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ORIGINAL RESEARCH

Is vaccination associated with better health in children? A secondary analysis using a large cross-sectional survey, the German KIGSS data file (Kindergesundheitssurvey – Children's Health Survey)

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ABSTRACT

OPEN ACCESS

We studied the question, whether vaccinated children are healthier than unvaccinated children. We used a large, representative cross-sectional survey of children (n = 16'662) aged 1 to 17 produced by the German Robert-Koch-Insitut, the children health survey, the Kindergesundheitssurvey. We compared the health status of n = 202 children without any vaccination with that of 15'344 children with vaccinations, using regression models. The principal outcome variable was a morbidity score, constructed out of the presence or absence of 11 diagnoses, which had been ascertained by doctors via a computer assisted diagnostic interview. We analyzed the influence of sociodemographic factors, previous infections, and, in a final step, of vaccinations on morbidity in a Poisson regression analysis. Secondary outcomes were the single diagnoses (atopic diseases, obstructive bronchitis, pneumonia, otitis media, heart disease, anemia, diabetes, thyroid disease, seizures, scoliosis, migraine), which we analyzed by logistic regression models. Unvaccinated children had a significantly higher likelihood to have contracted pertussis, measles, mumps and rubella. Vaccinated children had a higher likelihood to have contracted salmonella, scarlatina and chickenpox. After controlling for sociodemographic variables and previous diseases, the number of vaccinations received was an additional predictor (b = 0.004, p = .0007) to explain morbidity, i.e. children with more vaccinations had a higher morbidity score. The regression models explain between 0.5% to 8% of the total variance. The vaccinations associated with worse health outcomes are vaccinations against hemophilus influenza, mumps, diphtheria and tetanus. Vaccinations against polio, measles and hepatitis B are associated with beneficial health outcomes. Our data stem from a cross-sectional survey which does not allow for causal inferences and should be studied more carefully in large, three-armed, prospective longitudinal studies. We conclude from our analysis that vaccinated children are not healthier than unvaccinated children.

Keywords: vaccination, health, children, representative survey, regression analysis

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Introduction

Vaccinations are generally supposed to improve the health of children. The mechanism is stipulated to be immunity against specific pathogens [1,2]. Data from Africa show that vaccinations against measles reduce mortality, but much more than can be expected by the specificity of the vaccine [3-5]. Hence, one benefit of vaccinations might be via non-specific stimulation of the immune system, or perhaps by an ecological effect, by which other, more lethal noxes, are driven from ecological niches. This concept of non-specific benefit of vaccinations is quite an old one [6] and is now being revived [5].

Reemergence of nearly abolished diseases, like measles in the US, have renewed interest in the topic [7,8]. With a wider historical perspective it looks as if the attempt to eradicate one infectious agent by aggressive vaccination campaigns allows other bacteria or viruses to enter the scene [9]. This would emphasize host resistance, and perhaps natural immunological training, possibly through childhood diseases, more than is currently accepted. Already McKeown had observed that the big infectious diseases that threatened public health, like typhoid, diphtheria, tuberculosis, smallpox, were on the retreat long before any vaccinations came into wider use [10]. Thus, it might be the case that public health-related factors, like overall nutritional status of a population, socioeconomic status, hygiene and living standards are much more important than specific immunological status when a population is grappling with infectious diseases. This is, however, largely neglected in the current debate.

There are examples of outbreaks of infectious diseases in nearly completely vaccinated populations [11]. A meta-analysis of studies on 40 different influenza outbreaks in old-people's homes showed that despite the increase in influenza vaccination the attack rate of the influenza virus remained completely unaffected [12]. This tallies with a finding that influenza vaccination programs in the elderly, above 65 years of age, do not affect mortality and hospitalization [13]. A recent study could even show that college students vaccinated against influenza, when symptomatic, had a higher viral load in their exhalations than unvaccinated ones [14]. We found in a modeling study that COVID-19 related deaths in Europe during the first wave of the pandemic were associated with higher influenza vaccination rates in the elderly, after controlling for the variation in cases, and vitamin D status was a potential protective factor [15]. This points to the importance of the ecological network of pathogens, as well as of protective host factors.

Some negative reports, such as on the human papilloma virus vaccine (HPV) [16], have created doubts in the public about the general benefit or the benefit to harm ratio of vaccinations. While the generic immunological rationale is not seriously doubted, as far as we can see, the clinical effects are questioned in some cases [17]. This has to do with the fact that serious side effects may be more frequent than is currently assumed [18-21]. Especially, if the general attack rate and thus prevalence is low, and, as a consequence, the risk from the disease is low as well, then potential side effects of vaccination campaigns move into focus. In our own meta-review of a third of all Cochrane reviews after 2008 we found that only 5,8% of all reviews have high-quality outcomes that support efficacy of the interventions in question, while evidence of harm was found in 8,1% of the reviews that reported harms [22]. Jefferson and colleagues found that there was weak evidence that influenza vaccination in children protected against influenza and influenza-like illness and there was too little documentation of potential negative side effects [23]. While children, vaccinated in a randomized trial against influenza, were protected against influenza, they had a more than fourfold risk of contracting other respiratory related viruses [24].

