# Effect of vaccinations and school restrictions on the spread of COVID-19 in different age groups in Germany

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## ARTICLE INFO

## ABSTRACT

With the emergence of SARS-CoV-2, various non-pharmaceutical interventions were adopted to control virus transmission, including school closures. Subsequently, the introduction of vaccines mitigated not only disease severity but also the spread of SARS-CoV-2. This study leveraged an adapted SIR model and non-linear mixed-effects modeling to quantify the impact of remote learning, school holidays, the emergence of Variants of Concern (VOCs), and the role of vaccinations in controlling SARS-CoV-2 spread across 16 German federal states with an age-stratified approach. Findings highlight a significant inverse correlation (Spearman's $\rho = -0.92$, $p < 0.001$) between vaccination rates and peak incidence rates across all age groups. Model-parameter estimation using the observed number of cases stratified by federal state and age allowed to assess the effects of school closure and holidays, considering adjustments for vaccinations and spread of VOCs over time. Here, modeling revealed significant ($p < 0.001$) differences in the virus's spread among pre-school children (0—4), children (5—11), adolescents (12—17), adults (18—59), and the elderly (60+). The transition to remote learning emerged as a critical measure in significantly reducing infection rates among children and adolescents ($p < 0.001$), whereas an increased infection risk was noted among the elderly during these periods, suggesting a shift in infection networks due to altered caregiving roles. Conversely, during school holiday periods, infection rates among adolescents mirrored those observed when schools were open. Simulation exercises based on the model provided evidence that COVID-19 vaccinations might serve a dual purpose: they protect the vaccinated individuals and contribute to the broader community's safety.

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**Abbreviations**

Alpha (B.1.1.7)  The Alpha variant of SARS-CoV-2, first identified in the United Kingdom
Delta (B.1.617.2)  The Delta variant of SARS-CoV-2, initially identified in India
EMA          European Medicines Agency
NLME         Non-linear Mixed-effects (modeling)
NPI          Non-pharmaceutical Intervention
Omicron BA.1  A subvariant of the Omicron variant of SARS-CoV-2
Omicron BA.2  A subvariant of the Omicron variant of SARS-CoV-2
Omicron BA.4/BA.5  Further subvariants of the Omicron variant of SARS-CoV-2, grouped together due to their close
                   genetic relationship and similar epidemiological impact
PCR          Polymerase Chain Reaction
RKI          Robert Koch Institute
RSE          Relative Standard Error
SIR          Susceptible, Infectious, Recovered (model)
STIKO        German Standing Committee on Vaccination
VOC          Variant of Concern
WT           Wild Type

## 1. Introduction

In 2020, the emergence of SARS-CoV-2 resulted in a global pandemic of coronavirus disease (COVID-19), posing a critical challenge to healthcare systems worldwide and demanding effective strategies for the control of the spreading of infections (Ellen Ehni, 2021; Taylor, 2021). Prior to the approval of COVID-19 vaccines, non-pharmaceutical interventions (NPIs) —including school closures, restrictions on public spaces such as restaurants and leisure facilities, as well as mandatory FFP2 mask waring —were key strategies to mitigate virus spreading (Lionello et al., 2022). The efficacy and impact of these NPIs, especially in the pandemic's early stages, were subjects of considerable debate (Talic et al., 2021). School closures, in particular, presented notable logistical challenges, necessitating remote learning infrastructure and imposing substantial burdens on parents and children alike (Freundl et al., 2021). These closures not only disrupted education but also considerably impacted children's social development and well-being (Hume et al., 2023; Hussong et al., 2022; Paulus et al., 2022; Ravens-Sieberer et al., 2020). Considering the typically milder COVID-19 symptoms in children (Yuki et al., 2020) and their hypothesized lower contribution to virus transmission (Ludvigsson, 2020), the necessity of such measures was repeatedly questioned.

With the approval of COVID-19 vaccines, vaccinations emerged as a pivotal tool in reducing infection rates and disease severity (Pritchard et al., 2021). In Germany, however, the initial scarcity of vaccines sparked debates over prioritization strategies. At the end of 2020, the foremost aim of the German Standing Committee on Vaccination (STIKO) COVID-19 vaccination guideline has been to avert critical health incidents, such as hospital admissions and fatalities linked to COVID-19, alongside shielding healthcare workers and individuals in other susceptible professions from SARS-CoV-2 contagions, impeding the spread of the virus, ensuring safety in areas with numerous vulnerable persons and a pronounced likelihood of outbreaks, and upholding vital governmental operations and societal activities (Vygen-Bonnet et al., 2020). Hence, the vaccination rollout initially targeted and prioritized older individuals and workers in professions with a high risk of infection (Steiger et al., 2021). Moreover, the STIKO initially recommended vaccination primarily for adolescents at high risk of severe disease or in high-risk occupations, citing limited data on adverse reactions and estimated minimal impact on transmission rates in younger demographics (Robert Koch-Institut, 2021). This stance evolved over time, with STIKO later advocating for broader vaccination coverage among adolescents (Presse- und Informationsamt der Bundesregierung, 2021a).

The increase in Germany's vaccination efforts in early 2021 coincided with the second wave of infections (week 40 2020—week 08 2021), which, at that juncture, was the most critical wave, primarily impacting the elderly population (Dings et al., 2022). The subsequent third wave (week 09 2021—week 23 2021) saw a shift, with the younger population being more affected, suggesting a protective effect of vaccinations against infection among the older, vaccinated population. Yet, the extent of this protection across different age groups remained a matter of ongoing investigation (Bar-On et al., 2021; Chemaitelly et al., 2022; Sadarangani et al., 2021).

This evolving landscape of the pandemic (Markov et al., 2023; Roemer et al., 2023), marked by fluctuating incidence rates and the emergence of viral strains with increased transmissibility and virulence, potentially undermined the effectiveness of public health measures. The novel strains defined as variants of concern (VOC) added layers of complexity to the unfolding of the pandemic, characterized by variable disease severity, differences in immune status, and altered responses to interventions across age groups. All this underscored the necessity for a more nuanced understanding of the dynamics of SARS-CoV-2 transmissions (Nunes et al., 2024). Hence, it became increasingly important to examine how various factors, including

vaccination status and the implementation of NPIs, influenced the course of the pandemic across different segments of the population. To address this, we adapted and extended a Susceptible-Infectious-Recovered (SIR) model to describe the progression of infections over time across German federal states, stratified by age groups. We estimated the unknown model parameters using non-linear mixed effects (NLME) modeling. This statistical approach enables the analysis of data with both fixed and random effects which allowed us to analyze the differential impacts of fixed effects variables such as vaccination coverage, NPIs, including school closures with remote learning and school holidays, and the emergence of VOCs on SARS-CoV-2 incidence across various age groups over time, while providing a stochastic framework accounting for variability between geographical regions via random effects. Moreover, model simulations were conducted to explore the potential impact of prioritizing vaccinations for the younger population on the spread of SARS-CoV-2.

## 2. Methods

### 2.1. Dataset

Our study made use of an extensive dataset gathered from various sources, with the primary data coming from the Robert Koch Institute (RKI). A detailed list of all data sources can be found in Table 1.

For the period between December 21, 2020 and August 08, 2022, we collected detailed data from Germany including both the number of weekly and cumulative confirmed SARS-CoV-2 infections (Robert Koch-Institut, 2024) and vaccination records (Robert Koch-Institut, 2022), stratified by age groups and German federal states. To ensure analytical consistency, we standardized the age categories of the infection data to match those used in the vaccination dataset: 0–4, 5–11, 12–17, 18–59, and over 60 years. Additionally, we obtained the weekly fraction of confirmed cases infected with each VOC (Robert Koch-Institut, 2023). The dataset further encompasses dates of school holidays, school closures with remote learning and periods of mandatory mask wearing in school settings.

