Untangling the changing impact of non-pharmaceutical interventions and vaccination on European Covid-19 trajectories

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Untangling the changing impact of non-pharmaceutical interventions and vaccination on European Covid-19 trajectories

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Abstract

Non-pharmaceutical interventions (NPIs) and vaccination are two fundamental approaches to mitigate the coronavirus disease 2019 (Covid-19) pandemic. Vaccination strategies are generally less costly and socially/economically disruptive than NPI strategies, such as business closures, social distancing, and face mask mandates, as evidenced by highly vaccinated countries generally rolling back NPIs. However, the respective real-world impact of an NPI strategy versus vaccination strategy, or the combination of both, on mitigating Covid-19 transmission remains uncertain. To address this, we built a Bayesian inference model to explore the changing effectiveness of NPIs and vaccination based on the assembled large-scale dataset, including epidemiological parameters, variants, vaccines, and control variable. Here we show that NPIs were still considerably complementary or even synergistic to vaccination in the effort to curb the Covid-19 infection before reaching herd immunity. We found that (1) the synergistic effect of NPIs and vaccination was 46.9% (reduction in reproduction number) in September 2021, whereas the effects of NPIs and vaccination alone were 20.7% and 28.8%, respectively; (2) effectiveness of NPIs is less sensitive to emerging COVID-19 variants but decreases with vaccination progress, as NPIs may unnecessarily restrict the vaccinated population. The effectiveness of NPIs alone declined approximately 23% since the introduction of vaccination strategies, where the relaxation of NPIs promoted the decline from May 2021. Our results demonstrate that the decision to relax NPIs should consider the real-world vaccination rate of the relevant population, which is determined by the observed vaccine efficacy in relation to extant and emerging variants.

Key words: Covid-19; non-pharmaceutical interventions; vaccination; variants

Introduction

Governments worldwide have implemented a series of non-pharmaceutical interventions (NPIs) to varying extents since early 2020 against local transmission of the coronavirus disease 2019 (Covid-19)[1]. The impact of these NPI strategies has been well documented[2,3,4], yet the consequences of such socially and economically long-term restrictions have raised concerns in terms of economic recession[5] and unintended adverse mental-health outcomes[6]. The production and implementation of several vaccine candidates to prevent symptomatic Covid-19 and resultant hospitalization or death provided a promising opportunity to relax NPIs, addressing the economic and social burdens. However, clinical trials estimating vaccine efficacy were conducted when novel variants, such as the Delta-variant, had not yet emerged[7], with a notably larger transmission capacity. Moreover, the evidence based NPI implementation alongside vaccination progress is still unclear. As more countries worldwide increase vaccination rates, the effect of a combined vaccination and NPI strategy must be quantified over time and within the context of emerging or extant variants and their transmission capacity. This information is vital for informing policymakers who wish to promote public health while also easing the burden of invasive and restrictive NPIs.

Since the Pfizer vaccine was first authorised by the UK government on 2 December 2020, more countries, particularly in Europe, have begun their mass-vaccination programme. The effectiveness of the Pfizer vaccine against preventing symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was documented as 95.0% (95% credible interval (CI), 90.3% - 97.6%) as of November 2020[8]. Since then, five other Covid-19 vaccine products, including Moderna, Johnson & Johnson, AstraZeneca, Sinopharm.Beijing and Sputnik.V, have been approved in Europe with varied effectiveness against the transmission of SARS-CoV-2[9]. The cumulative number of confirmed Covid-19 cases in Europe for March 2021 was

8,410,531, representing a decrease of 83% in cases from December 2020 following the commencement of vaccination in Europe[10].

By mid-September 2021, the vaccination rate had reached 59.6% in the European Union, with 66.1% in the UK and 64.2% in Israel[10], reflecting the proportion of populations who received at least two doses of a Covid-19 vaccine. Despite these vaccination rates, a subsequent wave of Covid-19 cases emerged in July 2021 with daily confirmed cases of nearly 40,000, driven primarily by the emergence of the novel Delta variant. Vaccines were widely less effective against this more transmissible variant, and further not all vaccinated populations developed enough antibodies to prevent breakthrough infections. Since the Alpha variant was first identified in the United Kingdom[11], numerous more transmissible SARS-CoV-2 variants were already spreading in Europe, possibly causing new waves of infection with the emergence of immune evasion[12,13]. Vaccine efficacy against highly transmissible variants was weakened, as evidenced by the decrease in efficacy among the ChAdOx1 vaccine to 67.0% (61.3% - 71.8%)[14]. Despite this, many governments in Europe have stipulated various roadmaps to relax NPIs since June 2021[15]. Undoubtedly, the variation in vaccine efficacy among the differing vaccine candidates leads to diverse practical protection in preventing symptomatic infections and hospitalizations or deaths[16], resulting in uncertainty as to the true threshold of herd immunity. Under this situation, rushed relaxation of NPIs could bring a risk of Covid-19 resurgence.

