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Evaluating Age-specific rate of norovirus in German: a Bayesian Age-cohort analysis

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Abstract

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By Changrui Ou

Noroviruses are the leading cause of acute gastroenteritis worldwide. The GII.4 genotype has been the dominant genotype worldwide. While infants and young children are known to be susceptible to all noroviruses, the impact of novel GII.4 strain on adult's immunity response is not fully investigated. To examine the age-specific pattern of norovirus incidence in general population, we conducted a Bayesian Age-cohort model reporting age and cohort effect that accounts for the change of incidence among individuals who were born after 1995 in Germany. In terms of birth cohort, we found a significant signal of immune escape from the difference in incidence rate at age 5-15 between Cohort born in 2002, 2004, 2006, and the one born in 2012. In terms of age effect, incidence rate has the greatest decrease at age 7, while it has the greatest increase at age 1. These results have implications for future public health interventions and vaccine development to understand the further impact of early exposure of GII.4 strains on later experience of norovirus infection.

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Table of Contents

Chapter I: Background & Literature Review

Disease Burden

In spite of a significant global reduction in death from diarrheal disease[1], norovirus, as a global leading cause of Acute Gastroenteritis (AGE) is estimated to cause more than 200,000 deaths worldwide annually[2], resulting in economic burden both in health care delivery (US$4.2 billion, 95%UI: $3.2-5.7 billion) and society (US$60.3 billion ,95% UI: $44.4-83.4 billion)[3]. The disproportionate impact of norovirus disease burden is primarily evident in three factors:

(1) Age: norovirus affects the population at all ages but resulting in larger extents to burden on children and the elderly: Globally, proximity in prevalence of norovirus are shown between patients who are 0-4 year old (18%, 95%CI: 17-20%) and patients older than 5-year-old (18%, 95%CI: 13-24%)[4]. However, young children under age 5 are associated with the highest incidence rate and second highest mortality rate of norovirus disease[2, 5, 6], resulting in the greatest disease burden among all ages [2, 3]. Despite the highest incidence rate found in young children, both young and old patients are likely to suffer severe outcomes of norovirus[7]. The highest rate of hospitalization is in patients 0-4 year old (9.4 hospitalizations per 10,000 population) and patients who are over 65 year old (8.1 hospitalizations/10,000 population), who also have the highest mortality rate (0.20 deaths/10,000 population)[8].

(2) Region: norovirus outbreaks can be observed across various regions and both in developing and developed countries. In a systematic review by Ahmed et al, prevalence of norovirus was shown to be lower in developing countries with high all-cause mortality (14%, 95%CI: 11-16%; p=0·058) than in developed countries (20%, 95%CI: 17–22%) [4],which is likely explained by the predominance of other diarrhea-related pathogens[9] and potential diminishment of vaccine effectiveness against these

pathogens (e.g., rotavirus vaccine) in the low-income setting. Setting: High risk community settings for norovirus outbreak include healthcare facilities, schools, and cruise ships, where close contact and shared facilities the transmission of norovirus [10-12].

Epidemiology

Mode of transmission

Human noroviruses is primarily transmitted via: (a) Person-to-person contact (e.g., touching vomits or diarrheas from an infected people and touching their mouths); (b) Food-borne transmission (e.g., having food contaminated by norovirus), and (c) Water-borne transmission (e.g., drinking liquids from a contaminated water source). Person-to-person contact was reported as the main transmission route in more than 80% norovirus-related outbreaks [12-14]. While person-to-person transmission is most common, the impact of foodborne outbreaks is considered underestimated due to a lack of existing surveillance data [15, 16]. Despite the identification of norovirus in animals[17-19], zoonotic transmission route is still hypothetical due to a lack of evidence on its role on human infection.

Transmissibility

There are several Attributes of norovirus contribute to its heightened capacity for transmission:

(1) Low volume of inoculum to provide infection: The infectious dose required for norovirus infection is extremely low, ranging from 18 to 100 viral particles[20, 21].

(2) Prolonged viral shedding: The median of duration of norovirus detection after viral inoculation is 4 weeks (up to 8 weeks), and peak viral shedding happens 2-5 days after infection[22, 23]. Insignificant difference in viral shedding, including duration of viral

shedding and peak shedding titers, was found between asymptomatic and symptomatic infections, suggesting that the occurrence of symptom is related to host susceptibility to norovirus[24].

(3) Environmental stability: norovirus particles may maintain their infectivity for 2 weeks on any environmental surfaces and for over 2 months in water[25, 26]. Higher temperature is associated with diminishment of norovirus activity[27].

Genetic and Molecular Epidemiology

Genome

Noroviruses are a group of nonenveloped viruses with single-stranded RNA genome in the family Caliciviridae, noroviruses[23]. The norovirus genome includes three overlapping open reading frames (ORFs) - The first ORF (ORF1) encodes the region of RNA-dependent RNA polymerase (RdRp), which is critical in norovirus genome replication[28]. ORF2 encodes a viral capsid protein (VP1), while ORF3 encodes a minor structural protein (VP2) [21].