### 2.2. Model development

Our analysis involved an adaptation of the classical SIR compartmental model, specifically designed to estimate both the weekly new and total cumulative confirmed infections across the age groups and federal states in Germany. In this model, the population progresses through the stages of 'susceptible', 'infected', and 'confirmed cases'. Individuals in the 'infected' stage are considered as infected and capable of transmitting the virus. Those classified in the 'confirmed cases' category are assumed to be quarantined, which prevents further transmissions. A notable aspect of our model is the inclusion of immunity dynamics. It is assumed that individuals previously infected with wildtype (WT) or pre-Omicron VOCs are immune to reinfection with these strains for the period of investigation. However, these individuals remain susceptible to the Omicron variant (Arabi et al., 2023).

The transition dynamics for each stage and age group were modeled using a system of ordinary differential equations (ODEs). Parameters were sourced from existing literature along with unknown parameters estimated within our NLME framework. Fig. 1 presents a schematical representation of the used data and parameter identification processes, which are described in detail in sections 2.2.1–2.2.4. Random effects were used to allow the effective reproductive number (Rt) to vary across German federal states. Error models for both cumulative and daily data were considered using proportional and additive error structures. A full list of informed model parameters and fixed effects estimates is presented in Table 2 of the Results section.

The model was implemented in NONMEM® (7.4.3., ICON Development Solutions, Ellicott City, MD, USA). Here, the underlying set of ODEs was numerically solved via LSODA (Hindmarsh & Petzold, 2005). Model parameters were estimated via First Order Conditional Estimation with Interaction (FOCEI) (Wang, 2007). A significant ($p \leq 0.05$; chi-squared test) improvement of the objective function value ($-2$ log-likelihood), precision of parameter estimates reported as relative standard errors (RSE) (Mould & Upton, 2012), as well as visual inspection of the goodness-of-fit plots (Karlsson & Savic, 2007) were used as criteria for model selection.

**Table 1**
Overview of data sources and characteristics for model information and training.

| Data | Time resolution | Stratification | Source |
|---|---|---|---|
| Cumulative confirmed infections | Weekly | Age group, federal state | Robert Koch-Institut (2024) |
| Vaccinations | Daily | Age group, federal state, vaccination details (primary or booster vaccination) | Robert Koch-Institut (2022) |
| Fraction of confirmed cases infected with a specific VOC | Weekly | VOC | Robert Koch-Institut (2023) |
| School closure, school holidays, mask mandates | Daily | Federal state | Government websites, federal press reports |
| R(t) changepoints and between-state variability | Daily | – | Dings et al. (2022) |
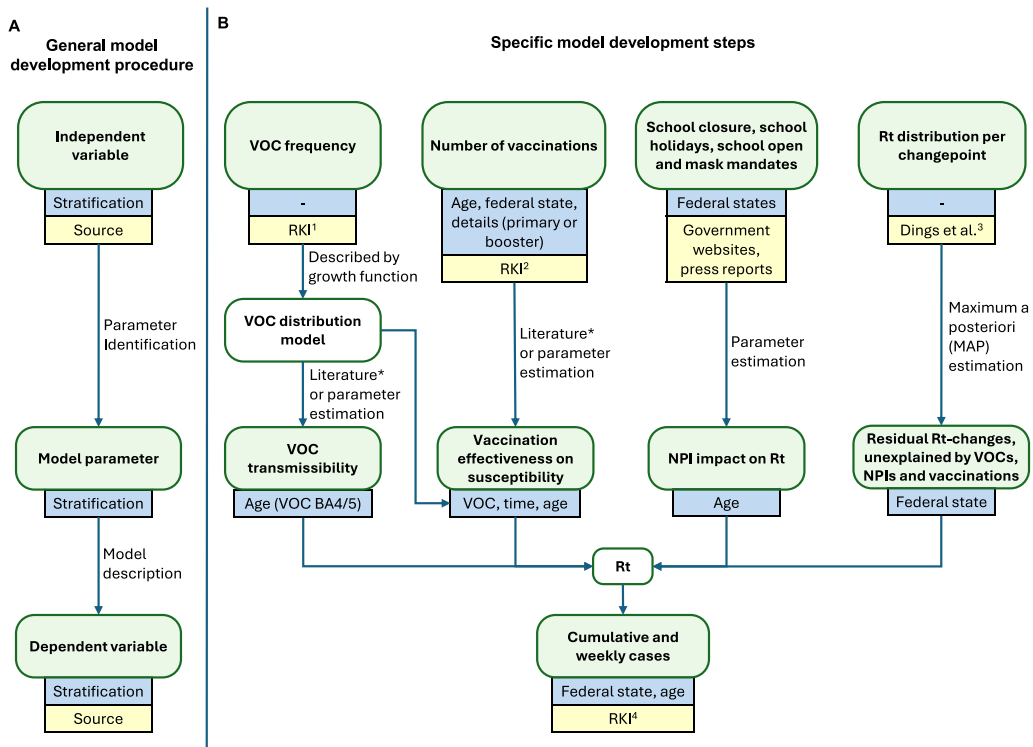
**Fig. 1.** (A) general model development procedure, (B) specific model development steps for the investigated variables. Sources: [1] (Robert Koch-Institut, 2023), [2] (Robert Koch-Institut, 2022), [3] (Dings et al., 2022), [4] (Robert Koch-Institut, 2024), * Sources for model parameters are listed in Table 1 and Supplementary Table 1.

The statistical programming language R 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) was employed for dataset generation, statistical analysis, and generation of plots. With the final model, we conducted simulations to project the impact of varying vaccine coverage levels on prospective incidence rates of different age cohorts.

### 2.2.1. Variants of concern

We obtained information on the proportion of individuals infected with key virus VOCs over time — Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron subvariants BA.1, BA.2 and BA.4/BA.5 — from the RKI (Robert Koch-Institut, 2023).

A specific growth function (Dings et al., 2022) was used to integrate the emergence of these VOCs in the model. This function (see Equation (1)) captures the exponential increase or logistic growth of VOCs within the population over time, thereby enabling dynamic adjustments to the model based on the evolving prevalence of these variants.

$$VOC_{variant}(t) = F_{max} \left/ \left( 1 + \frac{1 - F_{init}}{F_{init}} * e^{-k*(t - t_{init})} \right) \right. \tag{1}$$

Here, $k$ is a VOC-specific growth rate, $F_{init}$ is the initial fraction of infections with a specific VOC (fixed to 0.2% to estimate a corresponding initial time), $t_{init}$ being the initial time and $F_{max}$ is the maximum distribution. This function was fitted via least-squares to the fraction of cases infected with a specific VOC or WT reported by the RKI. Point estimates for parameters regarding VOCs Alpha, Delta, Omicron BA.1, BA.2 as well as BA.4/BA.5 are presented in Supplementary Table 1. The fraction of infected individuals over time with a specific VOC plotted in Supplementary Fig. 1.

In dependence of the fraction described by the growth function, changes in the effective reproductive number attributable to the emergence of the respective VOCs were implemented in the model according to transmissibility changes obtained from literature or derived from the slope of the growth function (see Supplementary Table 1). For VOC BA4/5, observed patterns of age-stratified infections significantly ($p < 0.001$) deviated from the overall population trends. Therefore, the change in transmissibility due to VOC BA4/5 was subsequently refined by stratifying data by age group to achieve enhanced precision.