Previous studies[17,18,19,20] have used epidemiological model-based numerical simulations to discuss NPI implementation in the post-vaccine rollout. For example, NPIs were estimated to have a higher impact in preventing infection than vaccination alone during the first phase of the vaccination campaign in Italy, assuming a variety of immunization rates through January 2022[19]. Further, using a mathematical model

informed by age structure within the UK, even with an optimistic scenario that vaccines can prevent 85% of infections regardless of variants, the reproduction number was still estimated as 1.58 (suggesting sustainable transmission) after full vaccination of the population in the absence of NPIs[20]. These results suggest that NPIs should be continually implemented during vaccination programmes and post-vaccination to prevent Covid-19 transmission. In addition, population immunity was directly defined as various scenarios in the mathematical models which may or may not reflect reality, and the geography of variant emergence and resulting vaccine efficacy are often absent or incomplete. The gap between the de facto vaccination-immune and the vaccinated population can lead to a misunderstanding of simulation results[16], where much uncertainty is introduced by varying vaccine efficacy and variant emergence[21]. Therefore, the respective real-world effectiveness of NPIs plus and vaccination strategies are still unclear, resulting in uncertainty as to which policies and interventions are most suitable.

Here, we estimate the real-world impact of vaccination programmes and the NPI strategies in mitigating Covid-19 transmission over time, against emerging variants and various settings. We adopted a data-driven approach to quantify the change in transmission across 27 countries, as a result of one or both of these strategies. Our results attempt to explore the relative impact of NPIs versus vaccination using large-scale and real-time data, including epidemiological parameters, variants, vaccines, and control variable. Before reaching herd immunity through vaccination alone, continuing NPIs will likely have an effect that is complementary or even synergistic to vaccination programmes in preventing transmission and reducing symptomatic and severe COVID-19. These results can potentially inform interventions that countries implement to

control transmission in current and future waves of infections with varying degrees of vaccination rates, to support prompt policy decisions.

Results

We analysed data from 26 European countries, including Austria, Belgium, Bulgaria, Switzerland, Czechia, Germany, Denmark, Spain, Estonia, Finland, France, Croatia, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Poland, Portugal, Slovakia, Slovenia, Sweden, and the United Kingdom, and Israel from 1 August 2020 to 20 September 2021. Although Israel is in Western Asia, for the purpose of these analyses it was considered closer to Europe in terms of lifestyle and public activities, and therefore with similar effects of NPIs as European countries. Thus, we include Israel in these analyses, especially with its exemplary vaccination progress (64.2% by 20 September 2021), which offered a natural comparison to other European countries. Given strong spatiotemporal heterogeneity in transmission (Fig. 1a), we used the instantaneous reproduction number (R_t) to represent the real transmissibility under government intervention and vaccination. The effectiveness of NPIs and vaccination, thus, was defined as empirical change of basic reproduction number (ΔR_0), i.e., the amount of reduction in instantaneous basic reproduction number ($R_{0,t}$) to obtain the real transmissibility R_t, where the instantaneous basic reproduction number ($R_{0,t}$) represents the daily transmissibility baseline varied with the changing coronavirus contexts over time (Fig. 1c). We also evaluated the practical vaccination rate, i.e., the fraction of the population that is effectively immune via vaccination amongst the whole population of interest, e.g., by country in this study, to estimate the real-world effect of vaccination against variants and various real-world settings, such as mobility, social distancing, mask usage, etc. As various countries implemented diverse NPIs packages

without coordination[22], we used government interventions' integrated stringency index as a proxy to estimate the general restraint of ‘lockdown style’ NPIs.