Anorexia, attention-deficit hyperactivity syndrome and obsessive-compulsive disorder have been seen more frequently after vaccinations [25], as well as neurodevelopmental disorders [26]. In particular, an association between childhood vaccinations with autism spectrum disorders has been debated intensely, with some authors claiming that such an association does not exist [27] and others arguing for such an association [28-31] Recently, an unpublished study was leaked during a court case, in which a large cohort of 1'597 unvaccinated children was prospectively compared with 16'511 vaccinated children. The adjusted hazard ratio for vaccinated children to develop any chronic health condition was 2.53 [32].

Aluminum, an adjuvant in vaccines meant to stimulate the immune system has also been blamed for potential side effects [33], and an autopsy study has found considerable amounts of this metal in ganglia and neurons of autistic children [34]. Indeed, most vaccines contain nano-particles of various metals, either from the production process or because they are used as adjuvants in traces which go undeclared [35], and it might be in fact adjuvants, not the vaccine itself, that pose the problem [36]. Without adjuvants, however, most vaccinations would not work, hence it is difficult to separate the two. In order to clearly decide whether vaccinations are beneficial, randomized studies would be necessary that do not compare against carrier, i.e. adjuvants minus the immunologically active ingredient, but in three arms, where one arm is an empty control, where only saline is used as a placebo. Those studies are rare. At any rate it would be very difficult in the current climate to conduct such a study, as ethical concerns have been raised [37].

Hence, a secondary approach is necessary to investigate, whether vaccinations are beneficial for children and improve their health status compared to children without any vaccinations. Here, we report such an analysis which was based on the large dataset of the German Children's Health Survey Study (KIGSS – Kindergesundheitssurvey). This is a large, nationwide cross-sectional and representative survey that surveyed more than 17'641 children between 0 and 17 years of age, or their parents respectively, by way of interview with caretakers and an interview by a medical doctor [38]. The study was conducted by the federal office Robert-Koch-Institut (RKI), which is a national public health office directly reporting to the Minister of Health. The data set is publicly available and can be received on special request.

A secondary analysis of KIGGS data by Schmitz et al. had found no difference between vaccinated and unvaccinated children regarding overall health and atopic diseases [39]. Vaccinated children had clearly less of the preventable diseases against which the vaccinations were directed. As this study touched only on the surface of this complex data-set, the purpose of the present study is to conduct a more thorough secondary analysis following an analytical plan that guards against p-hacking and harking – hypothesizing after the results are known [40,41].

Method

THE DATABASE

The database was received from RKI on request (Robert Koch Institute, Department of Epidemiology and Health Monitoring (2013): The German Health Survey for Children and Adolescents 2003-2006, Public Use File 4. Version. doi: 10.7797/9-200306-1-1-4 http://dx.doi.org/10.7797/9-200306-1-1-4.) It contains data of 17.460 cases with 1.206 variables. The method of data collection is described by Kurth and colleagues [42]. In brief, it is a large cross-sectional representative survey. First 167 sampling points all over Germany were chosen and then participants were enrolled following a random sampling scheme from local registers. This yielded a representative sample. Parents, children, and adolescents answered questionnaires and provided information in interviews. Physicians interviewed and checked

participants and conducted standardized tests. We used the central module of the study. This collected data on physical and mental health, living conditions, health status and behavior, social conditions and social and educational status of the parents, risk factors and health system utilization. Social indicators were expressed as a social index describing the social stratum of the child according to the highest stratum of either parent or the main caregiver according to Winkler [43]. A weighting variable was also introduced that codes for deviations of a case from overall representativeness, as some over- and under-sampling occurred due to the design. This weighting variable was used in all our analyses as recommended by the RKI.

Within this central module data are available on the vaccination status of children, the number of vaccinations received, and diagnoses of various important core diseases, made by physicians after a standardized computer assisted interview.

For this study the KIGSS-database has been prepared to allow the building of regression models. The variables coding the vaccination status for those vaccinations recorded, namely tetanus, diphtheria, polio, pertussis, hepatitis B, hemophilus influenza, measles, rubella and mumps, were used. Their original coding is "vaccination received, but not sufficiently vaccinated", "too young for vaccination", "not vaccinated", "vaccinated", and the number of vaccinations per vaccine is given which was collected in an indicator variable expressing the number of vaccinations of a particular vaccine. These numbers of vaccinations were added to form a new continuous variable that contains the cumulative number of vaccinations received.

One variable contains the vaccination status overall. It is coded:

- Vaccination certificate present
- Not vaccinated, without certificate
- Certificate present, but not complete
- No vaccination-certificate

This important variable was used to define unvaccinated children (the "cases"). Only children who had either a vaccination certificate or not, and for whom it is clear that they had not received any vaccinations were included into this analysis as cases. This leads to a different number of cases compared to Schmitz et al. [39], but defines cases and non-cases more clearly. In addition, the variables defining the vaccination doses were used to define cases. All those children in which the cumulative dose of vaccinations is zero were called "unvaccinated" and all others are vaccinated to some degree.