### 2.2.2. Vaccinations

We sourced the number of individuals vaccinated in each German federal state over time from the RKI's GitHub repository (Robert Koch-Institut, 2022). This data was broken down by age group, vaccine and the specific dose of the administered vaccine (primary or booster vaccination). Throughout our study period, a range of mono- and bivalent COVID-19 vaccines

received approval and became available in Germany. The analysis did not differentiate between vaccine technologies or manufacturers due to the predominance of the BNT162b2 vaccine (BioNTech/Pfizer, Mainz, Germany/New York, United States), representing 73% of administered COVID-19 vaccines by the end of the study period (Robert Koch-Institut, 2022).

In our analysis, we defined 'fully vaccinated' individuals as those who had received, in accordance with the label of the vaccine, one or two doses, with a two-week interval following the final dose. This definition was based on the recognition that the efficacy of most COVID-19 vaccines is limited immediately after the dose. Consequently, in our model, only individuals meeting these criteria were considered 'vaccinated'.

The effectiveness of full vaccinations and booster treatment against infections was implemented for WT/Alpha and VOC Delta via parametrization gathered from literature (see Table 2). For VOC Omicron, the effects of vaccinations were estimated via model fitting (see Table 2 for estimated vaccine effectiveness against infection). Given the known decline in vaccine effectiveness against infections over time, our analysis estimated a specific change point in the effectiveness for individuals aged 18 years and older.

### 2.2.3. Non-pharmaceutical interventions

We gathered data on periods with COVID-19 related school closures, school holidays and mask mandates for each federal state as well as nursery school attendance rules from diverse public sources, including official government websites and media and press reports.

The influence of these NPIs on the infection dynamics of each age was quantified via model parameter estimation. For this purpose, the largest age group (ages 18—59 years) was set as a reference group, and factors expressing increased or decreased virus transmission were estimated for each setting and age group.

### 2.2.4. Rt changepoints and residual variability in Rt

Temporal changes in the effective reproductive number not attributable to VOCs, vaccinations and the previously discussed NPIs were described using specific time points where shifts occurred. These time points and the corresponding median reproduction numbers (Rt's, see Table 2 of the Supplementary Materials) were anchored to values derived from the model previously developed by Dings et al. (Dings et al., 2022), which detailed cumulative cases in German federal states on a daily basis. In numerous instances, the timing of the changepoints could be attributed to modifications in NPI policies (Dings et al., 2022), as presented in Supplementary Table 2.

### 2.3. Model equations

For the structural model, equations (2)—(13) depict key model equations used to describe the number of confirmed cases over time per age group.

$$\frac{dS_{age}}{dt} = -\beta_{age}(t)*\frac{S_{age}(t)}{N_{age}}*I(t)*Nrel_{age} \tag{2}$$

$$\frac{dI_{age}}{dt} = \beta_{age}(t)*\frac{S_{age}(t) + VOC_{Omicron}(t)*SO_{age}(t)}{N_{age}}*I(t)*Nrel_{age} - \gamma*I_{age}(t) \tag{3}$$

$$\frac{dC_{age}}{dt} = \gamma*I_{age}(t) \tag{4}$$

$$\frac{dSO_{age}}{dt} = (1 - VOC_{Omicron}(t))*\gamma*I_{age}(t) - VOC_{Omicron}(t)*\beta_{age}(t)*\frac{SO_{age}(t)}{N_{age}}*I(t)*Nrel_{age} \tag{5}$$

$$\beta_{age}(t) = R(t)*\gamma \tag{6}$$

$$R(t) = \begin{cases} R_0*\log(u_{o,j}) \text{ for } t_0 \leq t \leq t_1 \\ R_1*\log(u_{1,j}) \text{ for } t_1 \leq t \leq t_2 \\ \vdots \\ R_n*\log(u_{n,j}) \text{ for } t_n \leq t \leq t_{n+1} \\ R_{n+1}*\log(u_{n+1,j}) \text{ for } t \geq t_{n+1} \end{cases} *VOC(t, age)*Veff_{age}(t)*NPI(t, age) \tag{7}$$

$$VOC(t, age) = \sum_{i=WT}^{n \in \{Alpha, Delta, BA.1, BA.2, BA.4/5\}} \varepsilon_i * \alpha_{i,age} * \begin{cases} frac_i(t) - frac_{i+1}(t), \text{for i} < n \\ frac_i(t), \text{for i} = n \end{cases} \quad (8)$$

$$Veff_{age}(t) = UVacc_{age}(t) + FVacc_{age}(t)*FI_{age}(t) + FBoost_{age}(t)*FI_{Booster}(t) \quad (9)$$

$$FI_{age}(t) = fs_{age,WT/Alpha}(1 - VOC_{Delta}(t)) + fs_{age,Delta}(t)(VOC_{Delta}(t) - VOC_{Omicron}(t)) + fs_{age,Omicron}VOC_{Omicron}(t) \quad (10)$$

$$FI_{Booster}(t) = fsb_{WT}(1 - VOC_{Delta}(t)) + fsb_{Delta}(VOC_{Delta}(t) - VOC_{Omicron}(t)) + fsb_{Omicron}VOC_{Omicron}(t) \quad (11)$$

$$NPI(t, age) = f_{dist}(t, age)*f_{school}(t, age)*f_{holiday}(t, age)*f_{nurs}(t, age) \quad (12)$$

$$f_x(t, age) = \begin{cases} f_{x,age} \text{ for times of remote learning (x = dist), school open (x = school),} \\ \text{school holidays (x = holiday), nursery school attendance rules (x = nurs)} \\ 1 \text{ otherwise} \end{cases} \quad (13)$$

with $S_{age}$, $C_{age}$, $I_{age}$ and $SO_{age}$ being the number of susceptibles, infected individuals, PCR-confirmed (and quarantined) cases and susceptibles for VOC Omicron, respectively, for each age group. Compartment I represents the sum of infected individuals through all age groups. The total population of the age group is given by $N_{age}$, and $Nrel_{age}$ is the relative proportion of that age group within the total population. The infection rate $\beta_{age}(t)$ depends on change points in the effective reproduction number R(t) (see Supplementary Table 2 and Supplementary Fig. 2), modulation of transmissibility due to emergence of VOCs denoted by VOC(t) (Equation (8)), the effectiveness of vaccinations against the VOCs (Equations (9)–(11)), and age-stratified effects of NPIs (Equations (12) and (13)).

Spontaneous changes in the effective reproduction number (Equation (7)) were estimated for previously derived change points via random effects $u_{i,j}$ for change point i and federal state j with population fixed effects $R_i$ adopted from previous work (Dings et al., 2022). Rt-modulators $f_x(t, age)$ for NPIs were estimated via fixed effects and set to 1 at time NPI-free time periods. The effect of VOCs on change in transmissibility over time VOC(t, age) per age group was calculated based on the fraction of the specific VOC i ($frac_i(t)$ at time t). Here, $frac_i(t)$ was computed via Equation (1). Moreover, $\varepsilon_i$ is the relative increase in transmissibility for VOC i as presented in Table 1 of the Supplementary Materials and $\alpha_{i,age}$ being the age-specific relative change in transmissibility for VOC i (see Table 2 in the results section). For this, $\alpha_{i,age}$ was not estimated (fixed to 1) for WT and VOCs pre-BA.4/BA.5. $FI_{age}(t)$ represents the fraction of vaccinated individuals prone to infection and was fixed to data available in existing literature or, if no data was available, estimated for each age group over time taking the age-specific vaccine effectiveness (fs, see Table 2) into account. In comparison, $FI_{Booster}(t)$ is defined as the fraction of individuals vaccinated by boosters, but still prone to infection based on the booster effectiveness (fsb, see Table 2). As a result of these, $Veff_{age}$ describes the decrease of the effective reproductive number due to vaccinations with $UVacc_{age}$, the fraction of the population not vaccinated, $FVacc_{age}$ the fraction of the vaccinated but not boostered population and $FBoost_{age}$ the fraction of the population that received at least one booster vaccination.