Classification

Norovirus was detected primarily via partial RdRp sequence[29, 30], until an updated method of dual-typing for norovirus designation is proposed[31]. Based on the diversity of complete VP1 amino acid sequence (> 85% sequence similarity would be categorized into a genotype[32, 33]) and nucleotide diversity of RdRp gene in ORF1, norovirus can be segregated into 10 genogroups, genotypes, and more than 60 RdRp types (P-type)[34]. Dual typing is considered to facilitate researcher to correctly identify norovirus strains recognizing that viral recombinants from ORF1-ORF2 joint region is common[35, 36].

Norovirus diversity and taxonomy

Norovirus can undergo rapid evolution through antigenic variation via two mechanisms: recombination and point mutations. Point mutation refers to the changes that occur at a single nucleotide base within a genome. Lindesmith et al. found that the emergence of GII.4 new variants was influenced highly by the antigenic variation of neutralizing epitopes A-E within capsid P2 domain[37], and further that flexibility of epitope D is one of the important factors for the evolution of GII.4 strain[38]. On the other hand, recombination refers to the exchange of genetic material between two different viral genomes that infect the same host cell. The GII.4 Sydney capsid persisted through recombination, with novel recombinants including GII.P16–GII.4 Sydney 2012[39].

Noroviruses are now classified into ten genogroups (GI-GX), among which GI, GII, and GIV is known to affect human infection[23]. The genetic diversity of norovirus is demonstrated in Genogroup I (9 genotypes) and Genogroup II (27 genotypes. GII is responsible for more than 90% sporadic infection and norovirus-related outbreaks worldwide[39, 40]. GII.4 has been the most common variant of sporadic infection and viral gastroenteritis outbreaks worldwide since 2001[41, 42].

The emergence of new GII.4 variants usually happens periodically for 2-4 years[43].There are six GII.4 variants (the 1996, 2002, 2004,2006b, 2009, and 2012 variants) that have been associated with the global epidemics identified in the global scale[39, 41], New Orleans 2009 and Sydney 2012 variant were shown to emerge through the mechanism of recombination[44], among which the Sydney capsid persisted over a decade with novel recombinants, such as GII.P16-GII.4 and GII.Pe – GII.4[39] In Europe, an increase in norovirus cases can also be attributed to non-GII.4 variants, specifically GII.P17-GII.17.[39]. Specifically in German, non GII.4 strain (GII. P16-GII.2) is also found attributed to steep rise in norovirus cases in Germany in 2016[45].

Epidemiological impact of genetic diversity

GII.4 variants are more likely to be spread from person to person[12], while GII.6 and GII.12 strains are more associated to foodborne outbreaks[46]. GII.4 is also more frequently found in hospital settings than GI and GII.non-4 genotypes. Young children (<5 yr.) are more susceptible than the older children to be infected with GII.4 variant[47]. GII.4 strain is more associated with healthcare setting than the non-GII.4 variant [48].Although other genotypes peak in winter months during most seasons, GII.4 winter seasonality was predominantly responsible for the U.S. norovirus winter seasonality between 2013 and 2016[49]. In comparison to other genotypes, GII.4 outbreaks have greater rates of hospitalization and fatality[50].

Immune escape of norovirus may have differential impacts for young children and adults. All norovirus subtypes affect norovirus-naïve children, while adults show higher susceptibility to new GII.4 variants despite immunity to previous GII.4 variants.[38, 47]. One of the factors affecting the evolution rate of norovirus may be the duration of population immunity. The duration of immunity to norovirus gastroenteritis ranges from 4.1 to 8.7 years[51]. However, its difference between young children and adults is unknown, which may be further elucidated by birth cohort studies [52].

Surveillance

Surveillance systems have been set up in some countries and regions. In the United States, there are two surveillance networks – CaliciNet[53] and National Outbreak Reporting System (NORS)[10] – that report norovirus gastroenteritis outbreaks, both established by CDC. The European Centre for Disease Prevention and Control (ECDC) monitors norovirus-related outbreaks via Food- and Waterborne Diseases and Zoonoses (FWD)

network, while the non-governmental initiative NoroNet also plays an important role in norovirus surveillance[39]. There are initiatives and networks assisting the norovirus surveillance in Low- and middle-income countries (LMICs), such as Global Enteric Multicenter Study (GEMS)[9]. In German, there is a national surveillance system on norovirus after it is recognized as a notifiable illness according to the Protection Against Infection Act of 2001[54].

