Dynamic Covid-19 IgG Monitoring in Chile: differential response to the inactivated virus from Sinovac and the mRNA vaccine from Pfizer-BioNTech.

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RESEARCH IN CONTEXT

Evidence before this study

Vaccination is critical for the control of Covid-19 and several vaccines have been deployed. Immunogenicity and efficacy of currently licensed vaccines have followed the clinical trial path, albeit with different strategies and different reported results. Recent effectiveness studies are also focusing on individual vaccine performance. Population-based studies simultaneously evaluating performance of two or more vaccines are scarce. We searched PubMed and medRxiv for articles published up to May 15, 2021, using the search terms ("COVID-19" OR "SARS-CoV-2" OR "2019-nCoV") AND ("vaccine" OR "vaccination") AND ("immunogenicity" OR "efficacy" OR "effectiveness"); the latter was replaced by "rollout" in an attempt to find more studies. Israel with one vaccine (BNT162b2 mRNA) and the UK with two vaccines (BNT162b2 mRNA and ChAdOx1 nCoV-19) report evaluations after vaccine rollout. For vaccine comparisons we identified only one relevant article from Scotland. Effectiveness of the first dose of the BNT162b2 mRNA vaccine was 91% (95% CI 85–94) for reduced COVID-19 hospital admission at 28–34 days post-vaccination, compared to 88% (95% CI 75–94) for ChAdOx1. Combined vaccine effects against hospital admission due to COVID-19 was 83% (95% CI 72–89 at 28–34 days post-vaccination) for those 80 years and older. We found

no studies on comparative immunogenicity and no studies evaluating inactivated vaccines which are being widely used in developing countries and in evaluation for use in developed countries.

Added value of this study

Chile is one of the leading countries in vaccine deployment with two vaccines, the inactivated vaccine from Sinovac representing 85% and the mRNA vaccine from Pfizer-BioNTech representing 15%. We implemented a longitudinal IgG surveillance strategy based on testing stations for SARS-COV-2 IgG rapid detection, implemented in large cities throughout the country in selected hotspots based on cellular-phone mobility data, aiming to replicate the diverse geographical distribution of the population of such cities. This is the only study to date simultaneously evaluating population IgG immunity for Sinovac as compared to the Pfizer-BioNTech vaccine during vaccine rollout. In a total of 31 729 participants enrolled at different timepoints from March 12 to May 15, 2021, 53% and 12% had received Sinovac or Pfizer-BioNTech vaccine and 35% had not received a vaccine. Four weeks after the first dose, IgG positivity for Sinovac was 22.3% (95% CI 17.3%, 27.3%) while for Pfizer-BioNTech it was 78.1% (95% CI 70.2%, 86.0%). During the third week after the second dose IgG positivity reached 76.6% (95% CI 74.4%, 78.8%) for Sinovac, while it reached 95% (95% CI 93.7, 96.3%) for Pfizer-BioNTech. A mild decline was then observed for Sinovac during the 5 to 9 weeks observation period after the second dose, while for Pfizer-BioNTech vaccine recipients, seropositivity remained high and stable. Overall, four or more weeks after a second dose, IgG positivity for Sinovac recipients was 67.4 % (95% CI 65.5%, 69.4%) and 93.5% (95% CI 90.2%, 96.8%) for Pfizer-BioNTech recipients. Significantly lower positivity levels were observed for both vaccines in men compared to women and for participants 60 years and older for both vaccines.

Implications of all the available evidence

Overall IgG positivity for Sinovac recipients reached 77% after full vaccination in a country with rapid vaccine rollout while one dose led to low IgG positivity levels. Seropositivity in Pfizer-BioNTech vaccine recipients surpassed 90% after two doses and 75% after one vaccine dose. A mild antibody decline is observed for Sinovac after 4 weeks of full vaccination but not for Pfizer-BioNTech recipients. Prolonged IgG monitoring will allow further evaluation of seropositivity overtime, providing data, in conjunction with effectiveness studies, for possible future reevaluation of vaccination strategies.

SUMMARY

Background: By May 15, 58 % of the Chilean population had received a SARS-COV-2 vaccine dose with either the inactivated vaccine from Sinovac (84%) or the mRNA vaccine from Pfizer-BioNTech (16%). In the absence of simultaneous real-world data for these vaccines we compared SARS-CoV-2 IgG positivity in a dynamic national monitoring strategy.