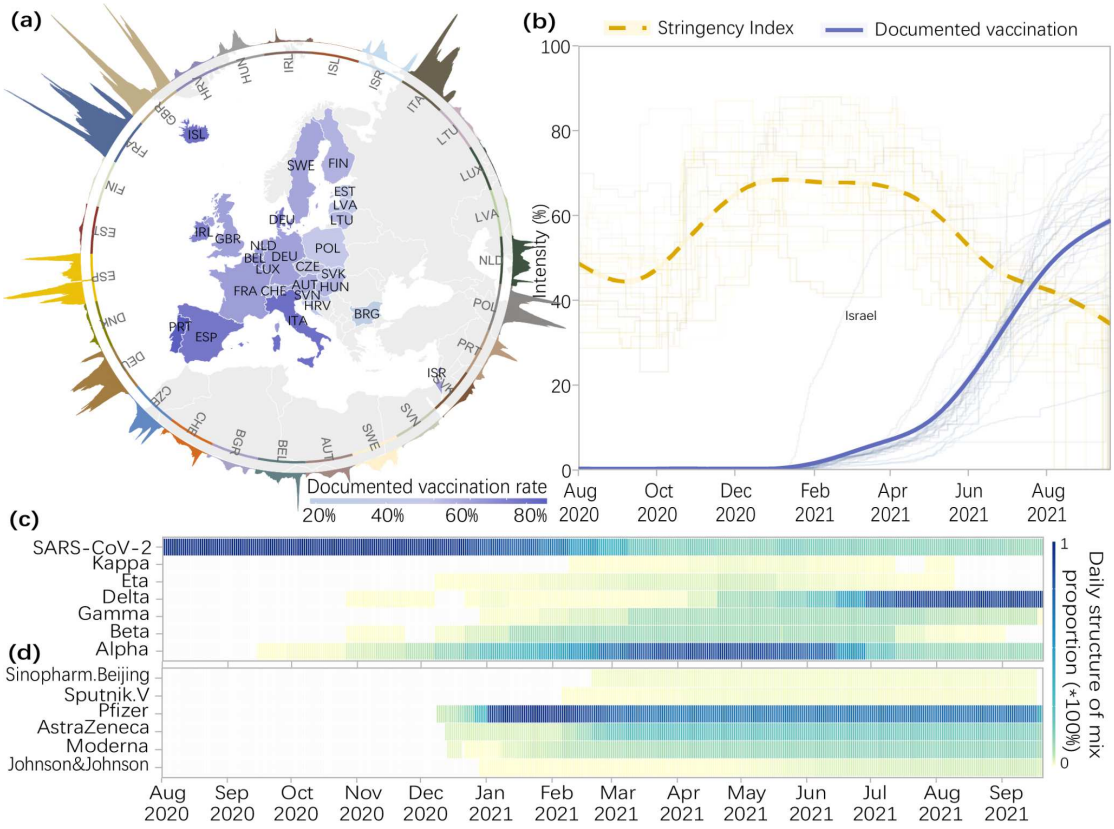

Fig. 1 Overview of the data context. (a) Daily confirmed cases between 1 August 2020 and 20 September 2021 (outside the circle) and the documented vaccination rate mapping on 20 September 2021 (inside the circle) of the studied 27 countries. (b) The shallow lines in the background are the stringency index of ‘lockdown’ style NPIs (in yellow) and the documented vaccination rate, respectively, across the 27 countries between 1 August 2020 and 20 September 2021. The corresponding two thick lines were fitted by the national data, representing the comprehensive circumstances in Europe (including Israel). (c) - (d) The daily proportion of the infections caused by the SARS-CoV-2 and its variants, and the daily proportion of different vaccine products used for vaccination from 1 August 2020 to 20 September 2021 in the 27 countries. Of note, 1 August 2020 is about two months before the variants Alpha emerged, we studied NPIs effect from the date to investigate the NPIs effectiveness over time, against variants and various settings.

Effect of NPIs and vaccination over time

The respective effects of NPIs and vaccination were estimated for Europe over time (Fig. 2). From 1 August 2020 to the start of vaccination in each of the studied 27

countries, the effectiveness of NPIs gradually climbed from 25.3% (95% CI: 22.7% - 27.8%) to 47.1% (43.2% -50.8%). With the progress of vaccination, the effectiveness of NPIs continually increased to 55.5% (52.7% - 58.2%), where the practical vaccination rate was 4%. Thereafter, the effect of NPIs gradually dropped to 20.7% (18.1% - 23.1%) on 20 September 2021, with the regional average practical vaccination rate of 46%. In contrast, the effectiveness of vaccination successively increased along with the improved practical vaccination rate, reaching 28.8% (23.8% - 33.6%) by 20 September 2021. It should be noted that the effect of vaccination exceeded that of the NPIs since August 2021. Though the efficiency of the vaccination had been flourishing since its roll-out, the Delta variant hindered its increase. The effect of vaccination between August and September 2021 was almost static.

We also evaluated $R_{0,t}$ during the study period. As variants successively emerged over time, $R_{0,t}$ increased from 3.18 (95% credible Interval: 3.02 - 3.35) on 1 August 2020 to 4.46 (4.17 - 4.76) on 20 September 2021. Before the onset of vaccination, NPIs alone controlled the practical transmissibility, measured by R_t, to about 1.07 (1.00 - 1.15) together with the unobserved confounders but still larger than 1. When countries started to vaccinate their population, despite $R_{0,t}$ increasing, R_t decreased to 0.77 (0.68 - 0.87) in June 2021. Thereafter, however, R_t increased to above 1 again (about 1.19 (1.11 - 1.28)) after the end of June. While the combination of NPIs and vaccination has decreased a larger share of $R_{0,t}$ during this period than before together with the same unobserved confounders.

