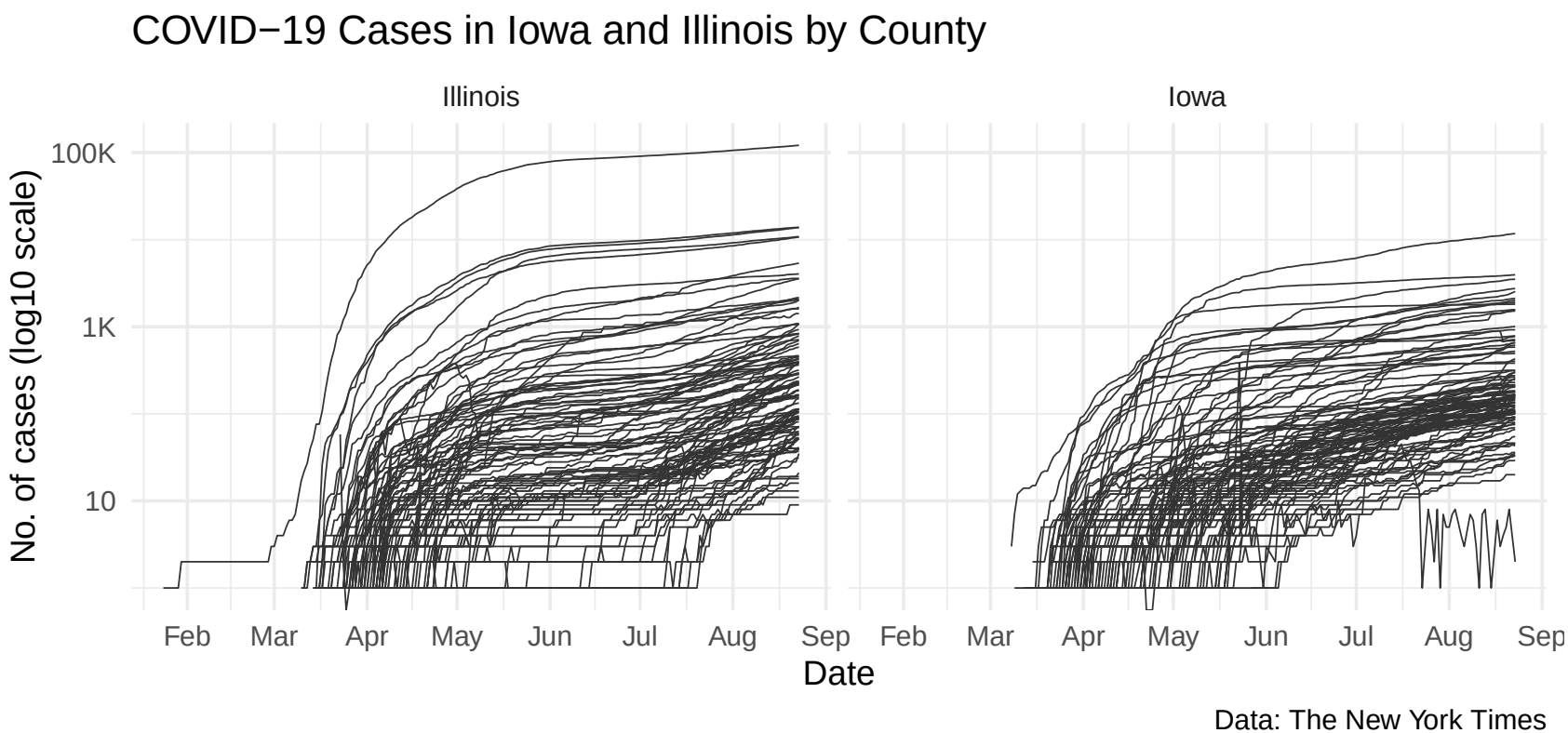
Freely available county level data from NYTimes[5]

```
library(covdata) # remotes::install_github("kjhealy/covdata")
library(dplyr); library(tidyr); library(ggplot2); library(readr)

# get population data from https://covid19.census.gov/datasets/
pop_county <- read_csv("https://opendata.arcgis.com/datasets/21843f238cbb46b08615fc53e19e0daf_1.csv") %>%
              dplyr::rename(fips = GEOID, population = B01001_001E, state = State) %>%
              dplyr::select(state, fips, population)

county_level <- nytcovcounty %>%
                dplyr::left_join(pop_county, by = c("state","fips")) %>%
                dplyr::mutate(cases.per.10k = cases/population * 1e4) %>%
                dplyr::filter(state %in% c("Iowa","Illinois")) %>%
                dplyr::group_by(county)

pop_state <- pop_county %>%
             dplyr::group_by(state) %>%
             dplyr::summarise(population = sum(population, na.rm = TRUE))