Dependent variables, i.e. those outcome variables to be predicted, were variables indicative of the health of the children. We used the variables collected through a computer assisted diagnostic interview conducted by a physician that clarified the absence or presence of one of the following diagnoses:

- Atopic diseases (defined by us as any one of the following diseases in combination or together: allergic rhinitis, asthma, atopic dermatitis)
- Obstructive bronchitis
- Pneumonia
- Otitis media
- Heart disease

- Anemia
- Diabetes
- Thyroid disease
- Seizures
- Scoliosis
- Migraine

We used the presence or absence of these diagnoses, detected via computer-assisted interview by a doctor, to construct a single outcome variable, the morbidity score: The presence or absence of these diagnoses were coded as 1 or 0 and added up to yield a morbidity score. This was our primary outcome. Secondary outcomes were the single diagnoses themselves.

All relevant categorical variables that we used as predictors of the abovementioned outcomes were dummy coded with 1 indicating the presence of the property (for instance smoking of mother), and 0 the absence. All three-staged categorical variables (smoking always, never, sometimes) were recoded into dichotomous dummy variables (never or sometimes = 0, always = 1). All sociodemographic variables describing the family were used. Income, profession of parents, education of parents had been condensed in a complex numerical scale of social stratum (variable 67: Winkler Index Score [43]). This variable was used as an indicator of social status. It ranges from 3 to 21 to describe social stratum. The full range of this variable is present in the database, and it is approximately normally distributed with a slight shift of the mean and a steeper slope towards the lower end.

STATISTICS AND ANALYSIS

The analysis followed a predefined protocol which defined all procedures before any analyses were conducted. It was uploaded to the Open Science Framework (https://osf.io/6z5yr).

First all data preparations, i.e. trimming the database and dropping all irrelevant variables and dropping inconsistent cases, were performed. No missing data imputation was performed. All data preparations were done strictly before any analyses. The definition of cases was performed subsequently following the procedure described. The analytical plan formulated linear modeling as the analytical strategy. Before that, an orienting analysis was calculated that tabulated past infections against vaccination status, following [39]. Pearson Chi^2, with Yates' correction for continuity in case of small cell numbers, was calculated as well as Odds Ratios. All analyses were limited to children older than 1 year.

The research question is whether children that are unvaccinated, i.e. have received no vaccinations, are healthier than other children. As children's health is likely influenced by many variables the best way to answer this question by this dataset is to build appropriate regression models in which basic sociodemographic information and variables describing the infection history are entered in a first step, and vaccination variables next to predict morbidity.

The primary analysis was the prediction of the morbidity score. As mentioned above, this consisted of the cumulated number of doctor-given diagnoses stemming from the computer aided physician interview added up to give a morbidity score. This is a count variable that is approximately Poisson distributed (Figure 1).