Chapter II: Manuscript

Title

Evaluating Age-specific rate of norovirus in German: a Bayesian Age-cohort analysis

Authors

Changrui Ou; Jessica Rothman; Ben Lopman, MSc, PhD

Abstract

Noroviruses are the leading cause of acute gastroenteritis worldwide. The GII.4 genotype has been the dominant genotype worldwide. While infants and young children are known to be susceptible to all noroviruses, the impact of novel GII.4 strain on adult's immunity response is not fully investigated. To examine the age-specific pattern of norovirus incidence in general population, we conducted a Bayesian Age-cohort model reporting age and cohort effect that accounts for the change of incidence among individuals who were born after 1995 in Germany. In terms of birth cohort, we found a significant signal of immune escape from the difference in incidence rate at age 5-15 between Cohort born in 2002, 2004, 2006, and the one born in 2012. In terms of age effect, incidence rate has the greatest decrease at age 7 ($\beta_{a=7} = -1.044, (95\%CI: -1.052, -1.037)$), while it has the greatest increase at age 1 ($\beta_{a=1}$=$1.142, (95\%CI: 1.137, 1.147)$). These results have implications for future public health interventions and vaccine development to understand the further impact of early exposure of GII.4 strains on later experience of norovirus infection.

Introduction

Norovirus is one of the leading pathogens of sporadic cases and outbreaks of acute gastroenteritis (AGE) worldwide, causing ~20% of diarrheal disease and more than 200,000 deaths worldwide annually[2]. Norovirus is often self-limiting and has short duration of illness. Vulnerable populations such as young children, elderly, and immunocompromised

individuals are likely to suffer prolonged morbidity and more severe outcomes of norovirus[7, 55]. Large norovirus gastroenteritis outbreaks can occur in the high risk community settings[8], including healthcare facilities, schools, and leisure facilities, where close contact and shared facilities facilitate transmission[12]. The heterogeneous distribution of norovirus infections emphasizes the importance of understanding the health impact of norovirus infection on different ages.

GII.4 virus is the most predominant genotype worldwide over at least two decades[39, 40]. GII.4 noroviruses has a remarkable ability to evolve rapidly due to its antigenic profile, resulting in escape from the herd immunity and contributing to recurring infection[37]. To date, there have been six GII.4 strains associated with global pandemics[39], among which GII.4 Sydney 2012 has been the prevalent strain over this decade and persists through recombination[39]. Additionally, although young children are susceptible to contracting various norovirus strains, adults tend to be more prone to infection from emerging GII.4 variants, despite previous exposure to the virus[38, 47]. Understanding the epidemiological impacts of genetic diversity and evolution of norovirus is critical for the development of targeted interventions and to inform surveillance efforts.

In Germany, norovirus was recognized as a notifiable disease in the Protection Against Infection Act of 2001 in German[54], and a national electronic database of norovirus is available at Robert Koch Institute (RKI), which plays a vital role in monitoring disease trends and outbreaks routinely. Several studies have used the RKI database to investigate various aspects of norovirus, including genotypic distribution[56], spatiotemporal trends[54], and the outbreak investigation[57]. By leveraging this uniquely detailed dataset, we are able to investigate the age-specific patterns of norovirus incidence and examine the impact of novel GII.4 variants, in which knowledge gap remains. In this study, we aim to estimate age-specific norovirus incidence rates for the individuals who

were born after 1995 in Germany.

Methods

There are four study steps following: 1) Data extraction and management into an analyzable form; 2) Fitting Bayesian Age-cohort (APC) model to data; 3) Calculating the age-standardized rate using a scaling factor. 4) Interpretation of the results.

Data source

We extracted data on cases count of norovirus illness in Germany (Date of query: Nov 11th, 2022), which is freely available at https://survstat.rki.de/Content/Query/Create.aspx. The population size was derived from the population number of age groups during the same time period, collected by United Nations Statistics Division[58].

Data structure

In our study, we required the age-specific rate at 1-year interval, encompassing 27 age groups (ages 0-26 years) and 21 reporting years (2001-2021). We defined a birth cohort as a group of individuals who were born in the same year, calculated as the difference between the reporting year and the corresponding age group.

Bayesian Age-cohort Models

Age-period-cohort (APC) analysis is a powerful method for examining disease patterns over three-time scales: age, period, and cohort. The definition of three time scales has been stated somewhere[59]. We further hypothesized the three-time effect in the context of norovirus epidemiology:

(1) *Age effect*: This refers to the biological and social effects of aging, including the

difference in host susceptibility and social mixing level of norovirus between different age groups.

(2) *Period effect*: This refers to an event that has an impact on all age groups at a particular point in time. We hypothesize the emergence of novel GII.4 strains as a period effect in that the incidence rate across all ages in years of emergence of novel GII.4 strains increases.

(3) *Cohort effect*: This refers to the experience unique to a group of individuals born in the same period, calendar year in this case. We hypothesize the early exposure of novel GII.4 strains as a cohort effect interested in our study, in that a birth cohort with early exposure to novel GII.4 strains may exhibit differences in varying infection rates or duration of immunity among different age groups, comparing with one without early exposure of novel GII.4 strains.