state_level <- county_level %>%
               dplyr::group_by(state, date) %>%
               dplyr::filter(date >= "2020-03-15") %>%
               dplyr::summarise(cases = sum(cases)) %>%
               dplyr::left_join(pop_state, by = "state") %>%
               dplyr::mutate(cases.per.10k = cases / population * 1e4, state = factor(state),
                             time = as.numeric(date - min(date)) + 1)
head(state_level)

## # A tibble: 6 x 6
## # Groups:   state [1]
##   state    date       cases population cases.per.10k  time
##   <fct>    <date>     <dbl>      <dbl>         <dbl> <dbl>
## 1 Illinois 2020-03-15    94   12821497        0.0733     1
## 2 Illinois 2020-03-16   104   12821497        0.0811     2
## 3 Illinois 2020-03-17   159   12821497        0.124      3
## 4 Illinois 2020-03-18   286   12821497        0.223      4
## 5 Illinois 2020-03-19   420   12821497        0.328      5
## 6 Illinois 2020-03-20   583   12821497        0.455      6
```

[5] https://github.com/nytimes/covid-19-data

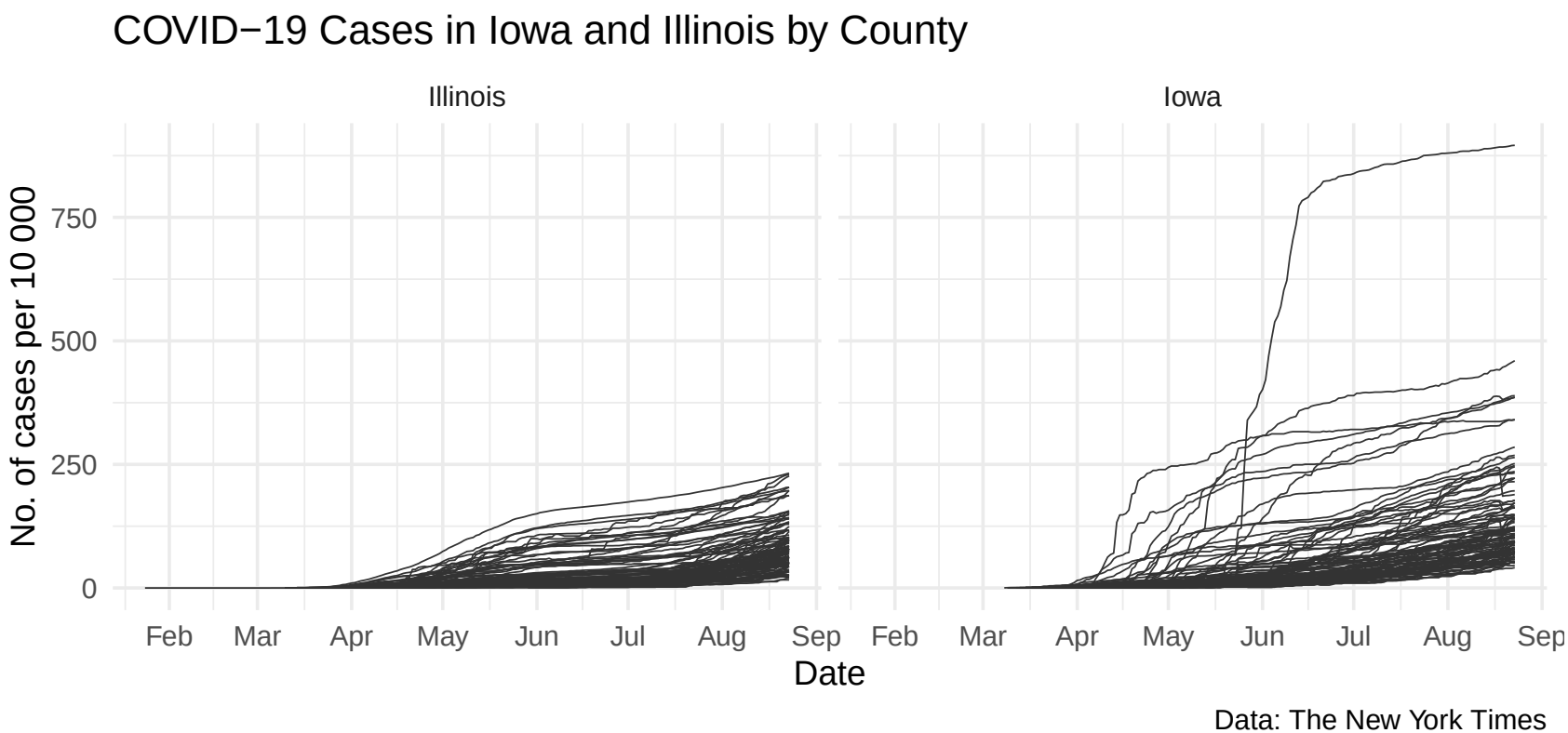
County level cases for Iowa and Illinois - log10 scale

```
ggplot(data = county_level, mapping = aes(x = date, y = cases, group = county)) +
  geom_line(size = 0.25, color = "gray20") +
  scale_x_date(date_breaks = "1 month", date_labels = "%b")+
  scale_y_log10(labels = scales::label_number_si()) +
  guides(color = FALSE) + facet_wrap(~ state, ncol = 2) +
  labs(title = "COVID-19 Cases in Iowa and Illinois by County",
       x = "Date", y = "No. of cases (log10 scale)", caption = "Data: The New York Times") +
  theme_minimal()
```



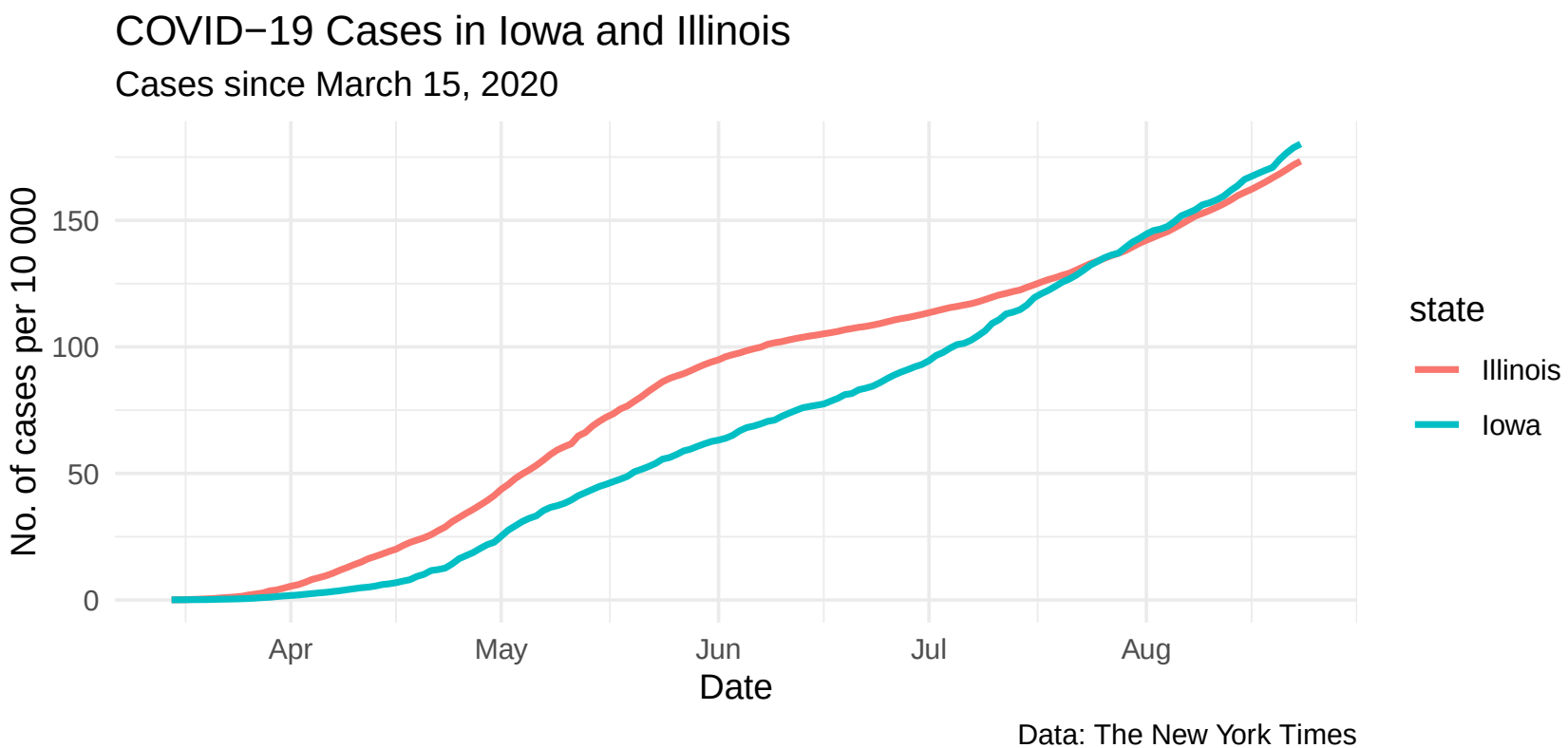
County level cases for Iowa and Illinois - per capita

```
ggplot(data = county_level, mapping = aes(x = date, y = cases.per.10k, group = county)) +
  geom_line(size = 0.25, color = "gray20") +