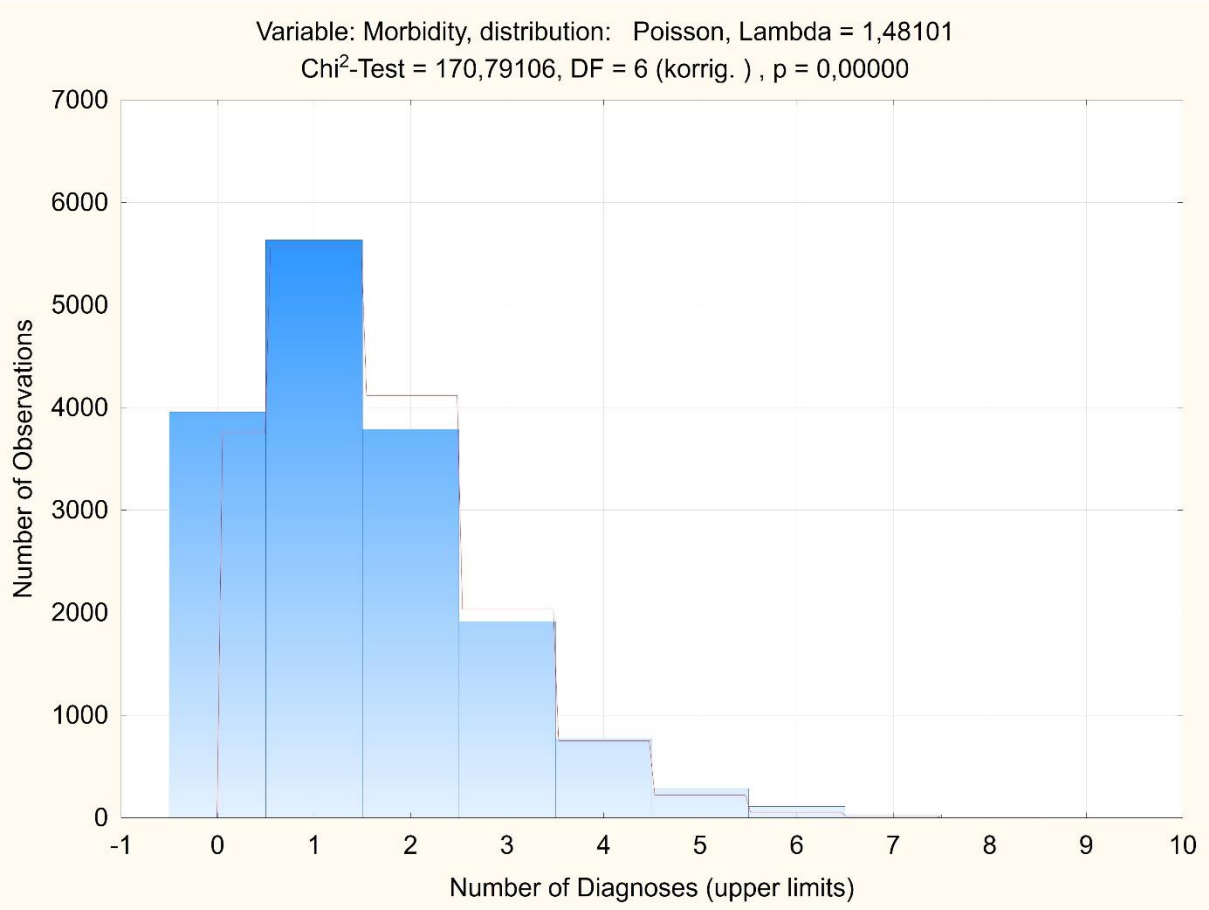

Figure 1 – *Distribution of the outcome variable "Morbidity Score" as the sum of all diagnoses certified by a doctor in a computer aided interview*

Note that, although the statistical adaptation tests are significant, the empirical distribution conforms well to the expected one. As the tests are overpowered with a large number of cases it is not surprising that the tests signal a lack of fit. However, visual inspection shows only a slight deviation from the expected ideal distribution. Hence a Poisson regression was used for this variable.

First all sociodemographic variables were entered and those variables that were not significant as predictors ($p<0.05$) were removed. In a second step the past occurrence or absence of those infectious diseases against which the vaccinations had been given were entered. As some children with vaccinations have also had these diseases and as their development might be different and might influence morbidity, these variables were used as predictors as well, after socio-demographic variables had been controlled for. They were entered together and those variables that were not significant as predictors were again removed.

In a third step vaccination status was entered. In a sensitivity analysis the number of vaccinations received were entered instead. The respective R^2 values or similar indices of fit are reported.

The main analysis was a Poisson regression model to predict the morbidity score.
As secondary analysis, separate logistic regression models were built following the same rationale, one for each disease category, predicting the presence or absence of the disease in question. Here, all relevant predictors were included, first without the number of vaccinations. Out of these the best fitting model was extracted, eliminating non-significant

predictors, and in a final step the number of vaccinations was entered as an additional predictor. Decisions between rival models were based on model fit statistic and Akaike's Information Criterion (AIC), such that the model with lower AIC and better model fit was chosen.

This yielded 11 different models in addition to the major one defining morbidity. The procedure for each model followed the same rationale described above: first, demographic variables were controlled, then infectious disease variables, and finally vaccination status was entered.

If for one particular disease the model was significant, including the vaccination status variable, i.e. clearly significant at a corrected $p < 0.004$ (i.e. 0.05/12), then the protocol stipulated an exploratory analysis to analyze whether any of the vaccinations is specifically associated with a particular disease. As there are tests for 9 different vaccines the corrected p-value at which an important effect was assumed was $p < 0.006$ (i.e. 0.05/9)

We built parsimonious models and the size of the database gave enough statistical power to model the anticipated 10 to 20 variables with sufficient stability and statistical power.

All modeling followed the appropriate strategies of parsimony versus good fit [44-49]. Statistica version 13 was used for all analyses.

Results

VACCINATION STATUS

The vaccination status according to the variable describing the overall status ("impfpop" in the database; variable 83 in our analytical data-set) is given in Table 1.

Table 1 – Vaccination status

	Number	Cum. Number	Percent	Cum. Percent
Vaccination certificate present	15'216	15'216	91.5	91.5
Not vaccinated. no certificate	128	15'344	0.8	92.3
Vaccination certificate not complete or partially missing	174	15'518	1.0	93.4
Vaccination certificate not available	1'104	16'622	6.6	100
Missing Data	0	16'622	0.0	100

The vaccination status according to number of vaccinations received (i.e. 0 vaccinations versus > 0) is given in Table 2.