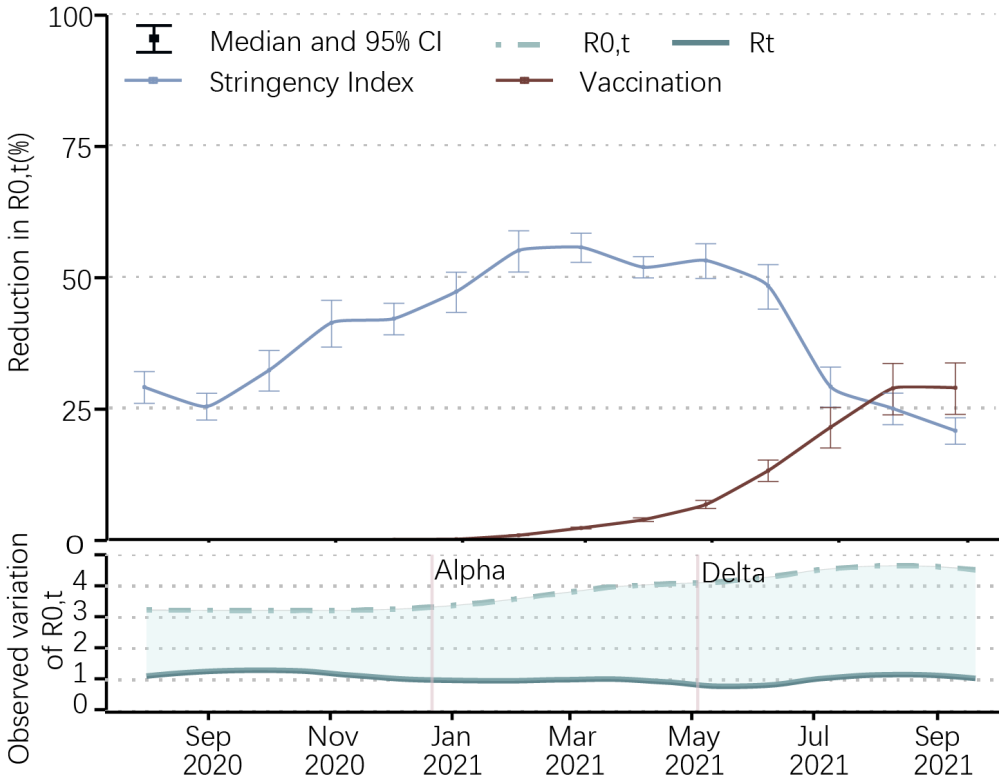

Fig. 2 The respective effectiveness of NPIs and vaccination across time. The effectiveness of NPIs and vaccination was estimated across 27 countries by month between 1 August 2020 and 20 September 2021. Within each country, the monthly effectiveness estimates were calculated by the coefficients of NPIs and vaccination through $1 - \exp(-\alpha_i \bar{x}_i)$, where $\bar{x}_i$ is the average of the national stringency index and the practical vaccination protection rate over each month, respectively. Then, we merged all the national results to the European case by meta-analysis. The bottom green shadow illustrates the observed reduction of the transmissibility in terms of the instantaneous basic reproduction number. The dates that Alpha and Delta dominated (>50%) in the transmitted coronavirus are indicated by pink lines.

Impact of vaccination on the effectiveness of NPIs

The effectiveness of vaccination increased across countries with the increased practical vaccination rate, against various conditions of variants, vaccine products, and societies. With a practical vaccination rate of between 30% and 40%, vaccination can reduce 19.9% (in median) of the basic reproduction number, while NPIs alone can reduce 40.4% of the basic reproduction number. However, when the practical vaccination rate exceeded 40%, the effectiveness of vaccination (30.0% in median) surpassed that of the implemented NPIs at the same period (16.5%). In our study, only six countries had not

reached such a high practical vaccination rate instead of the documented full vaccination rate by 20 September 2021, including Bulgaria (18.2%), Estonia (36.7%), Croatia (33.5%), Latvia (38.4%), Slovakia (33.5%) and Portugal (37.5%). Yet, facing more aggressive variants, such as the Delta variant, further steps in boosting practical vaccination rate were accompanied by a slowdown in the effect raise of vaccination where NPIs effect revived at this stage and advanced than the effectiveness of vaccination by 7.2%.

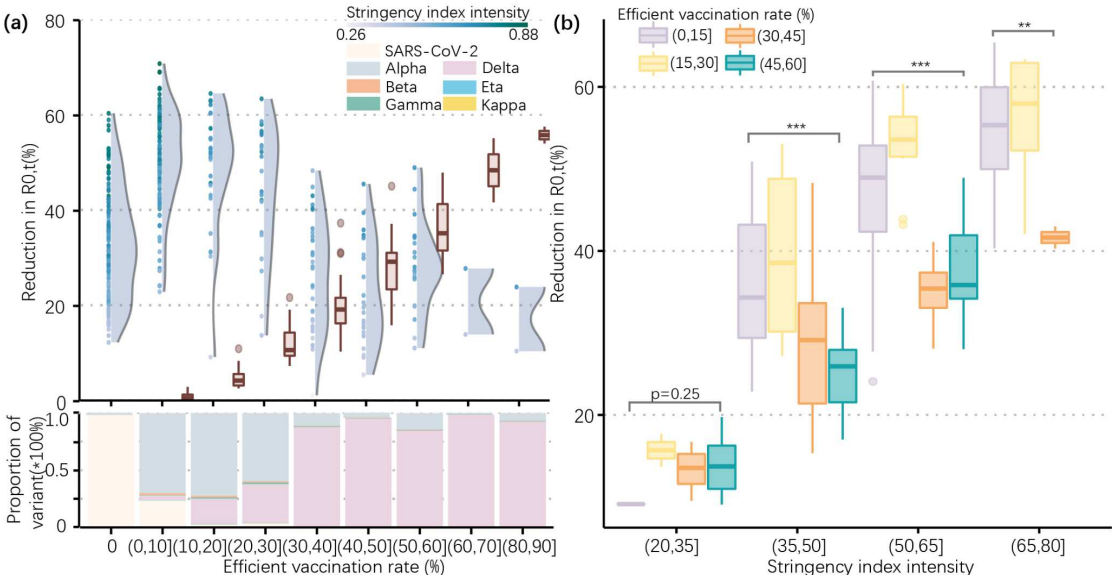

Fig. 3 The effectiveness of NPIs under different vaccination progress across countries. (a) The raincloud plot of NPIs effects (in blue) under different practical vaccination rates; and the box plot of vaccine effectiveness (red) on reducing the transmission of COVID-19 under different stages of the vaccination programme. The box is drawn from Q1 to Q3, with a horizontal line drawn in the middle to denote the median. The "raincloud" visualizes the stringency index intensity (point) and the probability density of its effectiveness with vaccination progress. The bottom bar plot illustrates the structure of the mix virus under the vaccination process. (b) The box plot of vaccine effectiveness for different practical vaccination rates under variations of stringency index. The difference between the effectiveness of NPIs under different practical vaccination rates was assessed by ANOVA.