## 3. Results

### 3.1. Data exploration

The data collection period extended from December 21, 2020 to August 08, 2022, coinciding with the initiation of the COVID-19 vaccination campaign in Germany. The first administration of a COVID-19 vaccine occurred on December 26, 2020. Fig. 2 illustrates the vaccination program's progression and impact in Germany comparing the vaccinated fraction of the population stratified by age to the relative incidence. The relative incidence was calculated as the weekly incidence/100 000 inhabitants of the respective age group divided by the weekly incidence/100 000 inhabitants of the total population.

During our study, we observed the prioritization and progression of COVID-19 vaccinations across different age groups in Germany. Initially, individuals aged over 80 years were assigned the highest priority for vaccination, due to their increased risk of severe disease outcomes. This was followed by vaccinations for younger adults who either had a high risk of severe disease or were employed in professions involving contact with high-risk patients. A notable shift in the pandemic's trajectory was observed in May 2021, marking a period when the vaccination campaign had predominantly targeted the elderly population (age 60+). Correspondingly, there was a substantial decline in the relative incidence rate within this age group. The expansion of the vaccination campaign to younger populations was shaped by key regulatory approvals. The European Medicines Agency (EMA) authorized the use of BNT162b2 for adolescents aged 12−17 on May 28, 2021, and later for children aged 5−11 on November 25, 2021 (European Medicines Agency, 2021a; 2021b). Following these approvals, Germany began offering vaccinations to adolescents from June 7, 2021 (Presse- und Informationsamt der Bundesregierung, 2021b). During the summer months of 2021, the relative incidence rates among the age groups 5−11 and 12−17 were observed to be similar

**Table 2**

Model parameter estimates or parameters derived from literature for base model, NPIs, age groups, vaccine effects and VOCs.

| Parameter | Description | Estimate (RSE) or literature value (source) |
|---|---|---|
| **Initialization of the model** | | |
| $R(0)$ | Population Rt value at study initialization (December 21, 2020) | 1.41 (30.9%) |
| $\gamma$ | Rate of exposed individual becoming a PCR-confirmed case [days$^{-1}$] | 1/7 (Dings et al., 2022) |
| $C(0)$ | Number of exposed individuals per 100.000 individuals at study initialization (December 21, 2020) | 106 (60.1%) |
| **Rt factor during school opening for each age group in comparison to reference group** | | |
| $f_{school,0}$ | Rt factor age 0–4 | 0.378 (8.4%) |
| $f_{school,5}$ | Rt factor age 5–11 | 0.445 (9.5%) |
| $f_{school,12}$ | Rt factor age 12–17 | 0.555 (8.6%) |
| $f_{school,18}$ | Rt factor age 18–59 (reference group) | 1.09 (1.9%) |
| $f_{school,60}$ | Rt factor age >60 | 1.05 (3.4%) |
| **Rt factor during school closure with remote learning for each age group in comparison to reference group** | | |
| $f_{dist,0}$ | Relative Rt age 0–4 | 0.811 (5.8%) |
| $f_{dist,5}$ | Relative Rt age 5–11 | 1.13 (4.2%) |
| $f_{dist,12}$ | Relative Rt age 12–17 | 1.48 (2.4%) |
| $f_{dist,18}$ | Relative Rt age 18–59 (reference group) | $f_{school,18}$ |
| $f_{dist,60}$ | Relative Rt age >60 | 0.528 (3.1%) |
| **Rt factor during school holiday for each age group in comparison to reference group** | | |
| $f_{holiday,0}$ | Relative Rt age 0–4 | 0.511 (13.4%) |
| $f_{holiday,5}$ | Relative Rt age 5–11 | 0.963 (5%) |
| $f_{holiday,12}$ | Relative Rt age 12–17 | 1.48 (4.8%) |
| $f_{holiday,18}$ | Relative Rt age 18–59 (reference group) | $f_{school,18}$ |
| $f_{holiday,60}$ | Relative Rt age >60 | 0.524 (7.9%) |
| **Rt changepoint and factor for nursery school children** | | |
| $CP_{NURS}$ | Approximated change date for nursery school attendance rules [days] | 616 (1.3%) = 2021/08/29 |
| $f_{nurs,0}$ | Rt factor after $CP_{NURS}$ age 0–4 | 0.464 (3.6%) |
| $f_{nurs,\neq0}$ | Rt factor after $CP_{NURS}$ age ≠ 0–4 | 1 (fixed) |
| **Rt factor for infections with VOC BA4/5 in comparison to reference group** | | |
| $\alpha_{BA5/5,0}$ | Relative Rt change for infections with VOC BA4/5 age 0–4 | 0.306 (12.1%) |
| $\alpha_{BA5/5,5}$ | Relative Rt change for infections with VOC BA4/5 age 5–11 | 0.232 (11.1%) |
| $\alpha_{BA5/5,12}$ | Relative Rt change for infections with VOC BA4/5 age 12–17 | 0.518 (9.6%) |
| $\alpha_{BA5/5,18}$ | Relative Rt change for infections with VOC BA4/5 age 18–59 (reference) | 1(fixed) |
| $\alpha_{BA5/5,60}$ | Relative Rt change for infections with VOC BA4/5 age > 60 | 1.27 (8.8%) |
| **Vaccination effectiveness** | | |
| $fs_{WT/Alpha}$ | Fraction susceptible for WT or VOC Alpha after full vaccination | 0.08 (Dagan et al., 2021) |
| $fs_{0,Delta}$ | Fraction susceptible for VOC Delta age 0–17 after full vaccination | 0.1 (Lopez Bernal et al., 2021; Sheikh et al., 2021) |
| $fs_{18,Delta}$ | Fraction susceptible for VOC Delta age ≥18 after full vaccination | 0.2 (Lopez Bernal et al., 2021; Sheikh et al., 2021) |
| $fsb_{Delta}$ | Fraction susceptible for VOC Delta after booster vaccination | 0.1 (Fabiani et al., 2022) |
| $fs_{18,Delta}$ | Fraction susceptible for VOC Delta age ≥18 after full vaccination after change date $CP_{Vacc18}$ | 0.3 (Fabiani et al., 2022) |
| $CP_{Vacc18}$ | Change point for vaccination effectiveness $fi_{18,Delta}$ [days] | 636 (0.3%) = 2021/08/18 |
| $fs_{Omicron}$ | Fraction susceptible for VOC Omicron after full vaccination | 0.68 (10.6%) |
| $fsb_{Omicron}$ | Fraction susceptible for VOC Omicron after booster vaccination | 0.338 (10.1%) |

\* WT = wild type, VOC = variant of concern, RSE = relative standard error.
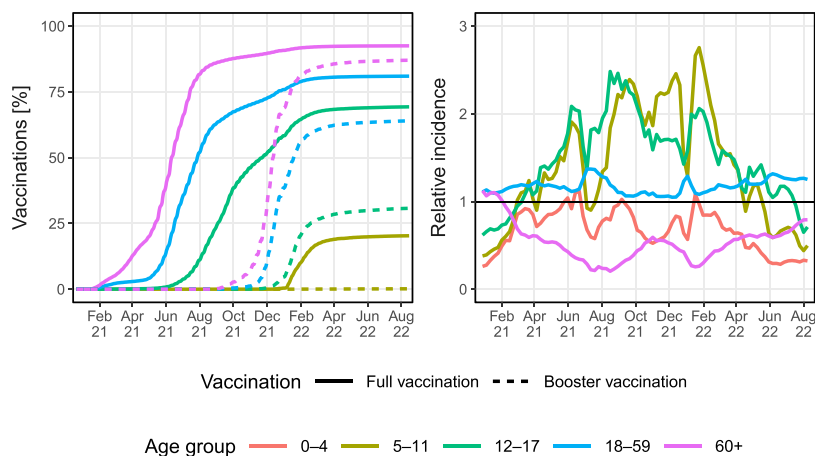


**Fig. 2.** Vaccinations per inhabitants [%] and relative incidences by age group. The relative incidence represents the incidence in the respective age group divided by the incidence across all age groups. Full vaccination: Individual received either one or two vaccinations depending on the respective vaccines' label. Booster vaccination: Individual received at least one additional vaccination after being fully vaccinated.