Table 2 – Vaccination status according to number of vaccines received: Not vaccinated - number of vaccinations = 0; vaccinated – number of vaccinations > 0

	Number	Cum. Number	Percent	Cum. Percent
Not vaccinated	202	202	1.2	1.2
Vaccinated	15'142	15'344	91.1	92.3
Missing Data	1'278	16'622	7.7	100

As can be seen, the number of vaccinated and unvaccinated children together is 15'344 cases (Table I2). This is the same number as those with certificate plus those that are unvaccinated and have no certificate (lines 1 and 2 in Table 1); however, the distribution of these numbers is different. While according to the official vaccination status variable only 128 children go unvaccinated, according to the variable counting number of vaccination doses these are 202 children (Table 2). This is due to the fact that some children from the category "Vaccination certificate present" (Table 1, line 1) are actually unvaccinated and hence enter the category "not vaccinated" in Table 2. This is the reason why for further analyses this variable was used as the indicator variable of the vaccination status. Note that in the following tables not all children could be analyzed due to missing data and that all analyses have been restricted to children older than 1 year, which yields different numbers depending on the analysis.

HEALTH STATUS

One variable asked the parents about the health status of their children which was indicated on a 5-point Likert-type scale (very good, good, average, bad, very bad). The health status according to vaccination status is given in Table 3. A larger proportion of parents of unvaccinated children indicate the health status of their children as very good, and 3% of these children, a higher percentage than vaccinated children have a bad health status. The statistical test indicates a clear deviation from chance expectation.

Table 3 – Subjective health status indicated by parents according to vaccination status; $Chi^2 = 50{,}4$; $DF = 4$; $p < 0.000001$

	Very good	**Good**	**Average**	**Bad**	**Very Bad**	**Total**
Unvaccinated	60	57	11	4	0	132
	45.4%	43.2%	8.3%	3%	0%	0.91%
Vaccinated	5'536	7'904	902	30	9	14'381
	38.5%	55%	6.3%	0.2%	0.1%	99.09%
All	5'596	7'961	913	34	9	14'513
	38.6%	54.8%	6.3%	0.2%	0.1%	100%

INFECTIONS

Do vaccinated children have less infections? To answer this question the frequency of all infectious diseases, as indicated by parent recall, were tabulated against overall vaccination status, i.e. vaccinated or unvaccinated. The question is, whether vaccinations might also confer unspecific beneficial effects that are not only specific for the infection vaccinated against, but also protective against other infections [5]. The result is presented in Table 4. Note that only clear cases (infection present or not) were analyzed and children older than 1 year of age.

Table 4 – Infections experienced in the past by vaccination status (in brackets: percentage) Chi² and associated p-value; Odds Ratio (95% confidence interval)

Infection occurred in the past	Unvaccinated	Vaccinated	Total	Chi²	p	OR
Pertussis				6.5	.01	1.88 (1.15-3.08)
Yes	19 (15.8%)	1'196 (9.1%)	1'215 (9.2%)			
No	101 (84.2%)	11'947(90.9%)	12'048 (90.8%)			
Total	120 (0.9%)	13'143 (99.1%)	13'908 (100%)			
Measles				21.4	.00001	2.87 (1.8-4.6)
Yes	22 (18.0%)	925 (7.1%)	947 (7.2%)			
No	100 (82.0%)	12'056 (92.9%)	12'156 (92.8%)			
Total	122 (0.9%)	14'048 (99.1%)	13'103 (100%)			
Mumps				15.4	.00009	2.94 (1.67-5.16)
Yes	14 (11.6 %)	554 (4.3%)	568 (4.3%)			
No	107 (88.4%)	12'432 (95.7%)	12'539 (95.7%)			
Total	121 (0.9%)	12'986 (99.1%)	13'107 (100%)			
Rubella				10.7	.001	2.2 (1.36-3.58)
Yes	20 (17.2%)	1'100 (8.6%)	1'120 (8.7%)			
No	96 (82.8%)	11'649 (91.4%)	11'745 (91.3%)			
Total	116 (0.9%)	12'749 (99.1%)	12'865 (100%)			
Chickenpox				13.6	.0002	0.52 (0.36-0.74)
Yes	75 (58.4%)	10'065 (73.1%)	10'138 (73.0%)			
No	52 (41.6%)	3'704 (26.9%)	3'756 (27.0%)			
Total	125 (0.9%)	13'769 (99.1%)	13'894 (100%)			
Scarlatina				9.1	.002	0.44 (0.26-0.76)
Yes	15 (12.9%)	3'244 (25.1%)	3'259 (25%)			
No	101 (87.1%)	9'662 (74.9%)	9'763 (75%)			
Total	116 (0.9%)	12'906 (98.7%)	13'022 (100%)			
Epstein Barr				0.08	.7	1.0 (0.32-3.2)
Yes	15 (12.9%)	3'244 (25.1%)	3'259 (25%)			
No	101 (87.1%)	9'662 (74.9%)	9'763 (75%)			
Total	116 (0.9%)	12'906 (98.7%)	13'022 (100%)			
Herpes				0.5	.5	0.85 (0.54-1.33)
Yes	24 (19.8%)	2'948 (22.5%)	2'972 (22.5%)			
No	97 (80.2%)	10'140 (775%)	10'237 (77.5%)			
Total	121 (0.9%)	13'088 (99.1%)	13'209 (100%)			
Salmonella				6.6	.01	n.a.
Yes	0	553 (4.2%)	553 (4.2%)			
No	117 (100%)	12'634 (95.8%)	12'751 (95.8%)			
Total	117 (0.9%)	13'187 (99.1%)	13'304 (100%)			
Hepatitis	(Excluding	Neonatal	Jaundice)	0.2	.6	n.a.
Yes	0	114 (0.9%)	114 (0.9%)			
No	121 (100%)	13'081 (99.1%)	13.202 (99.1%)			
Total	114 (0.9%)	13'195 (99.1%)	13'316 (100%)			