Fig. 3b showed that the effectiveness of NPIs has been weakened by vaccination progress. Amid different vaccination phases, we found that NPIs of similar stringency

index kept an obvious lower amount of the effect on mitigating Covid-19 transmission when the practical vaccination rate exceeded 30%. The stringency index of implemented NPIs higher than 65 has vanished when the practical vaccination rate exceeds 45%.

Relaxation of NPIs amid vaccination

With the fixed vaccination progress on 20 September 2021, we investigated the kind of change regarding the stringency index to stop Covid-19 across countries. Due to the sensitivity of vaccination effect in terms of the settings, we compared R_t on 20 September 2021 with Rt = 1 to estimate the amount of effectiveness should be increased (when $R_t > 1$) or could be relaxed (when $R_t < 1$) in terms of NPIs. Based on the practical vaccination rate of about 45% in Europe, NPIs effectiveness in reducing Rt should be about 35%. The stringency index of NPIs should maintain 60 currently, while it can relax to 44 in the post-vaccination era. Besides, we found that most countries should still have a higher stringency index. For example, it is better to increase 16 units of the stringency in Slovakia, while Finland could drop 7.5 units of stringency index down. To validate our evaluation, we also compared our results with an openness risk calculated by Hale et al[23]. It is noted that we compared the two kinds of measurements on 4 March instead of 31 July 2021 due to the limited available dates of openness risk. We found that our forecasted variations on NPIs implementation to stop Covid-19 were highly correlated ($R^2 = 0.49,\ p = 0.01$) to the openness risk (Fig. 4b).

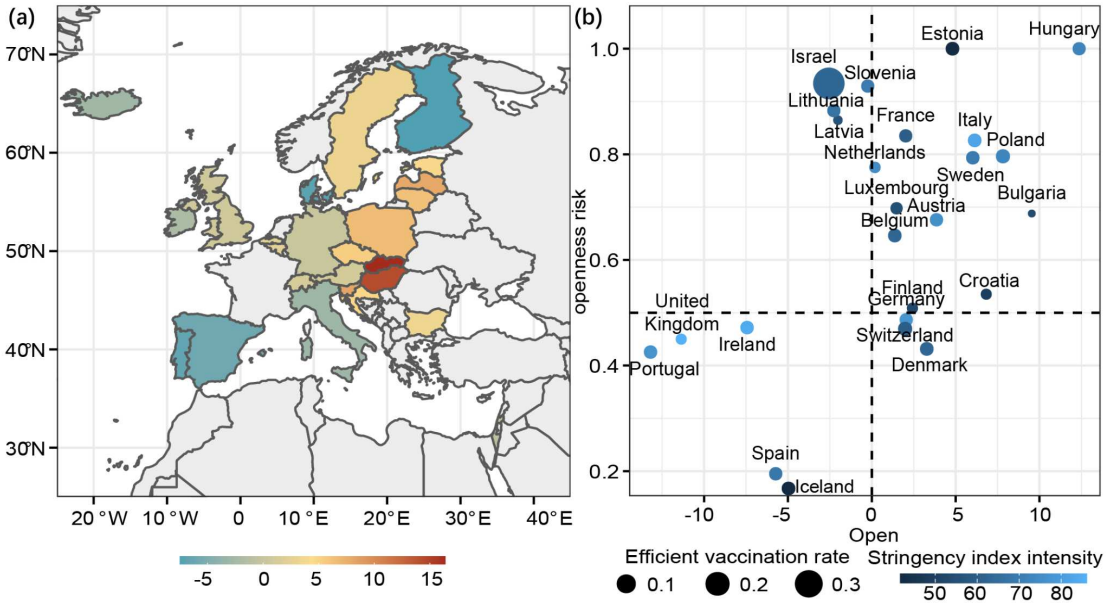

Fig. 4 The indispensable tension and possible relaxation of NPIs in stopping Covid-19 across countries. (a) With the situation of vaccination across countries by 31 July 2021, the mapping of differences between the evaluated stringency index of NPIs to stop Covid-19 (Rt=1) and the practical implemented stringency index on 31 July 2021. (b) The comparison between our evaluated differences in (a) and openness risk calculated by Hale et al[23] for the day of 14 March 2021.