(Fig. 2). However, a distinct change occurred from October 2021 onwards. The age group of 12−17year-olds began to show a decrease in infection rates, a trend attributed to the rising number of vaccinations within this demographic (Fig. 2).

At the outset of 2022, following the authorization of COVID-19 vaccinations for children aged 5−11 years, Germany experienced its fifth wave of SARS-CoV-2 infections (week 52 2021 − week 21 2022). This wave was notable for recording the highest number of confirmed infections in the country to date. During this period, there were substantial differences in vaccination coverage across different age groups. Our analysis, as illustrated in Fig. 3, revealed a strong inverse correlation (Spearman's ρ = −0.92 (95%CI -0.95 to −0.86) for full vaccinations and ρ = −0.93, (95%CI -0.95 to −0.88) for booster vaccinations, with p < 0.001) between the proportion of the vaccinated population and the maximum incidence rate observed in each age group and federal state, emphasizing the vaccination's effectiveness in preventing infections.

## 3.2. Mathematical modeling

We adapted an SIR model to represent three primary stages: Susceptible individuals, infected individuals capable of transmitting the virus, and confirmed cases. The confirmed cases stage includes individuals who tested positive for SARS-CoV-2 via PCR and were recorded in the RKI register. A key element of our model is its focus on the dynamics of VOC transmission. It incorporates the critical understanding that individuals previously infected with the original strain or earlier VOCs may retain susceptibility to emergent variants, exemplified by the Omicron variant. To illustrate the structure of our model, Fig. 4 provides a schematic diagram that visually represents the progression of the population through these stages, with each circle in the diagram corresponding to an ODE.

The foundational framework depicted in Fig. 4 was initially developed for the entire population. Here, it was adapted and applied to each age group. This adaptation allowed a nuanced examination of virus transmission dynamics within distinct age groups. A critical component of our analysis involved assessing the contribution of the infected population to the transmission level of each age group. This assessment was conducted by aggregating the counts of infected individuals across age groups and applying weights proportional to the population size of each age group. Such weighting was crucial to accurately reflect the varying degrees of exposure and transmission risk across different age groups.

The effective reproductive number was determined for each age group and observed to undergo changes with the emergence of the BA4.5 variant. Additionally, significant changes in Rt were identified for NPIs implemented by federal states, comprising school holiday schedules, COVID-19 related school closures accompanied by remote learning as well as restrictions for nursing school attendance (all p < 0.001). The influence of these factors was assessed for each age group, highlighting the impacts of public health measures on different segments of the population. A changepoint of the effective
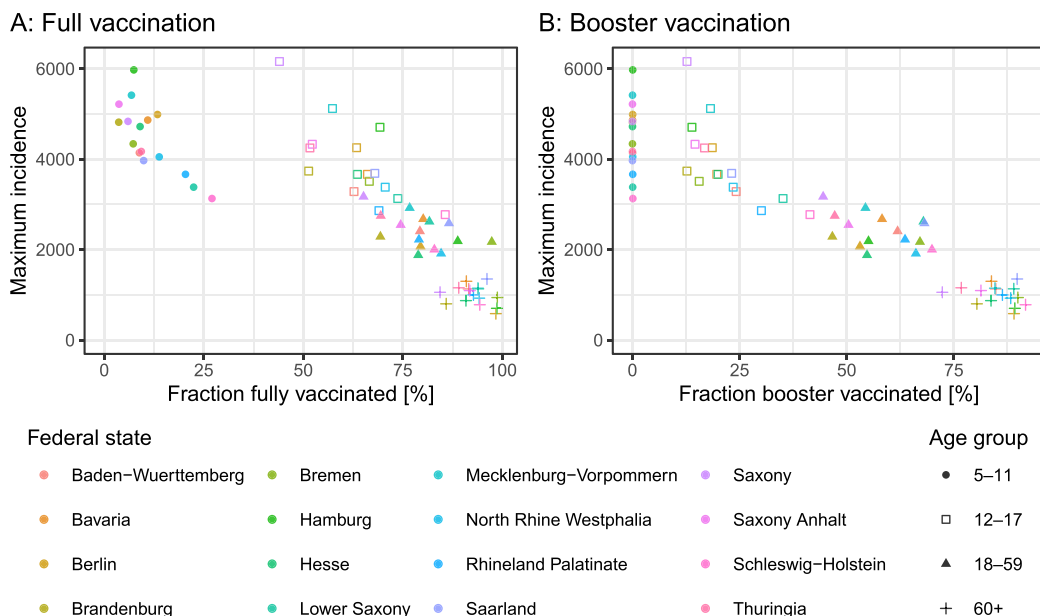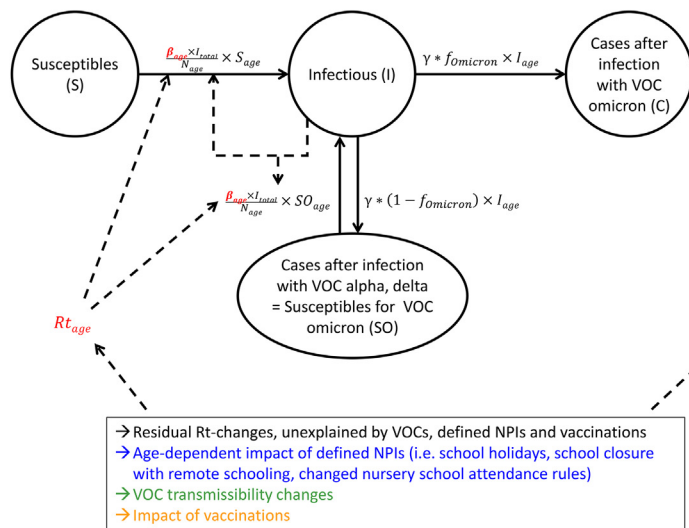


**Fig. 3.** Maximum weekly incidence/100 000 inhabitants from September 1, 2021 to August 8, 2022 vs vaccination rates for full vaccinations (A; Spearman's ρ = −0.92 with p < 0.001) and booster vaccinations (B; Spearman's ρ = −0.93 with p < 0.001) at the respective time point stratified by age group and federal state.