In general, with the exception of chickenpox which were experienced by 73% of all children, only a minority of all children suffered from any of these infectious diseases, whether vaccinated or not. The overall percentage is between 1% for hepatitis and 25% for scarlatina or 22.5% for herpes, and is below 10% for the other infections.

As can be seen, unvaccinated children have a significantly higher likelihood to have contracted pertussis (odds ratio = 1.88 [95% confidence interval: 1.15-3.08]), measles (odds ratio = 1.87 [95% confidence interval: 1.8 – 4.6}) mumps (odds ratio = 2.94 [95% confidence interval: 1.67 – 5.16]), and rubella (odds ratio = 2.2 [95% confidence interval: 1.36 - 3.58]). There were no significant differences for herpes, hepatitis, and Epstein Barr. Unvaccinated children had a significantly lower likelihood to have contracted salmonella infection ($Chi^2 = 6.6$, DF = 1; p = 0.01; OR not applicable), scarlatina (odds ratio = 0.44 [95% confidence interval: 0.26 – 0.76]), or chickenpox (odds ratio = 0.52 [95% confidence interval: 0.36 – 0.74]).

MODELING MORBIDITY

The principal analysis was the modeling of the morbidity score, the sum of all diagnoses per child, as the result of a Poisson regression. The results are presented in Tables 5 and 6. As can be seen, there is a tendency for a higher morbidity score for children living in the city, boys, older children, non-migrants (who are coded zero), children whose mothers smoked during pregnancy and kept smoking, children whose parents have a higher social status, who have a worse subjective health status, whose parents have allergies, and children who had taken medications during the past 7 days. Smoking indoors and smoking during breastfeeding, as well as *not* having had chickenpox, pertussis, scarlatina, salmonella or herpes are variables that are associated with increased morbidity. Interestingly, the number of vaccinations enters the model in the next step as a significant positive predictor, while all other predictors remain in the model, except smoking of mother, which just misses formal significance but was kept in the model to avoid distortions. Some parameter estimates change, but not substantially and not in direction. Parameter estimates for the variables in model 2, i.e. with vaccination numbers entered, are given in brackets, if they are different. It is interesting to observe that the number of vaccinations is a positive predictor, i.e. is associated with an increased morbidity score, while the infections themselves (pertussis, chickenpox, scarlatina, herpes, salmonella) remain as predictors in the model and their parameter estimates change only slightly or not at all.

The residual diagnostics show that the model fits reasonably well (Figure 2).

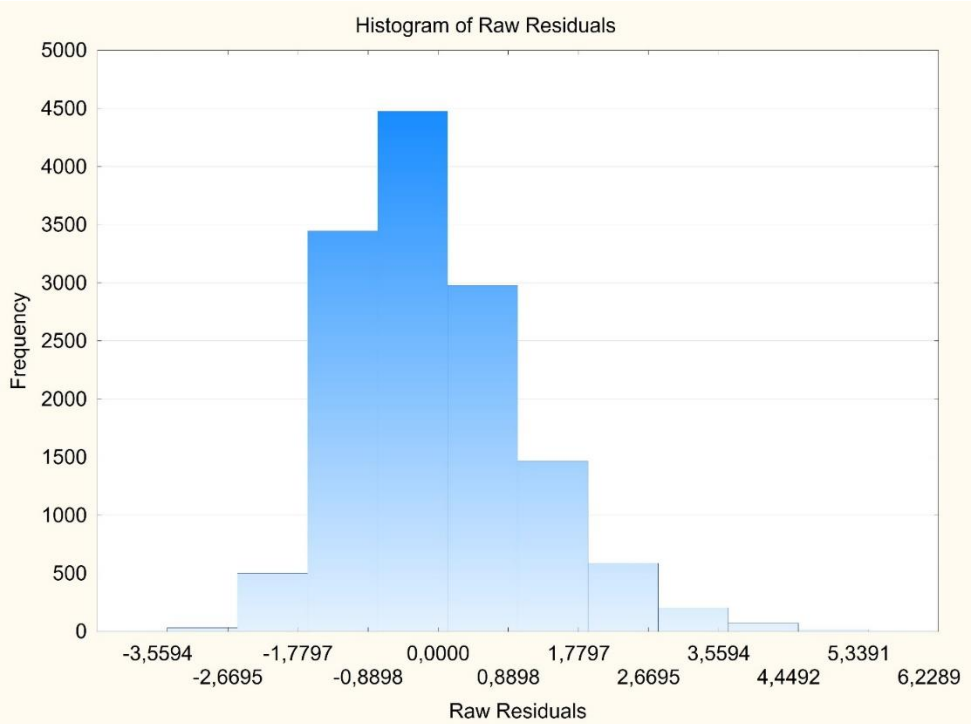

Figure 2 – *Distribution of residuals of Poisson regression model predicting morbidity*

An outlier diagnosis shows that for most cases the model is a reasonably good prediction, except for seven cases (Figure 3). We inspected these cases, but did not see any specific markers.