  scale_x_date(date_breaks = "1 month", date_labels = "%b")+
  scale_y_continuous(labels = scales::label_number_si()) +
  guides(color = FALSE) + facet_wrap(~ state, ncol = 2) +
  labs(title = "COVID-19 Cases in Iowa and Illinois by County",
       x = "Date", y = "No. of cases per 10 000", caption = "Data: The New York Times") +
  theme_minimal()
```



State level cases for Iowa and Illinois - per capita

```
ggplot(data = state_level, mapping = aes(x = date, y = cases.per.10k, color = state)) +
  geom_line(size = 1) +
  scale_x_date(date_breaks = "1 month", date_labels = "%b")+
  scale_y_continuous(labels = scales::label_number_si()) +
  labs(title = "COVID-19 Cases in Iowa and Illinois",
       subtitle = "Cases since March 15, 2020",
       x = "Date", y = "No. of cases per 10 000", caption = "Data: The New York Times") +
  theme_minimal()
```



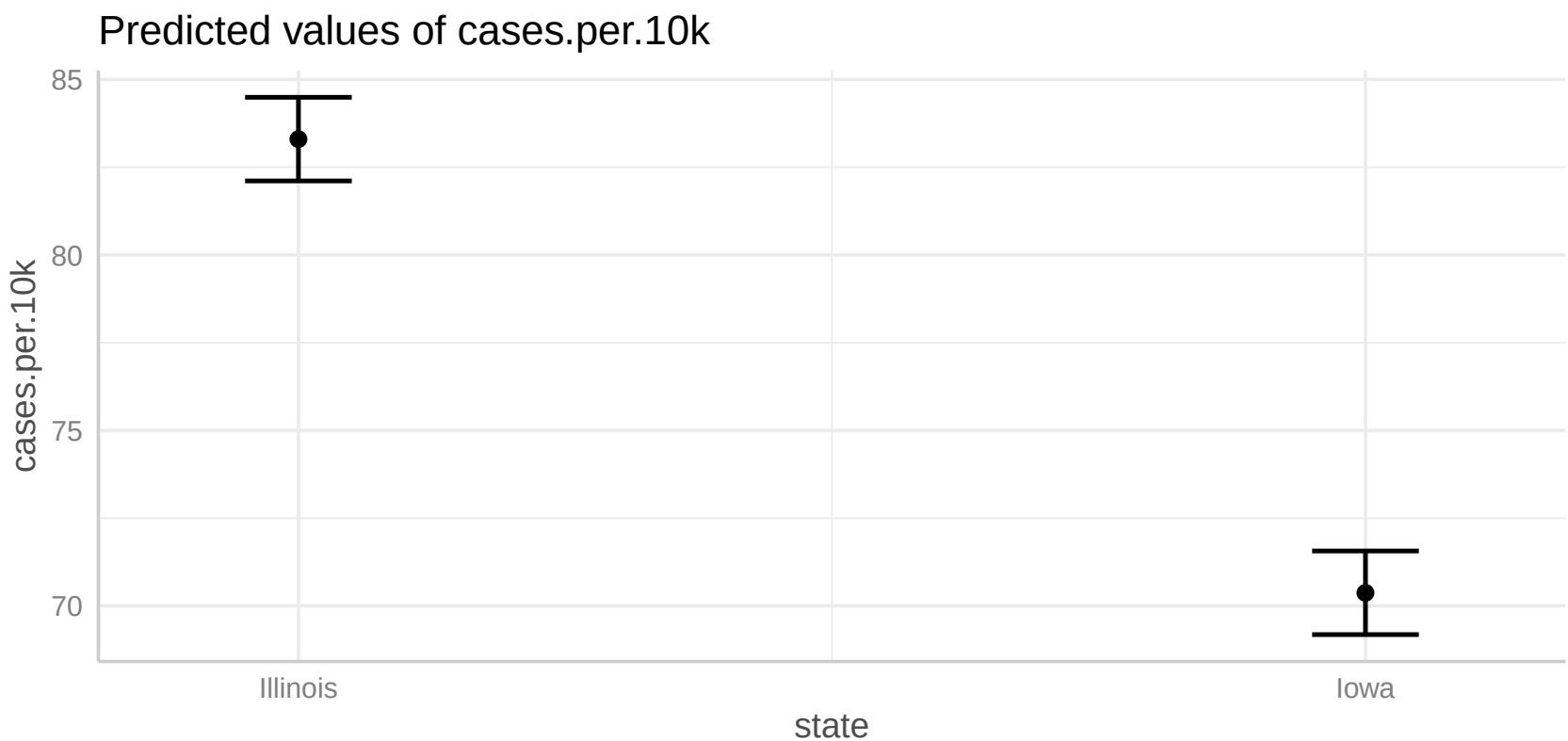
Are the findings in the paper reproducible?