**A: Schematic model representation**

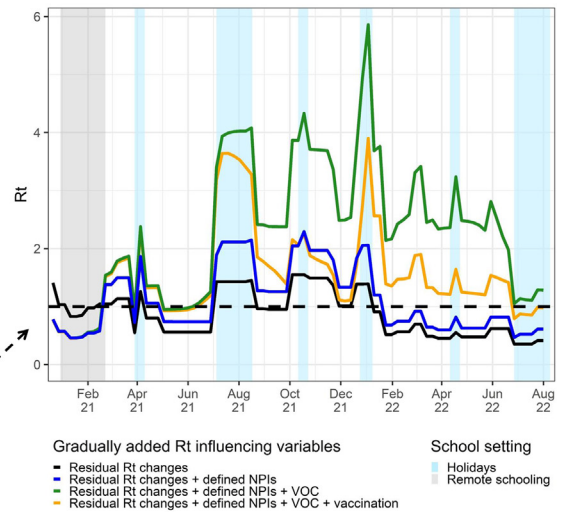**B: Deduction of the effective reproductive number**



**Fig. 4.** A: Schematic representation of the model. Each full circle represents one ODE. Each of the age groups is represented by one of such systems of ODEs. Full arrows indicate the flow of individuals between compartments during the infection process. Dashed arrows indicate the influential processes. B: Effective reproductive number (Rt) vs time for exemplary state North Rhine Westphalia and age group 12–17 years, including the gradual adding of the impact of defined NPIs, VOCs and vaccinations on Rt. NPI: non-pharmaceutical intervention; VOC: variant of concern.

reproductive number was estimated for small children (age 0–4) on August 29, 2021, which coincided with altered attendance rules for sick children in nursing schools.

All fixed effect parameter estimates and model parameters derived from the literature are presented in Table 2.

For model stability and as a reference point, an average deviation from the median Rt obtained from the previously developed model (Dings et al., 2022) was estimated for the largest age group (ages 18–59 years, $\varepsilon_{18}$ in Table 2) and not corrected for implemented NPIs. For all other age groups, the deviations of Rt ($\varepsilon_{age}$ in Table 2) were estimated and corrected for effects of school-related NPIs ($f_{NPI,age}$ in Table 2). These parameter estimates express the relative difference of Rt between different age groups. Fig. 5 visually contrasts the resulting Rt-ratios, calculated by dividing the Rt of each age group or setting by that of the reference group, across the age groups under various settings. It reveals that during periods of school closure with enforced remote learning, the number of SARS-CoV-2 infections among the younger age groups (0–4, 5–11, and 12–17 years) was markedly reduced compared to periods of in-person schooling. Interestingly, the reduction in transmission was less pronounced during school holiday periods. Notably, among adolescents (12–17 years), the rate of infection was observed to increase during school holidays compared to regular school attendance periods.

Furthermore, a drop in virus transmission among infants aged 0–4 was observed towards the end of summer school holidays 2021 (estimated changepoint on August 29, 2021). This drop occurred at a time when many nursing schools tightened attendance rules for sick children with symptoms that can be related to SARS-CoV-2 infections. A significant change (p < 0.001) in vaccine effectiveness of full vaccination against VOC Delta (10%) was estimated for individuals 18 years and older on August 18, 2021 ($CP_{Vacc18}$) due to vaccine waning. At this time, the vast majority of vaccinees 18 years and older were already vaccinated, as displayed in Fig. 2. For the newly emerging VOC Omicron, the effectiveness of the vaccination $VE_{Omicron}$ was lower than the effectiveness of the booster vaccination ($VBE_{Omicron}$). This is in line with the waning effect of the vaccination against VOC Delta, as most vaccinees have been vaccinated for a long time at the emerge of VOC Omicron.

With the emergence of VOC BA4/5, a shift in transmissibility across age groups has been observed, as indicated by the discrepancies between model predictions and the reported infection numbers in Germany. The absence of other plausible explanations for this shift suggests a change in age-dependent susceptibility to VOC BA4/5 as the primary cause (Miyahara et al., 2023; Wiedenmann et al., 2023). Accordingly, new transmissibility factors for each age group ($\alpha_{BA5/5,age}$) were estimated to reflect this change.

We observed moderate variability in Rt across different states, with a coefficient of variation (CV) ranging from 4.4% to 50.3% (see Supplementary Materials Table 2 and Fig. 2). This variability highlighted the differences in transmission dynamics between states. A comprehensive set of Goodness-of-Fit (GoF) plots for all German federal states, highlighting variations in incidence trends across states and age groups, is detailed in Fig. 3 of the Supplementary Materials. Fig. 6, in the main text, exemplifies the model's accurate representation of data for selected federal states. The data clearly demonstrate that the temporal patterns of incidence vary not only among the federal states but also across different age groups.
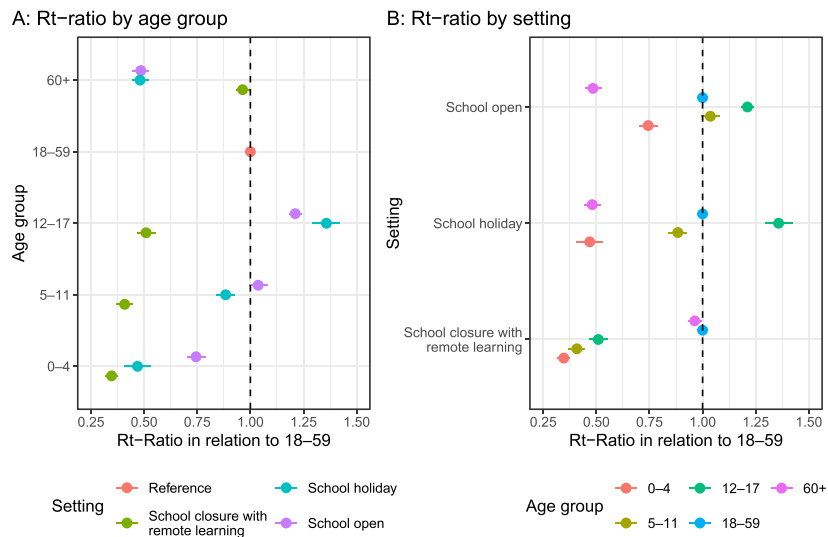
**Fig. 5.** Relative differences in Rt between age group under various NPIs in Germany. The reference category is the predominant age group (18−59 years). Data points represent the estimated Rt ratios, calculated by dividing the Rt of each age group or setting by that of the reference group. Error bars indicate the standard errors associated with these estimates.

Fig. 4 in the Supplementary Materials provides GOF plots that illustrate the model predictions of cumulative confirmed cases and incidence rates, segmented by age groups. Additionally, the figure includes plots of conditional weighted residuals for the predicted incidence rates.

Simulations were conducted to explore the potential impact of prioritizing vaccinations for the younger population (ages 5−17) on the spread of SARS-CoV-2. These simulations utilized vaccination rates for the adult and elderly populations (ages 18−59 and 60+, respectively) based on data from the German Federal Ministry of Health as of January 2023 (Bundesministerium für Gesundheit, 2023): 66% of the 18−59 age group and 85% of the 60+ age group had received booster vaccinations, while full vaccination rates stood at 17% and 5% for these groups, respectively. The vaccination scenarios for the younger population were categorized into three groups: no vaccinations; actual vaccination rates as of January 2023; and a high vaccination scenario, matching the booster rates of the 18−59 age group. The outcomes, illustrated in Fig. 7, indicate that vaccinating younger populations not only curtails the spread of infections among them but also offers indirect protection to the older age groups.

## 4. Discussion

This study utilized an adapted SIR model combined with NLME modeling techniques to analyze the spread of SARS-CoV-2 in Germany, stratified by age groups and federal states. Our findings reveal significant differences ($p < 0.001$) in the virus' spread among pre-school children (age 0−4), children (age 5−11), adolescents (age 12−17), adults (age 18−59), and the elderly (age 60+). Notably, the differential impact of NPIs, emergence of VOCs, and vaccination rates across these age groups provided insights into the dynamics of pandemic control and management.

