IVY

INFLUENZA AND OTHER VIRUSES IN THE ACUTELY ILL

Supplementary Material

Clinical Severity and mRNA Vaccine Effectiveness for Omicron, Delta, and Alpha SARS-CoV-2 Variants in the United States: A Prospective Observational Study

The IVY Network

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Contents of Supplementary Materials

I. Supplementary Appendix A. Investigators and Collaborators

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II. Supplementary Appendix B. Supplemental Methods

1. Enrollment practices

Adults admitted to 21 hospitals in the United States were enrolled into this study. Three cohorts of hospitalized patients were enrolled: COVID-19 cases, test-negative controls, and syndrome negative controls. Eligibility criteria for each cohort are detailed in the next section. In brief, cases had symptoms consistent with COVID-19 and a positive test for SARS-CoV-2. Test negative controls had symptoms potentially consistent with COVID-19 but had a negative test for SARS-CoV-2. Syndrome negative controls did not have symptoms consistent for COVID-19, were hospitalized for a reason other than acute respiratory illness and had a negative test for SARS-CoV-2. Enrollment of syndrome negative controls ended in October 2021 based on the findings that vaccine effectiveness results were nearly identical when separately using test negative controls and syndrome negative controls; the data demonstrated that test negative controls alone provided an adequate control group alone. After October 2021, enrollment of cases and test negative controls continued.

Patients were enrolled as cases and controls based on the results of clinical SARS-CoV-2 testing at the local hospital laboratory. Respiratory samples were also collected by study personnel and shipped to Vanderbilt University Medical Center for independent SARS-CoV-2 RT-PCR testing. Final case/control classification was based SARS-CoV-2 test results from both the local clinical laboratories and the central laboratory. Patients enrolled as a case or test negative control who had any positive SARS-CoV-2 test (either a clinical test or central laboratory test) within 10 days of symptom onset were classified as cases. Patients enrolled as a test negative control or syndrome negative control who had all SARS-CoV-2 tests return negative (both clinical tests and central laboratory tests) were included in the analysis as controls.

During the enrollment period, study personnel screened for eligible cases daily with the intent of enrolling all eligible cases. Study personnel also screened for eligible controls daily, with the intent of enrolling 1 control patient within 14 days of each case patient enrolled. If multiple potential control patients were eligible at the same time, study personnel randomly selected which patient to enroll as a control. As a public health surveillance project, written informed consent was not obtained for participation. A patient was considered enrolled in the surveillance program at the time that the first data were collected from the participant by study personnel.

2. Eligibility criteria

The section details the eligibility criteria for enrollment for the 3 cohorts of patients included in the study: COVID-19 cases, test-negative controls, and syndrome negative controls.

Covid-19 Cases

Summary for Cohort 1: Adult admitted to the hospital for acute Covid-19 who has tested positive for SARS-CoV-2.

Inclusion for Cohort 1 (cases):

1. Age ≥18 years old.
2. Hospital admission or in an emergency department awaiting hospital admission.
3. Symptoms and/or signs believed to be due to Covid-19, including at least 1 of the following: fever; cough; shortness of breath; loss of taste; loss of smell; use of respiratory support (high flow oxygen by nasal cannula, non-invasive ventilation or invasive ventilation) for the acute illness; new pulmonary findings on chest imaging consistent with pneumonia.
4. Clinically obtained test that is **positive** for acute SARS-CoV-2 infection. The positive test may be obtained before or after hospital arrival. Examples of acute SARS-CoV-2 tests include RT-PCR tests, nucleic acid amplification tests (NAAT), and antigen tests. Serology testing may not be used for eligibility.

Exclusion for Cohort 1 (cases):

1. Previous inclusion as a case.
2. The first positive test for acute SARS-CoV-2 infection is known to have occurred more than 10 days after onset of Covid-19 symptoms/signs listed in inclusion criterion #3. Patients with unknown onset date for Covid-19 symptoms/signs may be included.
3. Hospital presentation for the Covid-19 admission is known to have occurred more than 14 days after onset of Covid-19 symptoms/signs listed in inclusion criterion #3. Patients with unknown onset date for Covid-19 symptoms/signs may be included. Patients transferred from other hospitals may be included; the time of hospital presentation is the time of presentation to the first hospital.