Methods: Starting March 12, 2021, testing stations for SARS-COV-2 IgG detection were progressively installed in hotspots based on cellular-phone mobility tracking within large Chilean cities. Individuals voluntarily approaching the testing stations were invited to perform a lateral flow rapid test through finger prick and respond to a questionnaire.

Findings: 31 729 individuals were included in the analysis of which 53% and 12% had received Sinovac or Pfizer-BioNTech vaccine and 35% no vaccine. IgG positivity 4 weeks after the first and second dose was 22.3% (95% CI 17.3%, 27.3%) and 69.4 % (95% CI 67.3%, 71.5%) for Sinovac and 78.1% (95% CI 70.2%, 86.0%) and 92.7% (95% CI 89.6%, 95.8%) for Pfizer-BioNTech vaccine recipients. For unvaccinated individuals, positivity increased from 6% (95% CI 4.4%, 7.6%) to 14.2% (95% CI 11.9%, 16.5%). For Sinovac, seropositivity mildly declined by 8 weeks after the second dose (64.1%, 95% CI 61.8%, 66.4%). Positivity levels were lower in men for Sinovac, and for individuals over 60 years for both vaccines.

Interpretation: IgG positivity for Sinovac and Pfizer-BioNTech vaccines surpassed 75% at 2 weeks after the second dose with a mild decrease for Sinovac after week 4. Pfizer-BioNTech but not Sinovac vaccine recipients developed significant IgG response after the first vaccination. Men and older individuals had lower IgG positivity irrespective of the vaccine used.

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Introduction

Chile is one of the world leaders in SARS-CoV-2 vaccine uptake: approximately three and a half months after the launch of the vaccination campaign[1], by May 15, 2021, 58% of the 15 200 000 eligible population, those over 18 years of age, had received at least one dose and 49% two doses. The vaccine from the Chinese producer Sinovac (inactivated virus) represents 85% of the vaccine doses dispensed (13.6 million doses) while the Pfizer-BioNTech vaccine (mRNA) represents the remaining 14% (2.5 million doses).[2] The adenovirus vectored vaccine from Astrazeneca has been recently introduced with nearly 90 000 doses dispensed. In the Chilean Vaccination Plan, health care personnel were first vaccinated, and then a decreasing-age strategy was followed, which currently is vaccinating the 30-35 years age bracket, in addition to groups of teachers and school staff, essential workers and few other small subgroups. Nearly 85% of Chile's population over 60 years has received two vaccine doses by mid-May.

Efficacy reported for the inactivated Sinovac vaccine from the Brazilian health care worker trial ranged from 50% to 78% for PCR positive SARS-CoV-2 infections requiring or not requiring a medical intervention, respectively.[3] In contrast, for the mRNA vaccine from Pfizer-BioNTech, reported efficacy from the multinational trial was 95% for COVID-19 symptomatic cases.[4] The Chilean Health Ministry recently reported effectiveness of the Sinovac vaccine for symptomatic infection of 67% and 85% for hospital admission.[5,6]

In March 2021, we initiated COVID-19 IgG surveillance in large cities throughout the country, based on the implementation of strategically located testing stations, so as to obtain a geographically diverse representation within each city. Voluntary testing by a rapid lateral flow test (LFT) and a structured web-based questionnaire

performed by trained personnel and immediate on-line recording has allowed dynamic tracking of IgG positivity rates.[7] We report here results from the first 35 850 people tested, at a cutoff date of May 15, 2021, with emphasis on the results for vaccinated individuals, differentiating by demographic data, vaccination status, vaccine received, and time elapsed since the first and second doses.

Methods

Characteristics of the testing stations and participants

Jurisdiction in the public healthcare system is divided into 29 *health services* distributed throughout the country of which 22 had initiated participation in this surveillance program by the cutoff date. The remaining seven services are scheduled to begin data collection in early June. A total of 23 testing stations (The *Araucanía Sur* Health Service participated with 2 stations) strategically located in public open spaces have been implemented to date. These stations have been deployed in the most populated cities in Chile, aiming to replicate the diverse geographical distribution of the population of such cities. To achieve this, an optimization model (mixed-integer program) based on weekly analysis of national cellphone mobility data facilitated by Chile's largest telecom was, and still is, used to select sites with high affluence and wide county-level distribution of subjects, and to correct deviations from the target geographical distribution (elicited from census data); details of the model may be found in the supplement.