Discussion

We used a data-driven approach to estimate the respective effectiveness of NPIs and vaccination in 27 countries between 1 August 2020 and 20 September 2021. The documented vaccination rate was adjusted by the variants and vaccine products for each country to reflect the de facto population protected by the Covid-19 vaccine; to our knowledge, it has been rarely considered in previous studies. We found that the effectiveness of NPIs on mitigating Covid-19 would be depressed by vaccination. Since vaccination till September 2021, the effectiveness of NPIs has declined by about 23.3% on reducing R_t (from 55.6% to 32.3%). However, facing the higher transmissible variants, NPIs were complementary or even synergistic to vaccination in the effort to end the COVID-19 pandemic before reaching herd immunity, at least in the short term. Where the synergistic effect of NPIs and vaccination was 46.9% in September 2021.

Thus, moderately maintaining NPIs throughout the upcoming SARS-CoV-2 vaccination campaign is essential for maximizing the health benefit. Furthermore, the relaxation of NPIs should be cautiously considered against variants, vaccination phases, and various settings.

Both the effects of NPIs and vaccination were highly correlated to the implemented strength and practical vaccination rate, respectively. The documented effectiveness of Covid-19 vaccines was mainly conducted by clinical trials[24,25,26], which cannot represent the real-world effect in the local context. We adjusted the reported vaccination rate by the active contextual coronavirus and the employed vaccine products, accounting for the different effects of vaccines against various variants, to estimate the actual immune population by vaccination. Therefore, the higher practical vaccination rate indicates that more population is immune, resulting in a higher effect of vaccination on curbing Covid-19 transmission. Despite the effectiveness of NPIs documented being evaluated empirically in previous studies[27,28,29], the estimates were mainly in a point for all study periods. For example, Branuer et al.[30] provided evidence that the intervention with the stricter requirement had more effect. Implementing NPIs with higher strength, such as restrictions of gatherings of more than 10 people compared to that of more than 1000 people, would further decrease the potential contact population of infections. Under the circumstance, the susceptible population is harder to contact the infections and become new infections then, if the probability of getting infected after contact is unchanged. Our estimates of NPIs effectiveness are consistent with these findings, and we also provide the effectiveness of NPIs over time to counter the influence of policy fatigue[31].

It is important to recognize that NPIs and vaccination minimize the impact of the pandemic through distinct mechanisms[32]: the former decreases effective

transmission rates, and the latter increases the number of people who are non-susceptible to infection. Previous mathematical modelling studies[17,18,19,20] designed different vaccination progress simulating the possible trajectories of Covid-19 under the control of NPIs. We estimated the effects of NPIs and vaccination based on the observations of Covid-19 trajectories and data on NPIs and vaccination progress, which provided supplementary knowledge to previous studies by unveiling the impact of vaccination on the effectiveness of NPIs. Specifically, our results demonstrated that the effectiveness of NPIs declined with vaccination progress, instead of non-interfering with each other. In other words, with a more immune population, NPIs might have been less of an effect. NPIs aim to shrink the contact network of the infected population who are still active in society. With the progress of vaccination, the susceptible population in the contact network under the same NPIs would be reduced, leading to a lower efficacy of NPIs. Nonetheless, the progress of vaccination also accompanied various variants emerged, where the very transmissible Delta may confound the decreased effect of NPIs.

Our study was a real-world empirical example par excellence demonstrating that vaccination alone might not be enough to stop Covid-19 without NPIs implementation. Relaxing NPIs before attaining adequate vaccine coverage would enable infection of many more people before their vaccination than would occur if NPIs were to be maintained or increased. Locally, relaxation of NPIs increases the reproduction number, Rt, which enables greater transmission of the virus and a larger overall attack rate. These changes lead to a faster and larger accumulation of infections that could greatly outpace vaccination distribution efforts[33,34]. More importantly, compared with vaccination, NPIs effects were less sensitive to the variants. Of note, the Alpha variant emerged before any vaccination program, while NPIs still showed their

ability in controlling the transmission of Covid-19 against Alpha variants. For example, with respect to vaccination alone, facing aggressive variants such as the Delta variant, over 80% of people need to have immunity to achieve herd immunity (SI Fig. B5). Limited by the weakened effect of various vaccine products against different variants, such a high fraction may be hard to achieve. Furthermore, vaccination has reached most sectors of the population, though inoculation of children under 16 has yet to be recommended. The very population attacked by the recent outbreak of Covid-19, caused by the variants Delta, in China was children instead of previous young people[35], because most adults have been fully vaccinated. It evidenced the importance of the continued implementation of NPIs.

There are several limitations in this study. (1) Despite population structure seems to be a major confounder here, due to the limited data, we assumed that there is no significant difference across age groups either in the transmissibility or efficacy of vaccination. Age is more important to explain morbidity because older age cohorts are associated with more severe infection[36]. In addition, in countries with high attack rates, a portion of the vaccination goes to persons already infected, but the effect has not been considered due to inadequate data. (2) The estimated effectiveness of vaccination has not covered the whole vaccination progress. The implementation style of government intervention has differences across countries[1], especially for regions or continents. Despite the effectiveness of NPIs and vaccination may further vary with conditions change, broader trends in the results were highly consistent across experimental conditions (SI Fig B6). (3) The strength change of government intervention and vaccination may have a delayed impact on the effectiveness[37], and the antibody will decrease over time[38]. To avoid the effect of delay, we performed the estimation for each month and found that our main results were stable over time. (4) We used a general

proxy of NPIs to represent the situations of NPIs implementation instead of studying individual specific NPIs due to inadequate data and collinearity. More discussions can be found in SI.