Test Negative Controls

Summary for Cohort 2: Adult admitted to the hospital for an acute illness with symptom overlap with Covid-19 who has tested negative for SARS-CoV-2.

Inclusion for Cohort 2 (test negative controls):

1. Age ≥18 years old.
2. Hospital admission or in an emergency department awaiting hospital admission.
3. Symptoms and/or signs that overlap with Covid-19, including at least one of the following: fever; cough; shortness of breath; loss of taste; loss of smell; use of respiratory support (high flow oxygen by nasal cannula, non-invasive ventilation or invasive ventilation) for the acute illness; new pulmonary findings on chest imaging consistent with pneumonia.
4. Clinically obtained test that is **negative** for acute SARS-CoV-2. The negative test may be obtained before or after hospital arrival. Examples of acute SARS-CoV-2 tests include RT-PCR tests, NAAT, and antigen tests. Serology testing may not be used for eligibility.

Exclusion for Cohort 2 (test negative controls):

1. Previous inclusion as a control.
2. The first negative test for acute SARS-CoV-2 infection is known to have occurred more than 10 days after onset of symptoms/signs listed in inclusion criterion #3. Patients with unknown onset date for Covid-19 symptoms/signs may be included.
3. Hospital presentation for the admission is known to have occurred more than 14 days after onset of symptoms/signs listed in inclusion criterion #3. Patients with unknown onset date for symptoms/signs may be included. Patients transferred from other hospitals may be included; the time of hospital presentation is the time of presentation to the first hospital.
4. Any positive test for acute SARS-CoV-2 infection in the 14 days prior to hospital presentation or between hospital presentation and inclusion (patients with a positive acute SARS-CoV-2 test should be screened for potential inclusion as a case).

Syndrome-negative controls

Summary for Cohort 3: Adult admitted to the hospital for a reason other than an acute respiratory illness and who does not have a clinical suspicion for Covid-19.

Inclusion for Cohort 3 (syndrome negative controls):

1. Age ≥18 years old.
2. Hospital admission or in an emergency department awaiting admission.
3. Clinical impression that Covid-19 is not the reason for admission.
4. None of the following signs or symptoms that overlap with Covid-19 in the past 14 days: fever; cough; shortness of breath; loss of taste; loss of smell; use of respiratory support (high flow oxygen by nasal cannula, non-invasive ventilation or invasive ventilation) for the acute illness; new pulmonary findings on chest imaging consistent with pneumonia.

Exclusion for Cohort 3 (syndrome negative controls):

1. Previous inclusion as a control.
2. Any positive test for acute SARS-CoV-2 infection in the 14 days prior to hospital presentation or between hospital presentation and inclusion (patients with a positive acute SARS-CoV-2 test should be screened for potential inclusion as a case).

III. Supplementary Appendix C. Vaccine effectiveness for partial vaccination with an mRNA vaccine.

This section describes results for vaccine effectiveness calculations for partial vaccination with mRNA COVID-19 vaccines, defined as receipt of a single vaccine dose or receipt of 2 vaccine doses with COVID-19 illness onset within 14 days of receipt of the second vaccine dose. A single dose of an mRNA COVID-19 vaccine is not a recommended regimen by the United States (US) Centers for Disease Control and Prevention (CDC) and is not authorized or approved by the US Food and Drug Administration (FDA). Some people receive a first dose of an mRNA vaccine and then do not follow through with obtaining subsequent vaccine doses. Additionally, some individuals may receive a second vaccine dose and develop illness shortly after the second dose is received and before full immune protection associated with the second vaccine dose develops. Thus, we estimated the vaccine effectiveness of partial vaccination with mRNA vaccines. This is a combined analysis for the two mRNA COVID-19 vaccines available in the US -- BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). Further, little or no vaccine-associated protection against SARS-CoV-2 is expected over several days immediately following receipt of a first mRNA vaccine dose. We additionally estimated vaccine effectiveness in patients who received 1 mRNA vaccine dose 0-13 days before illness onset as a "bias indicator."