From March 12 to May 15 2021, adults over 18 years of age approaching the testing sites were invited to participate. A testing station included two study personnel, LFTs and a laptop computer with internet access. After informed consent, participants provided a blood sample through finger prick which was immediately applied to the LFT. During the 15-minute interval required for test evaluation, the second study person applied an on-line questionnaire including data on socio-demographic characteristics, commuting habits, and variables related with exposure and comorbidities (see supplement for questionnaire). Results were instantly uploaded to a centralized database harbored at the servers of ISCI, where the data is stored in an anonymized format.

COVID-19 IgG testing

The *Onsite* COVID-19 IgG/IgM Rapid Test Kit from CTK Biotech Inc, US, is being used according to the manufacturer's specifications (reported Covid-19 sensitivity and specificity for IgG is 96.7% and 98.1%, respectively[8]). Test results were read in 15 minutes by trained study personnel and entered on the electronic platform. Results were categorized as positive (visible bands on the IgG and test control positions), negative (visible band only on the test control position) or invalid (lack of any visible band); to the extent possible, invalid outcomes were re-tested on-site. For the study we considered only IgG results; individuals with a positive IgM were directed for PCR testing.

Data analysis and management

Data are presented in tables as counts, percentages and means (std), and in figures as means and 95% confidence intervals, using standard z-scores. Data from all participants with complete records were included in the analysis, with the exception of those under-aged, with no declared gender, or with an invalid test result. Because our aim was to determine the comparative effect of the vaccines, the analysis excludes participants who did not recall their complete vaccination status. Subsequently, participants with prior positive PCR test results were also excluded. Analyses (tables, figures and the calculation of interval confidence) were performed using the open-source Julia programming language[9]; the integer programs for the optimal location of testing sites were solved using the Gurobi solver.[10]

Seropositivity for the different subsets related to specific time periods after a dose for either vaccine included subjects tested at different dates; thus, in order to obtain a fair comparison with unvaccinated individuals we adjusted these groups by matching with the distribution of the vaccinated subset according to date, gender and age range (see the supplement for a detailed example). Mean comparisons between groups is done using standard difference-in-means z-scores.

Results

A total of 35 850 individuals were enrolled of which 31 729 individuals were included in the final analysis. Reasons for exclusion were incomplete vaccination status (3 544), vaccination with other vaccines (341), undeclared gender (31), underage (176), invalid test result (31) or a combination of these. Among the individuals included, 1 743 participants had a prior PCR positive result. All counties within each of the 22 participating Health Services (The *Araucanía Sur* Health Service had two study sites) were reasonably balanced in the study population as shown in supplementary Figure 2; supplementary Table 5 adds information on the contribution of each testing site to the overall population study. A total of 16 739 (53%) and 3 841 (12%) individuals had received at least one dose of the Sinovac or Pfizer-BioNTech vaccine and 11 149 (35%) no vaccine. For Sinovac 2 199 individuals had received only a first dose and 14 540 a second dose while for Pfizer-BioNTech 1 322 and 2 519 had received one or two doses. Compared with unvaccinated participants, vaccinated individuals were older and had more comorbidities (Table 1), an expected outcome of the national vaccination priorities. Also, a higher proportion of female and Chilean as compared to non-Chilean residents was observed among vaccinated participants, relative to those unvaccinated. Sinovac and Pfizer-BioNTech vaccine recipients were similar, although a higher proportion of older individuals received the former, which was also expected as early massive vaccination efforts began in the older age brackets, using mostly Sinovac.

Overall, as shown in Figure 1, SARS-CoV-2 IgG positivity increased from 10.8% (95% CI 8.7%, 12.9%) to 51.8% (95% CI 50.1%, 53.5%) throughout the study period. For unvaccinated individuals seropositivity increased from 6% (95% CI 4.4%, 7.6%) to 14.2% (95% CI 11.9%, 16.5%) while for individuals receiving any vaccine dose it ranged from 50.2% (95% CI 47.1%, 53.3%) to 69.7% (95% CI 58.4%, 80.0%).