A Bayesian Age-Cohort model using the Integrated Nested Laplace Approximation (INLA) approach was used to estimate the incidence of norovirus infection. INLA has been widely applied in epidemiological studies with its computational efficiency for fitting complex Bayesian models[60-66]. In terms of model fitting, we assumed that the distribution of case counts y_{ac} in age group a at birth cohort c follows a Poisson distribution with mean $N_{ac}\lambda_{ac}$ (Equation 1.1), with N_{ac} denoting the population size for each age group by given birth cohort. We specified the linear predictor $n_{ac} = \log(\lambda_{ac})$ (Equation 1.2) and considered the variability in age and cohort as the random effect. We assumed that both the parameters and their variances are drawn from inverse gamma distributions as priors. (Equation 1.3). In addition to these model components, we also incorporated random walk priors for the age and cohort effects to allow for smooth trends over time. This approach enabled us to capture non-linear patterns in the data while maintaining the interpretability of the model results.

$$y_{\alpha c}|\lambda_{\alpha c} \sim Poisson(N_{\alpha c}\lambda_{\alpha c}) \quad (1.1)$$

$$n_{ac} = \delta + \alpha_{\alpha} + \beta_c + \epsilon + Z_{\alpha c} \quad (1.2)$$

where:

α: age effects; β: cohort effects; δ: change in case reporting indicator; Z: overdispersion.

$$\alpha|\sigma_{\alpha}^2 \sim RW2(\sigma_{\alpha}^2)\,, \beta|\sigma_{\beta}^2 \sim RW2\left(\sigma_{\beta}^2\right), z_{\alpha c}|\sigma_z^2 \sim N(0, \sigma_z^2)\,, \epsilon \sim N(0, \sigma_{\epsilon}^2), \delta \sim N\left(0, \sigma_{\delta}^2\right) \quad (1.3)$$

$$\sigma_{\alpha}^2, \sigma_{\beta}^2, \sigma_z^2, \sigma_{\epsilon}^2, \sigma_{\delta}^2 \sim InverseGamma(1, 0.005)$$

Incidence rates adjustment

We adjusted the age-specific rate based on two considerations: (1) under-reporting bias, and (2) varying incidence rates at age of birth between different cohorts.

We applied a scaling factor sf to adjust the time-dependent under-reporting bias before 2011 due to change of case definition[67]. This is derived by dividing the mean rate at age 0 from pre-change period $\bar{r}_1$ (i.e., 2001-2010) by the mean rate at age 0 from post-change period $\bar{r}_2$ (i.e., 2011-2021) (Equation 1.4). We then derived the adjusted age-specific rate ar_a by dividing the scaling factor by age-specific rate in any age group α from 2001-2010, while maintaining the age specific rate from 2011-2021(Equation 1.5).

We furthered derived the cohort-specific rate ratio by dividing incidence rate of at age 0 in any given birth cohort by incidence rate of at age 0 from year 2011 as the reference group (Equation 1.6). This approach makes the strong assumption that rates among <1yr old children was the same every year. We further derived the adjusted age-specific rate by dividing this rate ratio by the incidence rate of age 0 in any given birth cohort. (Equation 1.7):

$$sf = \frac{\bar{r}_1}{\bar{r}_2} \tag{1.4}$$

$$ar_\alpha = \frac{r_{1\alpha}}{sf} \tag{1.5}$$

$$rr_{0,p_i|p_1} = \frac{r_{0,p_i}}{r_{0,p_1}} \tag{1.6}$$

$$ar_{a_0c} = \frac{r_{a_0c}}{rr_{0,p_i|p_1}} \tag{1.7}$$

Statistical testing

To further investigate the potential cohort effect on age-specific rates, we performed a multiple comparison on the age-specific rate for different cohorts using Bonferroni test. We further stratified the multiple comparison into three age group:(a) age 0-4, representing “young children”; (b) age 5-15, representing "older children”, and (c) age 16+, representing “young adults”. Our analysis is specifically designed to compare rates between cohorts while maintaining a consistent age group for each comparison.

Results

We first described the output from Bayesian INLA model, including the posterior precision parameter estimates and model diagnostics. We additionally illustrated age-specific rate grouped by age*cohort, age*period. Here, "age" denotes 1-year age intervals, "period" represents reporting years, and "cohort" refers to birth cohorts (i.e., a group of individuals born in the same period). We also highlighted the year of emergence of six key GII.4 strains in plots: (1) US 1995/96:1995; (2) Farmington Hills: 2002; (3) Hunter: 2004; (4) Den Haag: 2006; (5) New Orleans: 2009, and (6) Sydney: 2012. To capture the potential impact to early exposure of novel GII.4 strains, we also identified the birth cohort corresponding to the emergence of any GII.4 variant in its birth year.

Explanatory analysis of model components

We assessed how much the age and cohort effects vary between age groups and birth cohorts by examining the posterior precision parameter estimates derived from the Age-Cohort model output (Table 1). Key observations include:

(1) Incidence rate has the greatest decrease at age 7 ($\beta_{a=7} = -1.044, (95\%CI: -1.052, -1.037)$), while it has the greatest increase at age 1 ($\beta_{a=1}$=$1.142, (95\%CI: 1.137, 1.147)$).

(2) After controlling for cohort effect, the incidence rate increases for age groups 0-2, followed by a decrease in age groups 3-15, and reverses to increase again at age 16-26.

(3) After controlling for age effect, the incidence rate increases gradually with more recent birth cohorts.