Similar to the vaccine effectiveness calculation described in the main text for 2 and 3 doses of an mRNA vaccine, vaccine effectiveness for partial vaccination with an mRNA vaccine to prevent COVID-19 hospitalization was calculated by using a test-negative design, in which the odds of antecedent vaccination were compared between cases and controls. Three vaccination groups were considered: Group 1) Patients who received 1 vaccine dose 0-13 days before illness onset; Group 2) patients who received 1 vaccine dose ≥14 days before illness onset; and Group 3) patients who received 2 vaccine doses, with the first dose received ≥14 days before illness onset and the second dose received 0-13 days before onset. A multivariable unconditional logistic regression model was constructed with case-control status as the dependent variable, vaccination status (vaccinated vs. unvaccinated) as the primary independent variable and the following covariables selected *a priori*: calendar date of admission in biweekly intervals, US Department of Health and Human Services region (10 regions), age, sex, and self-reported race and Hispanic ethnicity. Vaccine effectiveness to prevent COVID-19 hospitalization [VE(hospitalization)] was calculated with the adjusted odds ratio (aOR) from this model as: VE(hospitalization) = (1 – aOR) × 100. For this one-dose vaccine effectiveness calculation, we combined all time periods (Alpha, Delta, and Omicron) together.

Overall, 255 vaccinated patients were included in Group 1, 493 in Group 2, and 185 in Group 3. The time between a receipt of the first vaccine dose and illness onset was short, with a median of 6 (IQR 3 to 9) days, 48 (IQR 21-132) days, and 32 (IQR 28-38) days between receipt of the first vaccine dose and the date of illness onset in groups 1, 2, and 3, respectively. The time interval is short because most people in the US who obtained one mRNA dose also received a second dose in the subsequent weeks. Thus, the vaccine effectiveness estimates reported here are generally limited to only the first several weeks after receipt of the vaccine. Waning effectiveness from a single mRNA vaccine dose is expected over time but could not be rigorously measured in this study due to the small number of patients with extended periods of time since a single vaccine dose.

Estimated vaccine effectiveness for Group 1 (single vaccine dose 0-13 days prior to illness onset) was 16% (95% CI: -10 to 36%), for Group 2 (single vaccine dose ≥14 days prior to illness onset) was 77% (95% CI: 71 to 81%), and for Group 3 (2 vaccine doses with second vaccine dose 0-13 prior to illness onset) was 84% (95% CI: 74 to 89%). Combining Groups 2 and Group 3 as "partially vaccinated" resulted in vaccine effectiveness of 79% (95% CI: 74 to 82%).

IV. Supplementary Tables

Table S1. COVID-19 vaccine effectiveness publications from the IVY Network.

The IVY Network publishes vaccine effectiveness (VE) estimates iteratively, with later publications adding sample size and focusing on specific questions that were not addressed in earlier publications. Some participants are included in multiple publications. The current manuscript includes participants enrolled between March 11, 2021, and January 14, 2022 with a focus on variant-specific VE and severity.

Publication	Primary Question Addressed	Data cut (cohort initiated March 11, 2021)	Sample size	Primary finding
Clin Infect Dis 2021. PMID: 34358310.	COVID-19 mRNA VE against hospitalization during the early phase of the US COVID-19 program.	May 5, 2021	1,212	mRNA VE against COVID-19 hospitalization among US adults = 87.1% (95% CI: 80.7 – 91.3%)
MMWR 2021; 70:1156. PMID: 34437524	COVID-19 mRNA VE against hospitalization beyond 12 weeks from full vaccination.	July 14, 2021	3,089	mRNA VE against COVID-19 hospitalization from 13 to 24 weeks post-vaccination among US adults = 84% (95% CI: 77 – 90%)
MMWR 2021; 70:1337. PMID: 34555004	Comparative effectiveness of COVID-19 vaccines available in the US for preventing COVID-19 hospitalizations among immunocompetent adults	August 15, 2021	3,689	VE against COVID-19 hospitalizations varied by vaccine product among immunocompetent adults – Moderna: 93% (95% CI: 91-95%); Pfizer BioNTech: 88% (95% CI: 85-91%); Janssen: 71% (95% CI: 56-81%).
JAMA 2021; 326:2043. PMID: 34734975	Effectiveness of mRNA vaccines to prevent disease progression to critical illness or death among adults hospitalized with COVID-19.	August 15, 2021	4,515	Prior vaccination was associated with a 67% (95% CI: 42-81%) relative risk reduction lower risk of progression to invasive mechanical ventilation or death among adults hospitalized with COVID-19, suggesting vaccination attenuated disease severity.
MMWR 2022; 71:118. PMID: 35085218.	Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults - United States, August-December 2021	August 19 to December 15, 2021	2,952	Three doses of mRNA COVID-19 vaccine provide greater protection against COVID-19 hospitalization than two doses. For immunocompetent adults ≥180 days from a second dose, VE against hospitalization was 97% for three doses and 82% for two doses. For immunocompromised adults, VE against hospitalization was 88% for three doses and 69% for two doses.