Figure 2 shows the IgG positivity dynamics according to time elapsed since inoculation, for both vaccines separately. Sinovac vaccine recipients had a test positivity of 22.3% (95% CI 17.3%, 27.3%) four weeks after the first dose, reaching 69.4 % (95% CI 67.3%, 71.5%) four weeks after the second dose. Pfizer-BioNTech vaccine recipients had a test positivity of 78.1% (95% CI 70.2%, 86.0%) four weeks after the first dose, reaching 92.7% (95% CI 89.6%, 95.8%) four weeks after the second dose. Seropositivity to Sinovac but not to the Pfizer-BioNTech vaccine declined by 8 weeks after the second dose. Seropositivity rates for unvaccinated individuals adjusted to the specific time-periods of the corresponding vaccine-week period for cases is also shown in Figure 2. The variation of positivity for unvaccinated individuals, potentially reflecting periods with different infection rates, was low, not surpassing the 16% absolute limit.

Overall, mean IgG positivity among Pfizer-BioNTech vaccine recipients is statistically higher than positivity among Sinovac vaccine recipients, for all age brackets and gender (Table 2). For the first four weeks after the first dose, cross-sectional SARS-CoV-2 IgG positivity across gender was similar for both vaccines. Regarding age, Sinovac vaccine recipients over 60 years of age had lower seropositivity rates, while no age related differences were observed for Pfizer-BioNTech vaccine recipients. The picture changes four or more weeks after the second dose. Positivity was higher in women than men (mean 70.7% vs 62.2%, p 1 for Sinovac, and mean 94.4% vs 90.2%, p<0.988 for Pfizer) , and mean positivity among participants 60 years of age and older were significantly lower than for those younger than 60 years (70.0% vs 62.3%, p 1 for Sinovac, and 96.5% vs 73.4%, p 1 for Pfizer). Seropositivity by vaccination status and adjusted unvaccinated individuals during three vaccine dosing periods and for all characteristics evaluated in the study is presented in Supplementary Table 6. In addition to the age and gender variations previously described, which were maintained 5-9 weeks after vaccination, no differences were observed for nationality, times leaving home per week (as a measure of potential exposure to Covid-19), or comorbidities.

Discussion

COVID-19 IgG antibody testing with rapid, easy to use LFTs detecting responses to infection and vaccination with different vaccine platforms, implemented in cell-phone based mobility hotspots throughout the country, is proving efficient to

simultaneously evaluate population immunity to different vaccines. In this first report, representing data obtained 3 months after initiation of the vaccination campaign in Chile, IgG positivity reached 69% and 93% for recipients of Sinovac and Pfizer-BioNTech vaccines respectively, four weeks after the second dose, a time when unvaccinated populations had an adjusted-seroprevalence of less than 16%.

IgG positivity was lower in men for both vaccines, albeit more pronounced for Sinovac. Positivity was lower in the elder over 60 years of age for both vaccines. Importantly, a declining trend in seropositivity was observed for Sinovac in the 4-8 week period after the second dose. The gender difference observed is not novel and has been previously discussed for other vaccines.[11] The lower positivity for elder population has not been reported in the phase I/II trials for these vaccines. The Pfizer vaccine induced high levels of humoral and T cell responses, with robust interferon-T cell responses to a peptide pool including the RBD in both younger and older Chinese adults (aged >65 years), and geometric mean neutralizing titers reached 1.3-fold for the older participants compared to a panel of COVID-19 convalescent human sera obtained at least 14 d after positive SARS-CoV-2 polymerase chain reaction test.[12] On the other hand, when the Sinovac vaccine was tested in older adults (aged 60 years) in a dose-escalation study with a two-dose vaccination schedule (days 0 and 28), neutralising antibody responses to live SARS-CoV-2 were not reduced in this population and was similar to the responses observed among adults aged 18–59 years.[13] Importantly, a recent report on the effectiveness of the Sinovac vaccine in Brazilian elder population during P.1 variant-associated epidemic of COVID-19 (non peer-reviewed publication) showed a vaccine effectiveness 14 days after the 2nd dose that declined with increasing age, 61.8%, 48.9% and 28.0% among individuals 70-74, 75-79 and 80 years of age, respectively.