Our work untangled the effectiveness of government interventions and vaccination on stopping Covid-19 transmission, providing evidence and basis to respond for future Covid-19 resurgence. Currently, NPIs are still the very approach to stop Covid-19, even with a high vaccination rate. In the long term, people who have been infected with SARS-CoV-2 can expect to become reinfected within one or two years, unless they take precautions such as getting vaccinated and wearing masks[39,40]. It suggested deploying NPIs replacing the Covid-19 vaccine booster shot while distributing limited vaccines to the area with low vaccination rates to ultimately stop Covid-19. With the more transmissible variants emerging in the future, NPIs were supposed to be continuously deployed due to their robust effect against variants. Overall, the global health community needs to work together to resolve the remaining knowledge gap on the effectiveness of the Covid-19 vaccine and share the evolving data in a timely manner to support timely policy decisions.

Methods

Data sources and processing

Epidemiological parameters. We used the instantaneous reproduction number (R_t) to represent real-world Covid-19 transmission. In this study, the daily estimates of Rt were calculated from the daily new cases using the Kalman filter[41]. In particular, the dynamics of R_t was considered as

$$R_t = R_{t-1} + \varepsilon_t, \qquad \varepsilon_t \sim i.i.d.N(0, {\sigma_\varepsilon}^2)$$

and output was defined as the growth rate (g_t) of Covid-19 infections, which is derived from the classic SIR model linking to R_t

$$g_t = \gamma(R_t - 1) + \eta_t, \qquad \eta_t \sim i.i.d.N(0, {\sigma_\eta}^2)$$

where γ is the daily transition rate from infected to recovered which is the inverse of the serial interval[42]. The Kalman smoother fitted g_t to the observed growth rates derived from the empirical cases data, to give best estimates of Rt in terms of minimizing mean-squared error. In contrast, to derive the empirical change of transmission trend, we also estimated the instantaneous basic reproduction number ($R_{0,t}$) to capture the intrinsic transmission capability caused by the coronavirus alone. We assembled the biweekly proportion of six main SARS-CoV-2 variants circulated and identified in each of 27 study countries, including lineages B.1.1.7 (*Alpha*), B.1.351 (*Beta*), P.1 (*Gamma*), B.1.617.2 (*Delta*), B.1.525 (*Eta*), and B.1.617.1 (*Kappa*), to estimate $R_{0,t}$ of COVID-19 transmission within each country, according to the basic reproductive number of each variant. We used the weighted average of the basic reproduction number of each coronavirus as the instantaneous basic reproduction number,

$$R_{0,t} = \sum_{i=1}^{7} w_{i,t} R_{0,i}$$

where $w_{i,t}$ is the weight of the basic reproduction number of the coronavirus i ($R_{0,i}$) at day t, calculated by the proportion of infections caused by that virus. The data of SARS-CoV-2 and its related variants was collected from Global Initiative on Sharing All Influenza Data (GISAID)[43] between 21 December 2020 and 20 September 2021. More details of data collation and analysis can be found in SI.

Stringency index of NPIs. We also used a large-scale dataset of non-pharmaceutical interventions collected and assembled by the Oxford Covid-19 Government Response Tracker (OxCGRT)[44]. The stringency index is a composite measure provided by OxCGRT based on their collected nine response indicators including eight containment and closure policy indicators (school closures, workplace closures, public events cancel, gatherings restrictions, public transport closures, stay-at-home orders, internal movement restriction, and international travel controls) and one indicator of public information campaigns, scaled range from 0 to 100 (100 represents implementing the strictest NPIs).

Vaccination data. We first collected the national daily full vaccination rate from *our world in data*[45]. Fully vaccination rate is the statistic of the fraction of the total population who received at least two doses of Covid-19 vaccine. However, different vaccines have various effects against different variants on preventing transmission. To adjust the difference of active variants and the vaccine products across countries, we estimated the practical vaccination rate to represent the practical population protected by the vaccine. To do so, we collected data on vaccine products used in each country over time since December 2, 2020. For each used Covid-19 vaccine product, we

evaluated the daily effect of the vaccine ($e_{i,t}$) as the weighted average of the effect of the vaccine i against the active coronavirus j within the corresponding dates t.

$$e_{i,t} = \sum_{j=1}^{7} vaccine_{i,j} * virus_{j,t}$$

Then, the daily protection rate of vaccination (E_t) was estimated by the weighted average of the daily effect of all used vaccines over time.

$$E_t = \sum_{i=1}^{6} P_{i,t} * e_{i,t}$$

where the weights ($P_{i,t}$) was the proportion of the corresponding used vaccine products. Finally, the national daily practical vaccination rate (EV_t) was estimated by the national daily full vaccination rate multiplying our calculated daily protection rate for the corresponding country.

$$EV_t = V_t * E_t$$

The clinical trial-based effectiveness of each vaccine product against SARS-CoV-2 as well as its different variants are listed in SI Table A2.