Publication	Primary Question Addressed	Data cut (cohort initiated March 11, 2021)	Sample size	Primary finding
Current manuscript	Clinical Severity and mRNA Vaccine Effectiveness for Omicron, Delta, and Alpha SARS-CoV-2 Variants in the United States: A Prospective Observational Study	January 14, 2022	11,690	VE against COVID-19 hospitalization during the period that Delta variant dominated was 85% (95% CI: 83 to 87%) for 2 mRNA vaccine doses and 94% (95% CI: 92 to 95%) for 3 vaccine doses; for the early period that Omicron variant dominated VE was 65% (95% CI: 51 to 75%) for 2 doses and 86% (95% CI: 77 to 91%) for 3 doses. In-hospital COVID-19 severity was lower for Omicron than Delta. Prior vaccination was associated with lower in-hospital COVID-19 severity for Alpha, Delta, and Omicron variants.

Table S2. Modified World Health Organization COVID-19 Clinical Progression Scale.

This scale was used in this analysis to assess disease severity among adults hospitalized with COVID-19.

Patient State	Descriptor	Severity Level
Uninfected	Uninfected; no viral RNA detected	0 [not studied in this analysis]
Ambulatory mild disease	Asymptomatic; viral RNA detected	1 [not studied in this analysis]
	Symptomatic; independent	2 [not studied in this analysis]
	Symptomatic; assistance needed	3 [not studied in this analysis]
Hospitalized: moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; standard oxygen therapy by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized, oxygen by high flow nasal cannula or non-invasive ventilation	6
	Invasive mechanical ventilation	7
	Invasive mechanical ventilation plus other organ support including ECMO, vasopressors or new renal replacement therapy	8
Death	Death	9

ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; NIV = non-invasive ventilation
[a]Uninfected and mild severity were not included in this analysis that was restricted to hospitalized, laboratory-confirmed COVID-19 patients.

Table S3. Vaccine coverage and vaccine effectiveness against hospitalization with control groups separated.

Two control groups were enrolled during this study. Test-negative controls were adults hospitalized with symptoms consistent with a COVID-like illness who tested negative for SARS-CoV-2. Syndrome-negative controls were adults hospitalized without symptoms consistent with COVID-like illness who tested negative for SARS-CoV-2. Vaccine effectiveness studies using a test-negative design often enroll only one control group consistent with the test-negative control group enrolled in this study. This study was designed with a second control group (the syndrome negative control group) due to concerns early in the COVID-19 pandemic about false negative SARS-CoV-2 RT-PCR tests among patients hospitalized with COVID-like illness. Using the test negative design, vaccine effectiveness estimates could be biased if patients with COVID-19 were misclassified as controls due to false negative RT-PCR testing. The syndrome negative control group was used to ensure vaccine effectiveness estimates were not rendered inaccurate due to false negative RT-PCR testing misclassifying patients with COVID-19 as controls. The syndrome negative control group had no symptoms of COVID-19 and negative SARS-CoV-2 RT-PCR testing, and hence, were less susceptible to misclassification.

Test negative controls were enrolled during the entire analysis period for this study (March 11, 2021 – January 14, 2022). Syndrome negative controls were enrolled from the beginning of the study (March 11, 2021) through October 2, 2021 (last admission date for a syndrome negative control participant). Analyses in October 2021 demonstrated that vaccine coverage in the two control groups and vaccine effectiveness results using the control groups separately were nearly identical (results shown below). These data suggested that false negative RT-PCR tests among patients enrolled as test-negative controls did not cause substantive biases. Thus, further enrollment of syndrome negative controls was halted, and enrollment of test-negative controls was continued with confidence in this group as the sole control group moving forward. For final analyses, the two control groups were pooled.