The decline in seropositivity overtime may prove important if associated with an increase in cases among vaccinated individuals, thus suggesting reduced protection. At the moment, based on our results, this may become important for Sinovac, but a more prolonged observation period is required. Establishing the correlation between IgG positivity measured by the LFT used in this study with neutralizing antibodies will also be important as the latter is considered an adequate correlate of protective immunity[14]; these studies are underway. If a further decline overtime is observed and is paralleled with increasing cases, a booster dose may have to be considered down the road.

Importantly, and consistent with antibody prevalence results from clinical trials,[15] IgG positivity is low with one dose for the inactivated vaccine, not surpassing 22% for people in their fourth week after vaccination. This is different from the Pfizer-BioNTech vaccine that reaches 76 % during the 4th week. This observation may also have programmatic implications as it provides an element of support for the use of one dose of Pfizer-BioNTech in a strategy to increase coverage in countries with low vaccine supply. Conversely, two doses is critical for Sinovac and a strong message of likely low protection levels before two weeks from the second dose should be conveyed to the population of the countries using this vaccine.

We did not find additional comparative studies for immunogenicity of two or more vaccines. Population-based studies simultaneously evaluating performance of two or more vaccines are scarce. In Scotland, effectiveness of the first dose of the BNT162b2 mRNA vaccine was 91% (95% CI 85–94) for COVID-19 hospital admission at 28–34 days post-vaccination, compared to 88% (95% CI 75–94) for ChAdOx1. Combined vaccine effects against hospital admission due to COVID-19 was (83%, 95% CI 72–89 at 28–34 days post-vaccination) for those 80 years and older.[16,17]

Interestingly, in our study we observed an IgG positivity for inactivated vaccine recipients of 69.4% four weeks after the second dose, in comparison with an effectiveness of 67% against symptomatic infection in a recent study in Chile with the inactivated vaccine.[5,6] For the Pfizer-BioNTech vaccine, we observed an IgG positivity of 92.7% four weeks after the second dose, in comparison with an estimated effectiveness of 94% in a recent study from Israel, seven days after the second dose.[18]

Our study has several limitations. SARS-COV-2 IgG detected by the LFT used in this study does

not assure protection, and therefore, a correlation study with neutralization antibody testing is warranted as mentioned above. The LFT used, *Onsite* COVID-19 IgG/IgM Rapid Test Kit from CTK Biotech Inc, United States showed robust responses with the two vaccines used in Chile in absence of specific pre-evaluations for vaccine related responses. The test had reported high sensitivity and specificity for Covid-19 infection. It is unclear how it will respond to other vaccines, from Astrazeneca for example, which has been recently introduced in Chile. Importantly, there is significant variability among LFTs[19] and interpretations may be misleading if a test with low yields is used. The study design did not contemplate a control group matched by gender and age, however, adjustments by age, gender and time points were made when comparing both vaccine groups to unvaccinated individuals. The ethnicity of the participants was homogeneous, so the observed results cannot be extrapolated to different ethnic populations.

In conclusion, IgG positivity for both Sinovac and Pfizer-BioNTech vaccines reached 69% and 93% respectively, 4 weeks after the second dose. Pfizer-BioNTech but not Sinovac vaccine recipients developed significant IgG response after the first vaccination. After four weeks of the second dose of the inactivated vaccine, a trend towards a decrease in IgG positivity was observed. This dynamic monitoring system can be replicated in other regions to longitudinally characterize population IgG positivity to SARS-COV-2 in presence or not of vaccination and determine antibody waning overtime, providing data, in conjunction with effectiveness studies for possible future reevaluation of vaccination strategies.

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Contributors. DS, MO, JPT, MZ, ES, LJB conceived the study. DS and LJB directed the ISCI team that worked on the testing site optimization module, and the web-based platform for collecting data. MZ led the teams for the field work. DS was responsible for database data cleaning and data analysis, generating tables and figures. DS, MO, JPT, LJB drafted the original manuscript. All authors provided important input to methods of the study, revised the manuscript, and approved the final version. LJB and MZ led the funding acquisition efforts. LJB, DS and MZ are the data guarantors with full access to the primary data, verifying that this manuscript is an honest, accurate, and transparent account of the study that has been conducted. All authors had full access to study results and had final responsibility for the decision to submit for publication.