Age & Cohort

We presented the age-specific rate at 1-year interval, grouped by birth cohorts (Figure 1). Generally, all birth cohorts exhibit a consistent pattern of norovirus gastroenteritis, characterized by the highest incidence at ages 0-2, followed by a sharp decrease in incidence rate, plotted on the log scale in Figure 1. All cohorts reach the lowest incidence rate on older children (5-15), succeed by a gradual increase to the end of cohort's follow-up. (Figure 1b). Notable observations from key cohorts exposed to norovirus strains early on include:

(1) Cohort born in 2006 and 2009 exhibit a higher incidence rate at age 1 compared to the cohort born in 2012.

(2) Cohort born in 2006 displays a pronounced decline at ages 4-5.

(3) Cohort born in 2004 reveals a sharp decrease at ages 6-7.

(4) Cohort born in 2012 becomes the cohort with the highest age-specific rate after age 5.

Age & Period

The age-specific rates are plotted by year of reporting (Figure 2) We categorized the period using the year of emergence of any GII.4 strains (Figure 2a) to examine the period effect of the GII.4 strain emergence. Overall, all periods exhibit a similar early-life pattern observed in the age-cohort plot, characterized by a sharp increase in incidence rate at age 1 followed by a decline from ages 2 to 7. Notable observations from key periods exposed to norovirus strain include:

(1) The age-specific rate in the emerging year of New Orleans 2009 is higher than that in the year when Sydney 2012 emerges.

(2) Beyond age 7, years of emergence of New Orleans 2009, Den Haag 2006b, and Hunter 2004 emerge demonstrates a potential reinfection signal as the incidence rate begins to rise, while the year when Sydney 2012 emerges maintains a downward trajectory but at a diminished rate before eventually reversing the trend at age 12.

Pairwise Comparison

We presented the results of multiple comparisons between age-specific rates for birth cohorts exposed to novel GII.4 strains during their birth years. (Table 2). Our findings reveal that the incidence rates among birth cohorts exhibit no significant differences for age groups 0-4 and 16+ but the age group 5-15 (i.e., older children). Key observations from pairwise comparison with key birth cohorts in the age group 5-15 include:

(1) Except for the cohort born in 2009, the incidence rate of all birth cohorts born in years with novel GII.4 strain emergence is not significantly different from those born in years with no emergence of novel GII.4 strain.

(2) The incidence rates of cohorts with the early exposure of novel GII.4 strain are insignificant different from the cohort with adjacent strains (e.g., cohort 2002 – 2004, 2004 – 2006, …), while, except for the pair of 2004 and 2009 cohort, a pair of cohorts that is non-adjacent are showing significance in norovirus infection rates.

Discussion

Main findings

Our study disentangles the effect of age, period, and cohort on norovirus incidence patterns using a Bayesian Age-Cohort Model, revealing several main findings. Firstly, our findings demonstrate a clear age-specific pattern with the highest incidence rate at under 2 years of age, which is consistent with previous estimates of age-specific rates of norovirus infection that over 80 percent of infections occur by age 5[68-70]. Secondly, Incidences at age 1 detected in the year of New Orleans 2009 and Den Haag 2006b are higher comparing to the subsequent Sydney 2012. suggesting that the 2009 and 2006b norovirus strains possess a greater virulence or signal of immune escape than the Sydney 2012 variant. Patterns of incidence change beyond age 7 are also different between the year of Sydney 2012 and the older variant, suggesting that the duration of immunity of norovirus is also variant-specific. The cohorts with early exposure of novel GII.4 strains is only significant different when the pair of GII.4 strains are not adjacent, which suggests that the impact of early exposure to novel GII.4 strains on the incidence rates of norovirus may be more pronounced when comparing cohorts exposed to non-adjacent or non-consecutive GII.4 strains, as opposed to adjacent or consecutive pairs.

Limitations

There are several limitations to this study. One such limitation is the "sudden decrease" in incidence rates from 2009 to 2010 across all age groups, which is attributed to the application of the scaling factor to the data, potentially weakening its validity. Although there is no established methodology to address this bias due to changes in case definitions, we attempted to make the two different periods more comparable. Another limitation arises from the choice of the model. In our study, a full APC model yielded a higher value for

model diagnostics $\left(\mathrm{DIC}_{\mathrm{Age-period-cohort}} = 556.45 \text{ vs. } \mathrm{DIC}_{\mathrm{Age-Cohort}} = -214288.51\right)$, suggesting that the Age-Cohort model is a better fit for the data. However, the period effect of norovirus (i.e., the emergence of novel GII.4 strain in given years) is known for affecting the rates across all the age groups due to a lack of immunity against the new strains[47]. Thus, the choice of APC model should be prudent and alternative models to account for the potential period effects are recommended if any.

Strength

Bayesian Age-Cohort Model, combining with a series of adjustment of potential bias such as under-reporting bias, allows for a comprehensive and valid examination of age and cohort effects on norovirus incidence patterns. Additionally, the study is based on publicly available data, which enables other researchers to replicate and extend the findings.