Control participants with admission dates March 11, 2021 – October 2, 2021		
	Test negative control group (n = 2289)	Syndrome negative control group (n = 1542)
Vaccinated with ≥2 doses of mRNA COVID-19 vaccine, no. (%)	1382 (60.4)	896 (58.1)
Vaccine effectiveness of 2 doses of an mRNA vaccine to prevent COVID-19 hospitalization using a single control group, adjusted VE (95% CI)	86 (84-88)	86 (84-88)

Table S4. SARS CoV-2 variants identified by sequencing**.**

This table displays the SARS-CoV-2 variants identified by viral whole genome sequencing during the Alpha period (March 11 – July 3, 2021), Delta period (July 4, 2021 – December 25, 2021), and Omicron period (December 26, 2021 – January 14, 2022).

SARS-CoV-2 Variant	**Sequenced Cases during Alpha Period (March 11 – July 3, 2021) [n = 421]**	**Sequenced Cases during Delta Period (July 4 – December 25, 2021) [n = 1930]**	**Sequenced Cases during Omicron Period (December 26, 2021 – January 14, 2022) [n = 248]**
Alpha	242 (57.5%)	5 (0.3%)	0 (0%)
Delta	46 (10.9%)	1867 (96.7%)	58 (23.4%)
Beta	6 (1.4%)	0 (0%)	0 (0%)
Gamma	38 (9.0%)	6 (0.3%)	0 (0%)
Omicron	0 (0%)	37 (1.9%)	190 (76.6%)
Other variant*	89 (21.1%)	15 (0.8%)	0 (0%)

*Other variants included: B.1.526 (14), B.1.621 (12), B.1.526.1 (11), B.1.429 (11), B.1 (10), B.1.1.519 (7), B.1.2 (7), B.1.526.3 (4), B.1.621.1 (4), B.1.1.28 (3), B.1.526.2 (3), C.37 (3), B.1.525 (2), B.1.623 (2), B.1.628 (2), B.1.1.318 (1), B.1.1.372 (1), B.1.361 (1), B.1.441 (1), B.1.517 (1), B.1.612 (1), B.1.637 (1), C.36.3 (1), R.1 (1).

Table S5. Patient characteristics of by sequence-confirmed cases.

This table displays patient characteristics of controls and COVID-19 cases with sequence-confirmed Alpha, Delta, and Omicron variant COVID-19 include in vaccine effectiveness analyses. Alternatively, baseline characteristics based on period of enrollment (Alpha, Delta, and Omicron periods) are shown in Table 1.