In our analysis, the transition to remote learning has been instrumental in safeguarding children and adolescents from SARS-CoV-2 infections. This measure effectively decreased exposure risks in these younger age groups. Nonetheless, this protective strategy for the youth has coincided with an increased infection risk among the elderly, particularly those over 60 years of age, who are at the highest risk for severe outcomes from SARS-CoV-2 infections. This observation marks a deviation from the patterns observed during school holidays and periods when schools were operational, where the elderly were less frequently infected relative to the general population, benefiting from focused protective measures. The paradoxical increase in the elderly's infection risk during remote schooling periods could be attributed to the shift in caregiving roles, with grandparents more frequently stepping in to care for children while parents were occupied with work. This scenario likely facilitated greater virus transmission to the elderly. Evidence of this effect can be found in several studies (Chung et al., 2023; de Leeuw et al., 2023; Gilligan et al., 2020; Plagg et al., 2021; Stokes & Patterson, 2020).

To accurately assess the impact of school holidays on infection rates, analyzing data from the German federal states offered a unique advantage due to the staggered timing of school holidays across different states (von Bismarck-Osten et al., 2022). This variability allowed for a clearer distinction between the effects of school holidays and the overall trends in virus transmission. Specifically, among adolescents (age 12−17), the risk of infection remained notably high during school holidays. This sustained risk may be attributed to increased travel during these periods, as suggested by some studies (Plümper &
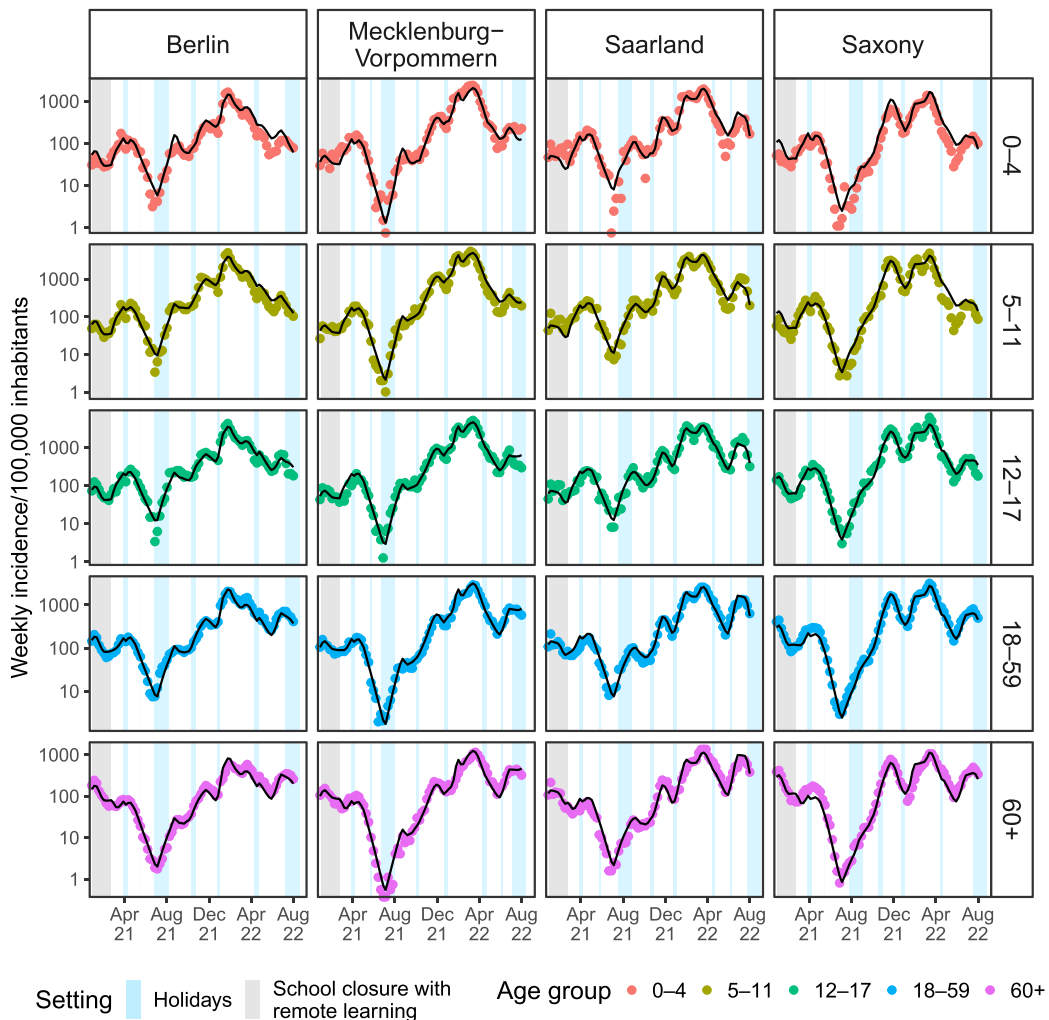
**Fig. 6.** Observed and model predicted weekly incidence/100 000 inhabitants by age group for four exemplary states. Points represent observations. Lines represent model predictions. Grey shaded areas indicate school closure with remote learning. Blue shaded areas indicate school holidays. While areas represent open schools. The full panel presenting all German states is shown in Fig. 4 of the Supplementary Materials.

Neumayer, 2021). Supporting evidence from a study conducted in the summer of 2021 highlighted that for adolescents, the opportunity to travel was among the least influential factors in their decision to get vaccinated (Rothoeft et al., 2023). This suggests adolescents did not perceive their holiday activities to be notably constrained by the pandemic. Generally, the risk of infection for adolescents when schools were operational were higher compared to younger children, likely due to factors such as larger class sizes (Goldstein et al., 2021).

The existing literature on the effectiveness of school closures as NPI presents mixed results (Walsh et al., 2021). While aligning with some studies (Mendez-Brito et al., 2021), the findings of the present simulations, showing that the shift to remote learning proved to be a crucial step in notably lowering infection rates among children and adolescents, differ from the results of a quasi-experimental study conducted in Germany that indicated that neither the summer nor the fall school closures significantly contained the spread of the virus among children or older generations (von Bismarck-Osten et al., 2022). Additionally, Bismarck-Osten and coworkers found no evidence that the return to full-capacity schooling after summer holidays increased infections among children or adults and the number of infections among children was found to increase during the last weeks of the summer holiday and decrease in the first weeks after schools reopened, attributed to travel returnees. While the authors did not explore the effects of VOCs, our analysis expands on this by offering a more detailed examination that includes the impacts of vaccinations and specific VOCs.

In particular, the model-based exploratory analysis comparing age-stratified incidence rates across German federal states with the progression of the 2021 vaccination campaign revealed insightful trends. Following the spring 2021 prioritization of vaccinations for the elderly (60+), a notable decrease in infection rates was observed in this age group during the summer, aligning with the vaccination strategy. In contrast, school-aged children and adolescents (5–11 and 12–17 years old)
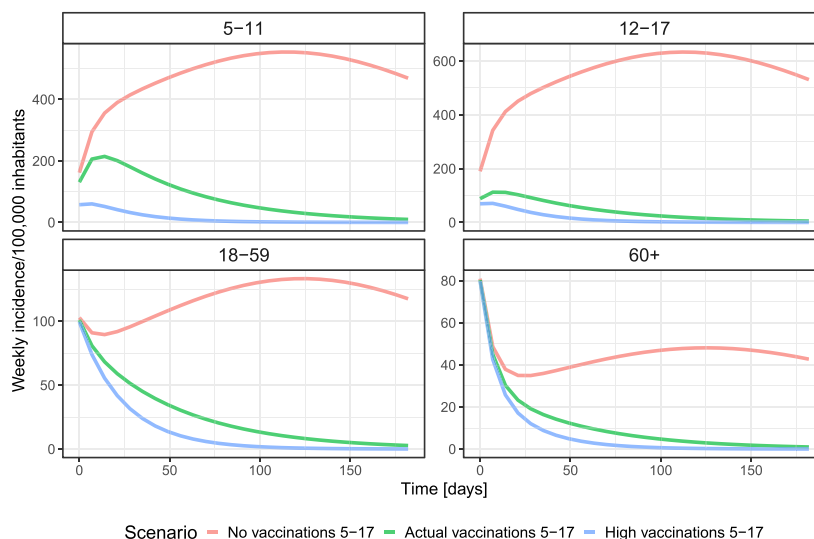
**Fig. 7.** Simulations comparing vaccination rates among younger populations (ages 5–11 and 12–17) under three distinct scenarios. Red lines depict the baseline scenario where the younger cohorts are unvaccinated. Green lines represent the real-world scenario, reflecting the vaccination uptake among these age groups as observed in January 2023. Blue lines illustrate a hypothetical scenario where young individuals are vaccinated at rates comparable to those seen in the 18–50 age group as of January 2023. In all scenarios, vaccination rates among older groups (aged 18–59 and 60+ years) are held constant.