Implications

The insights gained from understanding age-specific patterns of norovirus incidence can inform targeted public health interventions: One of our findings from pairwise comparison is that there is significant difference between different birth cohorts with early exposure of novel GII.4 strains, which can serve as aggregated evidence that the immunity response is strain-specific. Identifying differences in virulence and immune escape among norovirus strains can also contribute to the development of effective vaccines or treatments that take strain-specific characteristics into account.

Unsolved question and future research

There is a need for further research to explore the age-specific rate in German using genotyping data, which allows us the examine the impact on norovirus infection due to

specific strains. Also, the predictive features of Bayesian APC analysis are not within our research question but recommended to study on in the future.

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Tables & Figures

Table 1. Summary estimates (mean, standard deviation, 2.5% quantile, median and 97.5% quantile) of all precision (inverse variance) parameters (Age and Cohort) in AC model

Age	Mean	SD	0.025Q	0.5Q	0.975Q
0	0.640	0.003	0.635	0.640	0.645
1	1.142	0.003	1.137	1.142	1.147
2	0.412	0.003	0.407	0.412	0.418
3	-0.167	0.003	-0.173	-0.167	-0.161
4	-0.449	0.003	-0.455	-0.449	-0.443
5	-0.584	0.003	-0.591	-0.584	-0.578
6	-0.853	0.004	-0.860	-0.853	-0.846

Cohort	Mean	SD	0.025Q	0.5Q	0.975Q
1995	-1.465	0.005	-1.474	-1.465	-1.456
1996	-1.411	0.004	-1.420	-1.411	-1.403
1997	-1.368	0.004	-1.377	-1.368	-1.360
1998	-1.303	0.004	-1.311	-1.303	-1.294
1999	-1.226	0.004	-1.234	-1.226	-1.218
2000	-1.204	0.004	-1.212	-1.204	-1.196
2001	-1.126	0.004	-1.133	-1.126	-1.118

7	-1.044	0.004	-1.052	-1.044	-1.037
8	-1.001	0.004	-1.009	-1.001	-0.993
9	-0.884	0.004	-0.892	-0.884	-0.876
10	-0.822	0.004	-0.830	-0.822	-0.814
11	-0.785	0.004	-0.793	-0.785	-0.776
12	-0.779	0.004	-0.788	-0.779	-0.770
13	-0.728	0.005	-0.737	-0.728	-0.718
14	-0.602	0.005	-0.611	-0.602	-0.592
15	-0.373	0.005	-0.383	-0.373	-0.364
16	-0.060	0.005	-0.069	-0.060	-0.052
17	0.302	0.004	0.293	0.302	0.310

2002	-0.942	0.004	-0.950	-0.942	-0.935
2003	-0.743	0.004	-0.751	-0.743	-0.736
2004	-0.542	0.003	-0.549	-0.542	-0.535
2005	-0.325	0.003	-0.331	-0.325	-0.318
2006	-0.076	0.003	-0.082	-0.076	-0.070
2007	0.164	0.003	0.158	0.164	0.169
2008	0.340	0.003	0.335	0.340	0.345
2009	0.462	0.002	0.457	0.462	0.467
2010	0.528	0.002	0.523	0.528	0.532
2011	0.582	0.003	0.577	0.582	0.587
2012	0.709	0.003	0.704	0.709	0.713

18	0.365	0.004	0.357	0.365	0.374
19	0.554	0.004	0.546	0.554	0.563
20	0.676	0.005	0.667	0.676	0.685
21	0.718	0.005	0.708	0.718	0.727
22	0.768	0.005	0.758	0.768	0.779
23	0.797	0.006	0.786	0.797	0.808
24	0.873	0.006	0.861	0.873	0.886
25	0.920	0.008	0.905	0.920	0.935
26	0.963	0.011	0.942	0.963	0.984

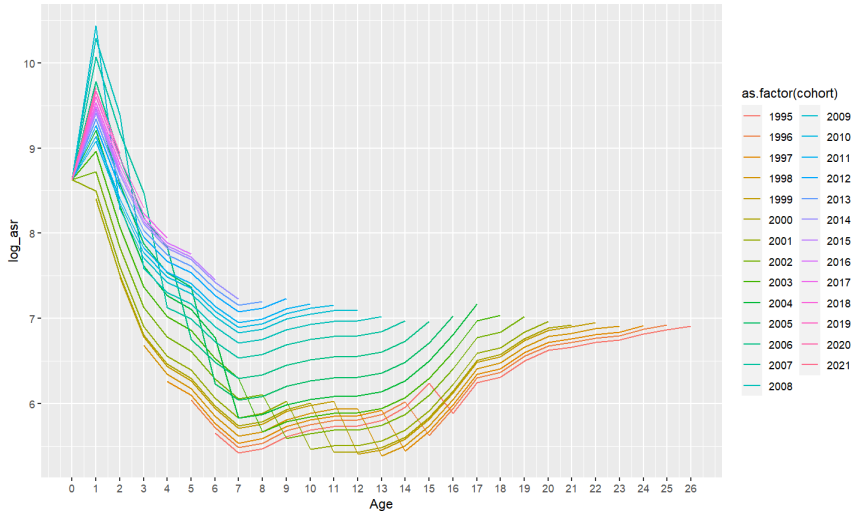
2013	0.788	0.003	0.783	0.788	0.793
2014	0.861	0.002	0.856	0.861	0.866
2015	0.894	0.002	0.889	0.894	0.899
2016	0.927	0.002	0.923	0.927	0.932
2017	0.981	0.003	0.976	0.981	0.986
2018	1.051	0.003	1.046	1.051	1.055
2019	1.111	0.003	1.106	1.111	1.117
2020	1.162	0.003	1.157	1.162	1.168
2021	1.171	0.004	1.163	1.171	1.179