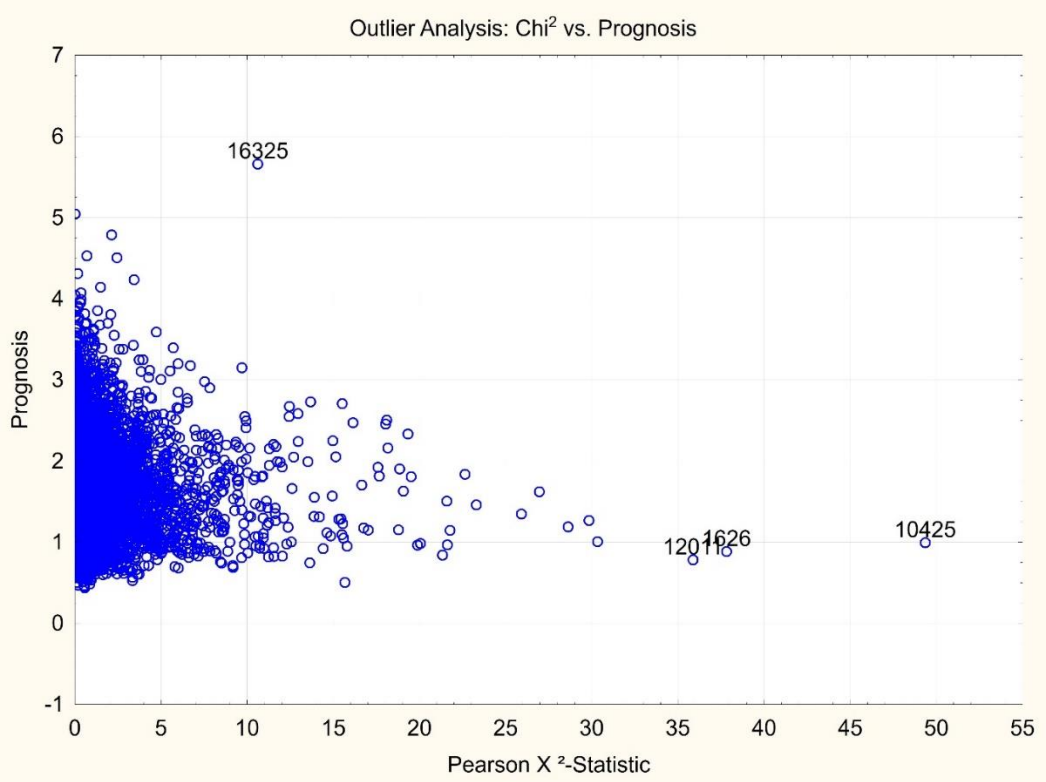

Figure 3 – *Outlier diagnostic of Poisson regression model predicting morbidity*

Table 5 – Poisson regression model of the principal analysis: explaining morbidity – Model 1: all significant sociodemographic and health variables as predictors and model fit statistics; model 2: all previously significant predictors and number of vaccinations entered in a last step (new parameters in brackets, if different)

	B	**Standard Error**	**95% Confidence Interval of B**	**Wald Statistic**	**p-value <=**
Intercept	0.16 (0.04)	0.08 (0.09)	-0.0007 – 0.3	3.8 (0.14)	0.05 (0.7)
Rural/city	0.01 (0.02)	0.006	0.0006 – 0.03	4.2 (5.6)	0.04 (0.01)
Gender	0.11	0.01	0.08 - -0.14	68.0	0.000001
Age	0.02	0.001	0.018 – 0.02	190.8	0.000001
Migrant	-0.20 (-0.16)	0.02	-0.24 - -0.25	78.3 (49.5)	0.000001
Smoking of mother	0.04 (0.03)	0.02	0.008 – 0.08	6.0 (3.4)	0.01 (0.06)
Smoking indoors	-0.05 (-0.06)	0.02	-0.09 - -0.01	6.2 (8.0)	0.01 (0.005)
Smoking while pregnant	0.08	0.02	0.034 – 0.12	11.7	0.0006
Smoking while breastfeeding	-0.08 (-0.07)	0.03	-0.14 - -0.02	8.3 (4.9)	0.004 (0.03)
Social status	0.01	0.002	0.009 – 0.01	55.4 (49)	0.000001
Subjective health status	0.32 (0.33)	0.01	0.3 – 0.34	846.6 (807.6)	0.000001
Had pertussis	-0.05 (-0.06)	0.02	-0.09 - -0.02	8.2 (7.9)	0.004 (0.005)
Had chickenpox	-0.12	0.01	-0.15 - -0.09	72.6 (62.4)	0.000001
Had scarlatina	-0.13	0.01	-0.16 - -0.1	98.8 (84.9)	0.000001
Had herpes	-0.08 (-0.09)	0.01	-0.11 - -0.05	34.0	0.000001
Had salmonella	-0.12 (-0.13)	0.03	-0.18 - -0.07	21.5 (23.4)	0.000003
Parents have allergies	0.21	0.01	0.18 – 0.23	241.0 (228.8)	0.000001