Patient Characteristic	**All controls (n=5962)**	**Sequenced Alpha cases (n=247)**	**Sequenced Delta cases (n=1971)**	**Sequenced Omicron cases (n=227)**
Age in years, median (IQR)	63 (50-72)	60 (48-68)	60 (47-71)	61 (48-71)
Female sex, No. (%)	2975 (49.9)	115 (46.6)	886 (45.0)	114 (50.2)
Race and ethnicity, No. (%)				
Non-Hispanic White	3611 (60.6)	123 (49.8)	1072 (54.4)	80 (35.2)
Non-Hispanic Black	1240 (20.8)	70 (28.3)	413 (21.0)	72 (31.7)
Hispanic, any race	772 (12.9)	45 (18.2)	345 (17.5)	55 (24.2)
Non-Hispanic, Other	253 (4.2)	8 (3.2)	98 (5.0)	18 (7.9)
Unknown	86 (1.4)	1 (0.4)	43 (2.2)	2 (0.9)
US Census region, No. (%)				
Northeast	885 (14.8)	26 (10.5)	383 (19.4)	47 (20.7)
South	2371 (39.8)	80 (32.4)	627 (31.8)	98 (43.2)
Midwest	1374 (23.0)	91 (36.8)	519 (26.3)	48 (21.1)
West	1332 (22.3)	50 (20.2)	442 (22.4)	34 (15.0)
Resident of long-term care facility, No. / Total (%)	321/5778 (5.6)	4/245 (1.6)	74/1867 (4.0)	14/216 (6.5)
≥1 prior hospitalization in past year, No. / Total (%)	3031/5537 (54.7)	65/215 (30.2)	522/1778 (29.4)	109/224 (48.7)
Current tobacco use, No. / Total (%)	1016/5302 (19.2)	21/200 (10.5)	173/1650 (10.5)	31/202 (15.3)
Number of chronic medical conditions‡, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Categories of medical conditions‡				
Chronic cardiovascular disease	4158 (69.7)	137 (55.5)	1165 (59.1)	150 (66.1)
Chronic pulmonary disease	1973 (33.1)	65 (26.3)	430 (21.8)	63 (27.8)
Diabetes mellitus	1962 (32.9)	75 (30.4)	646 (32.8)	75 (33.0)
Immunocompromising condition	1458 (24.5)	46 (18.6)	376 (19.1)	77 (33.9)
Obesity, No. / Total (%)	2391/5900 (40.5)	146/243 (60.1)	1022/1949 (52.4)	97/225 (43.1)
Vaccination status				
Unvaccinated	2054 (34.5)	226 (91.5)	1361 (69.1)	92 (40.5)
2 doses (<150 days)	2029 (34.0)	21 (8.5)	189 (9.6)	18 (7.9)
2 doses (≥150 days)	1411 (23.7)	0 (0)	380 (19.3)	77 (33.9)
3 doses	468 (7.8)	0 (0)	41 (2.1)	40 (17.6)
If vaccinated, vaccine product received, No. / Total (%)				

Patient Characteristic	**All controls (n=5962)**	**Sequenced Alpha cases (n=247)**	**Sequenced Delta cases (n=1971)**	**Sequenced Omicron cases (n=227)**
BNT162b2 (Pfizer-BioNTech)	2269/3908 (58.1)	13/21 (61.9)	396/610 (64.9)	92/135 (68.1)
mRNA-1273 (Moderna)	1615/3908 (41.3)	7/21 (33.3)	210/610 (34.4)	41/135 (30.4)
Mixed products	24/3908 (0.6)	1/21 (4.8)	4/610 (0.7)	2/135 (1.5)
Days since dose 3 if 3 doses received, median (IQR)	41 (23-64)	---	38 (21-71)	69.5 (36-107.5)

Definitions: IQR = interquartile range; US = United States

‡ Chronic medical conditions were obtained from structured medical chart review and body-mass index calculated using documented height and weight.

Table S6. Sensitivity analyses limited to cases with sequence-confirmed variants.

Results presented in the main text classified COVID-19 cases into SARS-CoV-2 variant categories based on whole genome sequencing results if a variant was identified by sequencing and by the predominant circulating variant at the time of hospitalization for cases without a variant identified by sequencing. In the sensitivity analyses below, analyses were limited to cases with a sequencing-confirmed variant (that is, there was no imputation of variant category for cases that did not have a variant identified by whole genome sequencing). Sample sizes were small for some of these sensitivity analyses, resulting in wide confidence intervals and loss of precision compared to the primary results. However, the pattern and directionality of results in these sensitivity analyses were consistent with the primary results presented in the main text.

Sensitivity Analyses Limited to Sequencing-Confirmed Variants			
Analysis	Alpha Variant (n = 247)	Delta Variant (n = 1971)	Omicron Variant (n = 227)
Vaccine effectiveness of two doses of mRNA vaccine to prevent COVID-19 hospitalization, adjusted VE (95% CI)	91% (86 to 95%)	84% (82 to 86%)	59% (38 to 73%)
Comparison of COVID-19 disease severity on WHO ordinal scale among unvaccinated cases using Alpha variant as referent, adjusted proportional odds ratio (95% CI)	referent	1.24 (0.96 to 1.60)	0.38 (0.23 to 0.61)
Vaccine effectiveness of mRNA vaccination (2 or 3 doses) to prevent progression to invasive mechanical ventilation or death after hospital admission, adjusted VE (95% CI)	94% (50 to 99%)	50% (35 to 61%)	31% (-55 to 70%)

V. Supplementary Figures

Figure S1. Flow diagram of participant participation.