Table 2. Pairwise comparison of age-specific rate among different cohorts with early exposure of any six GII.4 strains

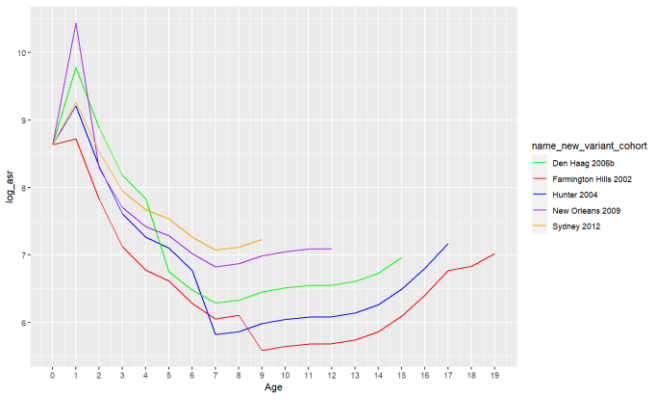
Cohort	Ref Cohort	P value		Age group
Den Haag 2006b	Farmington Hills 2002	1.000000	ns	Young children: 0-4
Den Haag 2006b	Hunter 2004	1.000000	ns	Young children: 0-4
Farmington Hills 2002	Hunter 2004	1.000000	ns	Young children: 0-4
Den Haag 2006b	New Orleans 2009	1.000000	ns	Young children: 0-4
Farmington Hills 2002	New Orleans 2009	0.820000	ns	Young children: 0-4
Hunter 2004	New Orleans 2009	1.000000	ns	Young children: 0-4
Den Haag 2006b	No variant	1.000000	ns	Young children: 0-4
Farmington Hills 2002	No variant	1.000000	ns	Young children: 0-4
Hunter 2004	No variant	1.000000	ns	Young children: 0-4
New Orleans 2009	No variant	1.000000	ns	Young children: 0-4
Den Haag 2006b	Sydney 2012	1.000000	ns	Young children: 0-4
Farmington Hills 2002	Sydney 2012	1.000000	ns	Young children: 0-4
Hunter 2004	Sydney 2012	1.000000	ns	Young children: 0-4
New Orleans 2009	Sydney 2012	1.000000	ns	Young children: 0-4
No variant	Sydney 2012	1.000000	ns	Young children: 0-4

Cohort	Ref Cohort	P value		Age group
Den Haag 2006b	Farmington Hills 2002	1.000000	ns	Older children: 5-15
Den Haag 2006b	Hunter 2004	1.000000	ns	Older children: 5-15
Farmington Hills 2002	Hunter 2004	1.000000	ns	Older children: 5-15
Den Haag 2006b	New Orleans 2009	0.450000	ns	Older children: 5-15
Farmington Hills 2002	New Orleans 2009	0.010000	**	Older children: 5-15
Hunter 2004	New Orleans 2009	0.080000	ns	Older children: 5-15
Den Haag 2006b	No variant	1.000000	ns	Older children: 5-15
Farmington Hills 2002	No variant	1.000000	ns	Older children: 5-15
Hunter 2004	No variant	1.000000	ns	Older children: 5-15
New Orleans 2009	No variant	0.070000	ns	Older children: 5-15
Den Haag 2006b	Sydney 2012	0.030000	*	Older children: 5-15
Farmington Hills 2002	Sydney 2012	0.000475	***	Older children: 5-15
Hunter 2004	Sydney 2012	0.000000	**	Older children: 5-15
New Orleans 2009	Sydney 2012	1.000000	ns	Older children: 5-15
No variant	Sydney 2012	0.000000	**	Older children: 5-15
Farmington Hills 2002	Hunter 2004	0.650000	ns	Young adult: 16-26

Cohort	Ref Cohort	P value		Age group
Farmington Hills 2002	No variant	1.000000	ns	Young adult: 16-26
Hunter 2004	No variant	0.100000	ns	Young adult: 16-26



(A)