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Data sharing: Because of data protection regulation, data cannot be shared directly by the authors. Data is accessible to authorised researchers after application to the Chilean Ministry of Health.

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Table 1: Characteristics of Study Population by Vaccination Status

Characteristics	**Total**	**Unvaccinated**	**Sinovac**	**Pfiezer-BioNTech**
Age range				
18-39	14290 (45.0%)	7083 (63.5%)	5886 (35.2%)	1321 (34.4%)
40-49	6606 (20.8%)	2476 (22.2%)	3158 (18.9%)	972 (25.3%)
50-59	5744 (18.1%)	1234 (11.1%)	3207 (19.2%)	1303 (33.9%)
60	5089 (16.0%)	356 (3.2%)	4488 (26.8%)	245 (6.4%)
Gender				
Male	13340 (42.0%)	5063 (45.4%)	6704 (40.1%)	1573 (41.0%)
Female	18389 (58.0%)	6086 (54.6%)	10035 (59.9%)	2268 (59.0%)
Nationality				
Chile	30440 (95.9%)	10398 (93.3%)	16328 (97.5%)	3714 (96.7%)
Other	1289 (4.1%)	751 (6.7%)	411 (2.5%)	127 (3.3%)
Previous positive COVID-19 PCR	1743 (5.5%)	612 (5.5%)	907 (5.4%)	224 (5.8%)
Previous positive COVID-19 IGG	291 (0.9%)	53 (0.5%)	192 (1.1%)	46 (1.2%)
Times leaving home per week				
less than 3	10933 (34.5%)	3974 (35.6%)	5604 (33.5%)	1355 (35.3%)
3 to 5	10336 (32.6%)	3709 (33.3%)	5446 (32.5%)	1181 (30.7%)
6 to 7	7800 (24.6%)	2623 (23.5%)	4206 (25.1%)	971 (25.3%)
more than 7	2660 (8.4%)	843 (7.6%)	1483 (8.9%)	334 (8.7%)
Comorbidities				
Obesity	1497 (4.7%)	472 (4.2%)	835 (5.0%)	190 (4.9%)
HTA	5034 (15.9%)	625 (5.6%)	3700 (22.1%)	709 (18.5%)
Diabetes	2470 (7.8%)	354 (3.2%)	1734 (10.4%)	382 (9.9%)
Cancer	337 (1.1%)	47 (0.4%)	238 (1.4%)	52 (1.4%)
Chronic pulmonary disease	1482 (4.7%)	403 (3.6%)	873 (5.2%)	206 (5.4%)
Chronic cardiovascular disease	844 (2.7%)	152 (1.4%)	590 (3.5%)	102 (2.7%)
Total	**31729**	**11149 (35.1%)**	**16739 (52.8%)**	**3841 (12.1%)**

Table 3: Seropositivity after the First and Second Vaccination for Sinovac and Pfizer-BioNTech Vaccines, by Gender and Age

	First dose - weeks 1 to 4	**Second dose - weeks 5 to 9**		
	Sinovac	**Pfizer-BioNTech**	**Sinovac**	**Pfizer-BioNTech**
Gender				
Male	16.2% (13.6%, 18.9%)	46.5% (42.1%, 50.8%)	62.2% (60.5%, 63.8%)	90.2% (86.6%, 93.9%)
Female	17.1% (14.7%, 19.5%)	45.2% (41.1%, 49.2%)	70.7% (69.5%, 71.9%)	94.9% (93.1%, 96.7%)
Age				
18-39	19.7% (16.4%, 23.0%)	54.4% (49.3%, 59.4%)	70.0% (68.4%, 71.6%)	97.0% (95.1%, 98.8%)
40-49	16.1% (12.9%, 19.3%)	38.9% (33.9%, 44.0%)	70.4% (68.1%, 72.8%)	96.2% (93.5%, 99.0%)
50-59	16.0% (12.8%, 19.3%)	43.4% (38.0%, 48.7%)	68.7% (66.0%, 71.4%)	94.5% (91.5%, 97.5%)
60	9.8% (4.9%, 14.7%)	44.8% (26.7%, 62.9%)	62.3% (60.5%, 64.1%)	73.4% (64.5%, 82.3%)