Control variables. We used the daily air temperature to account for the seasonal and weather effect on human behaviour, especially human mobility, which possess significant influence on Covid-19 trajectories. We assembled daily air temperatures for all study countries, which were derived from the Global Land Data Assimilation System[46]. Although humidity can better inform us of the weather (such as rainy days), we only used temperature as a control variable in this study, since the humidity was highly associated with the temperature during our study context.

Assessing the effectiveness of NPIs and vaccinations

We measured the empirical change from the instantaneous basic reproduction number ($R_{0,t}$) to the instantaneous reproduction number (R_t) as an outcome variable, representing the amount of the reduction in the Covid-19 transmissibility against different variants context, and interventions and vaccination settings over time. The implemented NPIs and vaccination were two major factors that lead the $R_{0,t}$ to R_t, therefore, we used the generalized linear model to describe the relationship between $R_{0,t}$ and R_t.

$$R_t = R_{0,t}\exp\left(-\alpha x - \beta y - \gamma z + \varepsilon\right)$$

where x, y, and z are the stringency index of NPIs, practical vaccination rate, and air temperature, respectively. The unobserved confounders of the change between $R_{0,t}$ and R_t were represented by the residuals ε. To estimate the model parameters, we further built a Bayesian framework to provide the estimates with prior knowledge. We assumed that $R_t \sim \text{negative binomial}(R_{0,t}\exp\left(-\alpha x - \beta y - \gamma z\right), \sigma)$, where $\sigma \sim \text{half\_normal}(0, 0.5)$. The effect of NPIs can be calculated by $1 - \exp(-\alpha x)$, and $1 - \exp(-\beta y)$ for vaccination. Under the situation, the effect was defined by the amount of the reduction in $R_{0,t}$ regarding R_t, i.e., $1 - R_t/R_{0,t}$.

We used generalized additive regression to study the effectiveness of NPIs and vaccination together. Wherein the outcome variable is the change of R_t, i.e., the change of transmission pattern, and the explanatory variables are NPIs stringency index and vaccination rate. The category, as well as the implementation intensity of NPIs, varied over time, and the vaccination rate also varied over time and across countries. The variations in independent variables allow us to differ the effect of different interventions. Thus, we can assign the variation of Rt to the impact of NPI and vaccination.

To differentiate the impact of vaccination from the effectiveness of NPIs, we first estimated the NPIs effect before the start of the vaccination programme from 1 August 2020. Then, we estimated the separate effect of NPIs and vaccination for each country from their beginning of vaccination to 20 September 2021. Finally, the impact of vaccination on the effectiveness of NPIs was defined by the difference between NPIs effect before and after the vaccination onset. Then, we merged the country-level results to represent the circumstance in European countries and Israel.

The uncertainty of $R_{0,t}$ and R_t was incorporated in our estimation by simultaneous sampling 30 pairs of $R_{0,t}$ and R_t from their distributions for each estimation of the effectiveness. We estimated the effect of NPIs and vaccination for every month to account for seasonal and other calendar effects. All 9,720 estimations (30 pairs of $R_{0,t}$ and R_t × 27 countries × 12 months) were performed using Markov chain Monte Carlo (MCMC) methods. Sensitivity analyses were also performed to assess model robustness in terms of our assumptions. More details can be found in Methods and SI.

Meta-analysis

We pooled the national effectiveness across the studied 27 countries to the regional effect through meta-analysis with the random-effect model[47]. The heterogeneity between national effectiveness was estimated using Cochran's Q and I^2 statistics[48]. We used leave-one-out meta-analysis to evaluate the regional results by omitting one country at a time, aiming to show the individual result effect on the overall estimate derived from the other 26 countries. All calculations were performed using the R meta package[49]. Model validation and more details can be found in SI.

Sensitivity analysis

There were limited studies[50] about the effect of vaccines against the existing variants. We assumed that the unknown effects of different vaccines against various variants were the same as the corresponding vaccine products against SARS-CoV-2 transmission. To assess the impact of our assumption on estimating the effectiveness of NPIs and vaccination, we additionally designed two scenarios of the values of the unknown vaccine effect: i) The same as the corresponding vaccine products against Alpha variant virus transmission; ii) The same as the corresponding vaccine products against Delta variant virus transmission. More details can be found in SI.

Data and code availability

All source code and data necessary for the replication of our results and figures are available at: https://github.com/wxl1379457192/Vaccine-NPIs-in-Europe

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Author contributions

YG, WBZ, XLW and SJL conceived and designed the study, built the model, collected data, finalised the analysis, interpreted the findings, and wrote the manuscript. YZS and MXL collected data. CWR, HYL and JHW interpreted the findings, and revised drafts

of the manuscript. WY, NWR, EC, SHQ, FA and AJT interpreted the findings, and commented on and revised drafts of the manuscript. All authors read and approved the final manuscript.

Ethical approval

Ethical clearance for collecting and using secondary data in this study was granted by the institutional review board of the University of Southampton (No. 61865). All data were supplied and analysed in an anonymous format, without access to personal identifying information.

Competing interests

The authors declare no competing interests.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The views expressed in this article are those of the authors and do not represent any official policy.

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