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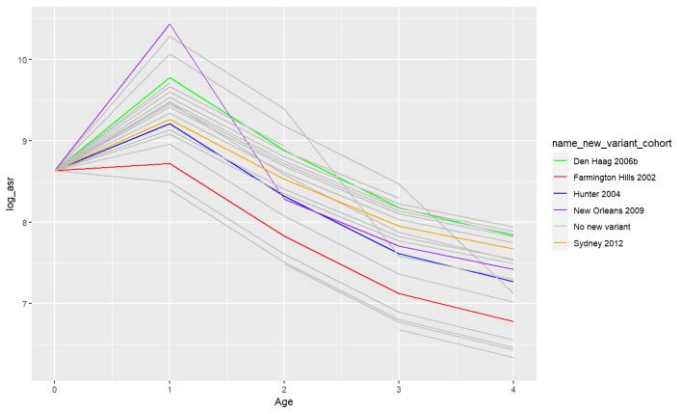
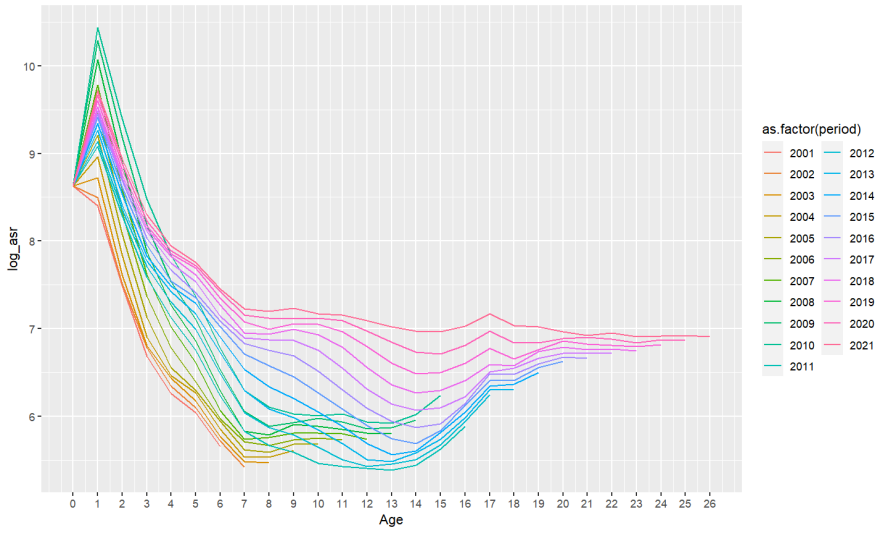


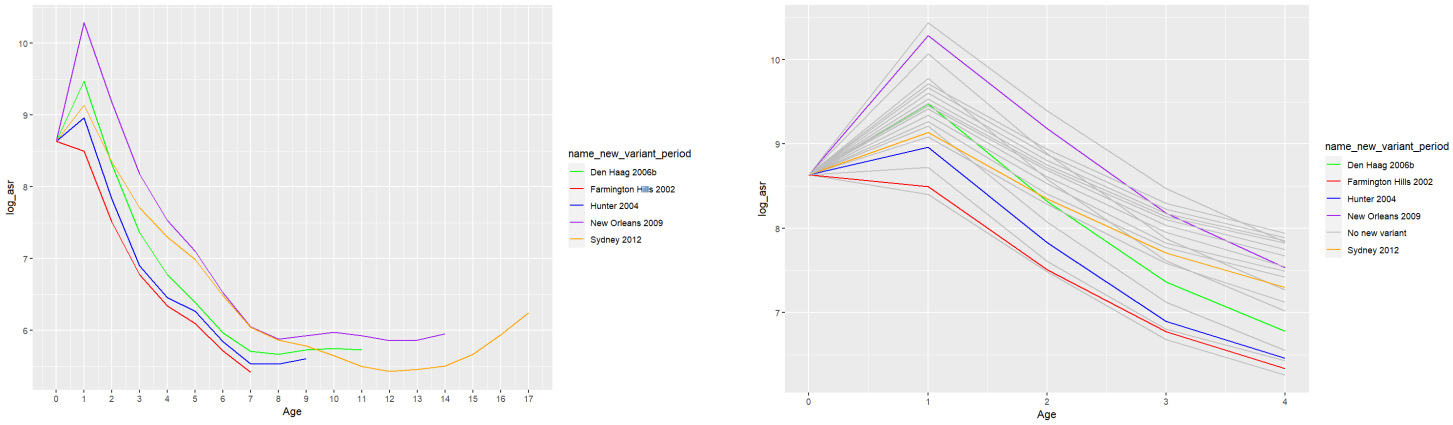
(C)

Figure 1 represents the age-specific rate of norovirus infection in Germany, each line represents a birth cohort (i.e., a group of individuals born at the same period); Panel (A) shows the age-specific rate of norovirus in German across all birth cohorts (1995-2021); Panel (B) shows age-specific rate in birth cohorts exposed to novel

GII.4 strain at age of birth, and (C) Age-specific rate in birth cohorts with early exposure of GII.4 strain, restricting to age 0-4.



(A)



(B)

Figure 2 represents the age-specific rate of norovirus infection in German, each line represents a reporting year; Panel (A) shows the age-specific rate of norovirus in German across all reporting years (2001-2021); Panel (B) shows age-specific rate in reporting year when a novel GII.4 strain, and (C) Age-specific rate in reporting year when a novel GII.4 strain, restricting to age 0-4.