experienced the highest incidence rates during the summer of 2021. However, from October 2021, a reduction in infections among adolescents (age 12–17) could be observed, correlating with the expansion of vaccination efforts to this age group. This temporal association suggests a potential impact of vaccination efforts on reducing infection rates. The relationship between vaccination campaigns and infection dynamics is further explored by analyzing the peak weekly infection numbers in conjunction with vaccination rates across various age groups and federal states. In this context, a robust and statistically significant correlation could be identified between the proportion of the population that received full vaccination, those administered booster doses, and the observed peak incidence rates (both $p < 0.001$ and Spearman's $\rho < -0.9$).

Incorporation of vaccination effects into the model allowed adjusting the infectivity for each age group in proportion to the corresponding vaccination coverage within that group. Differing degrees of immunity conferred by full vaccination and booster doses were modeled to reflect variations in protection levels across the population. The efficacy of vaccines against infections caused by the SARS-CoV-2 WT, as well as the Alpha and Delta VOCs, was parameterized based on efficacy data derived from the literature (Dagan et al., 2021; Lopez Bernal et al., 2021; Sheikh et al., 2021), which also accounted for the waning of vaccine-induced immunity over time (Fabiani et al., 2022). For the Omicron VOC, in the absence of specific studies addressing vaccine efficacy at the time of model development, efficacy rates for full and booster vaccination were estimated at 32% and 66.2%, respectively. These estimates align with the observed reduced vaccine effectiveness against the Omicron variant reported in subsequent research (Chenchula et al., 2022; Jacobsen et al., 2022; Khoury et al., 2021; Zou et al., 2022). In Germany, vaccines were initially offered to the elderly and those in high-risk jobs. The outcomes of our simulations support the effectiveness of this strategy and further reveal the added benefit of vaccinating younger groups, which indirectly safeguards the broader community.

Our study adds to the existing body of scholarly literature on the effectiveness of school closure on the spread of SARS-CoV-2. However, while most studies on this topic are susceptible to confounding due to the simultaneous implementation of other NPIs, vaccinations and the emerge of VOCs (Walsh et al., 2021), our study integrated comprehensive age- and federal state-stratified data coupled with an analysis approach exploiting fixed and random effects. Thereby, our study provides a more contextual insight into the spread of SARS-CoV-2 across different age groups and federal states in Germany, highlighting the interplay between NPIs, vaccinations, and VOCs.

On the other hand, this study encounters several limitations that must be acknowledged. A primary limitation arises from the method of recording vaccination data, which is based on the site of vaccination rather than the individual's place of residency. In contrast to this, confirmed cases were reported based on the individual's place of residency. This discrepancy introduces a potential source of error in estimating the vaccinated population fraction, particularly in federal states with smaller populations where cross-state vaccinations are more impactful. This discrepancy was notably observed in the city states Bremen and Hamburg which reached vaccination coverages of 99.0% and 99.3%, respectively, in the age group of 60+ when vaccination numbers are compared to the number of inhabitants. Additionally, the stratification of vaccination data into specific age groups was constrained by data availability, leading to non-uniform age group distributions. This limitation restricts the precision of our model, especially in accurately incorporating infection patterns across different age groups, as it prevented the use of contact matrices to model the age-specific transmission of infections.

A major limitation arises from the availability of data regarding the number of infections. Our analysis relies on confirmed SARS-CoV-2 infection counts which necessitates the assumption of a consistent ratio of undisclosed or unconfirmed cases across all age groups and over time. Various attempts have been made to estimate the number of undetected infections by leveraging case-fatality ratios, test-positive rates or data from seroprevalence studies (Barbarossa et al., 2020; Rocchetti et al., 2020; Schneble et al., 2021; Staerk et al., 2021). However, these attempts were mostly limited to describing the situation in Germany in the year 2020. Since the beginning of 2021, seroprevalence studies contained less informative value, as sero-positivity could be obtained via infection and vaccination. Additionally, a shift in the age-dependent case-fatality ratio was already discussed to occur during the second wave of infections (Schneble et al., 2021) and even before the emergence of the first VOC. Hence, leveraging case-fatality ratios for the estimation of undetected cases is an intractable challenge with the emergence of VOCs and vaccinations. Moreover, due to the lack of individual-level vaccination data in Germany, it was not possible to implement a time-dependent decline in vaccine efficacy. Instead, a reduced efficacy against the VOC Delta variant was modeled using a change point as described in the Methods section. Lastly, one should account for variability in testing strategies, which could affect the accuracy of estimated model parameters (Nunes et al., 2024). However, the test positivity rate was not available stratified by age group, which rendered its informational content less valuable for our purpose. Amidst the unknown proportion of undetected cases, the implementation of routine screening among children through Point-of-Care antigen tests in schools, contrasted with the selective testing of adults, introduces a bias that may overestimate or under-estimate the actual infection rates within these groups, respectively. Particularly, the shift to remote schooling and the consequent reduction in routine testing among children could obscure the true rate of asymptomatic infections, potentially overstating the impact of school closures on infection rates in this age group. The study acknowledges the challenge of capturing the varied implementation of NPIs across federal states yet offers insights into their diverse impacts. Given the complexity and varied nature of NPIs, coupled with the constraints in age stratification, our study focused selectively on key NPIs that directly affected younger age groups, notably policies regarding the operation and closure of schools. This selective consideration may not fully capture the comprehensive impact of NPIs on virus transmission dynamics across all de-mographics and settings.

## 5. Conclusions

In this study, we employed mathematical modeling to dissect the interplay between NPIs, vaccination strategies, and the dynamics of SARS-CoV-2 spread across different age groups within the German population. Our findings underscore the differential impact of school closures and vaccination efforts on modulating infection rates among children, adolescents, and the elderly. Key insights reveal that remote schooling effectively reduced viral spread among the youth, whereas vacation periods saw elevated transmission rates among adolescents, suggesting a nuanced role of behavioral factors in infection dynamics. Notably, the initial prioritization of vaccinations for the elderly and high-risk occupations, followed by extended coverage to younger demographics, demonstrated a discernible reduction in infection rates across all age groups, corrobo-rated by a significant correlation ($p < 0.001$) between vaccination rates and lowered incidence peaks.

## Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Christiane Dings:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Dominik Selzer:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nicola Luigi Bragazzi:** Formal analysis, Writing – review & editing. **Eva Möhler:** Writing – review & editing. **Markus Wenning:** Writing – review & editing. **Thomas Gehrke:** Writing – review & editing. **Ulf Richter:** Writing – review & editing. **Alexandra Nonnenmacher:** Writing – review & editing. **Folke Brinkmann:** Writing – review & editing. **Tobias Rothoeft:** Writing – review & editing. **Michael Zemlin:** Writing – review & editing. **Thomas Lücke:** Writing – review & editing. **Thorsten Lehr:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2024.07.004.

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