```
fit3 <- glm(cases.per.10k ~ state*time, data = state_level)
summary(fit3)
```

```
##
## Coefficients:
##                 Estimate Std. Error t value Pr(>|t|)
## (Intercept)     -7.07540    1.22153  -5.792 1.66e-08 ***
## stateIowa      -17.88124    1.72751 -10.351  < 2e-16 ***
## time             1.10890    0.01300  85.300  < 2e-16 ***
## stateIowa:time   0.06078    0.01838   3.306  0.00105 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for gaussian family taken to be 59.87398)
##
##     Null deviance: 953056  on 323  degrees of freedom
## Residual deviance:  19160  on 320  degrees of freedom
## AIC: 2251.3
##
## Number of Fisher Scoring iterations: 2
```

Model-based predictions

```
library(ggeffects)
ggeffects::ggpredict(fit3, terms = "state") %>%
  plot()
```



Session Info

```
R version 3.6.2 (2019-12-12)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Pop!_OS 19.10

Matrix products: default
BLAS:   /usr/lib/x86_64-linux-gnu/openblas/libblas.so.3
LAPACK: /usr/lib/x86_64-linux-gnu/libopenblasp-r0.3.7.so

attached base packages:
[1] tools     stats     graphics  grDevices utils     datasets  methods
[8] base

other attached packages:
 [1] ggeffects_0.14.1   covdata_0.4.4      NCStats_0.4.7      FSA_0.8.30
 [5] forcats_0.5.0      stringr_1.4.0      dplyr_1.0.2        purrr_0.3.4
 [9] readr_1.3.1        tidyr_1.1.2        tibble_3.0.3       ggplot2_3.3.2.9000
[13] tidyverse_1.3.0    knitr_1.29

loaded via a namespace (and not attached):
 [1] sjlabelled_1.1.3   tidyselect_1.1.0   xfun_0.16          haven_2.3.1
 [5] snakecase_0.11.0   colorspace_1.4-1   vctrs_0.3.4        generics_0.0.2
 [9] utf8_1.1.4         rlang_0.4.7        pillar_1.4.6       glue_1.4.2
[13] withr_2.2.0        DBI_1.1.0          dbplyr_1.4.2       modelr_0.1.5
[17] readxl_1.3.1       lifecycle_0.2.0    plyr_1.8.6         munsell_0.5.0
[21] gtable_0.3.0       cellranger_1.1.0   rvest_0.3.5        evaluate_0.14
[25] labeling_0.3       curl_4.3           fansi_0.4.1        highr_0.8
[29] broom_0.7.0        Rcpp_1.0.4.6       scales_1.1.1       backports_1.1.9
[33] formatR_1.7        jsonlite_1.7.0     farver_2.0.3       fs_1.3.2
[37] TeachingDemos_2.12 digest_0.6.25      hms_0.5.3          stringi_1.4.6
[41] insight_0.8.1      grid_3.6.2         cli_2.0.2          magrittr_1.5
[45] crayon_1.3.4       pkgconfig_2.0.3    ellipsis_0.3.1     MASS_7.3-51.5
[49] xml2_1.3.0         reprex_0.3.0       lubridate_1.7.4    assertthat_0.2.1
[53] httr_1.4.1         rstudioapi_0.11    R6_2.4.1           compiler_3.6.2
```