	B	Standard Error	95% Confidence Interval of B	Wald Statistic	p-value <=
Number of medications within the last 7 days	0.08	0.006	0.07 – 0.09	206.6 (195)	0.000001
Number of vaccinations received	**0.004**	**0.001**	**0.002 – 0.006**	**11.5**	**0.0007**
Scaling factor	1.000000	0.000000			

The model has a reasonably good fit (see Table 6): The Chi^2- value divided by degrees of freedom is close to one, which is a good indicator of fit considering the large number of cases. An alternative model using vaccination status as a dummy variable leads to the same conclusions, but has worse fit (Δ AIC = 5 with same DFs).

Table 6 – Model Fit Statistics, in brackets statistics for full model including number of vaccinations

Model Statistics Degrees of Freedom (DF)	Akaike Information Criterion	Bayes Information Criterion	Ch^2/DF
14'663 (13.775)	42'810 (40'239)	42'947 (40'058)	1.057 (1.04)

MODELING DIAGNOSES

As defined in the protocol, for each of the diagnoses that were summed up in the morbidity score separate logistic regressions were calculated as a secondary analysis. Atopic eczema, asthma and allergic rhinitis were combined to the category "atopic disease" to reduce the number of analyses. In all analyses, intercepts are not reported, as they are irrelevant for our question.

The analyses are summed up in Table 7. The single analyses are presented in the supplementary material as the results of the respective logistic regression analyses with full statistics (95% confidence intervals, Wald statistic, p-level). All variables mentioned in Table 7 or in the supplementary tables (S1-S10) are significant predictors. The models explain between 1% and 8% of the total variance and have all reasonably good fit (Table 8).

The following variables are frequent significant predictors:

Gender: Boys are more likely to be diagnosed with atopic diseases, obstructive bronchitis, pneumonia and otitis media, and girls are more likely to have been diagnosed with anemia, thyroid diseases, scoliosis and migraine.

Migrant status: Migrant children are more likely to have been diagnosed with atopic diseases, otitis media, scoliosis and migraine, and less likely to have been diagnosed with heart disease, anemia or thyroid diseases.

Less problems after birth are predictive especially of less heart disease and anemia, but also for fewer diagnoses of pneumonia, otitis, seizures, thyroid disease, scoliosis.

A better subjective health status is unsurprisingly associated with the absence of all diseases. Parental allergies are associated with atopic diseases, obstructive bronchitis, otitis media, anemia and migraine.

Breast-feeding is only associated with fewer diagnoses of scoliosis. If the mother is a non- smoker or did not smoke during pregnancy this is associated with fewer cases of otitis media, and smoking during nursing is associated with otitis. Not smoking during pregnancy is also associated with smaller likelihood of scoliosis. Smoking of the father is associated with migraine, similar to smoking indoors which is associated with a higher likelihood for atopic diseases and scoliosis, and absence of smoking indoors is associated with fewer cases of migraine.

It is interesting to observe that *lower* social status as expressed in the Winkler-Index is associated with a smaller likelihood of pneumonia, otitis media and scoliosis, but the effects are small, while a lower social status is associated with a higher likelihood for seizures.

The absence of past infectious diseases is mostly associated with a lower likelihood of diseases, except for measles which are somewhat protective against heart disease, or chickenpox and herpes which are associated with less likelihood of atopic diseases, and scarlatina with less likelihood of obstructive bronchitis. In most other cases, infectious diseases are rather associated with a higher incidence of diagnoses, especially so for otitis media.

Table 7 – Summary of logistic regression analyses on single disease categories; given are the Odds Ratios per variable predicting the *absence* of the respective disease; all variables are significant predictors; for full statistics (95% confidence intervals, Wald statistic, p-value) see supplementary material

	Atopic Disease	**Obstructive Bronchitis**	**Pneumonia**	**Otitis media**	**Heart disease**	**Anemia**	**Seizures**	**Thyroid disease**	**Diabetes**	**Scoliosis**	**Migraine**
Rural/city			0.93					1.20			
Gender	0.83	0.61	0.86	0.90		1.26		2.46		1.43	1.30
Age	0.93	1.04	0.99	1.01				0.87		0.79	0.82
Migrant	1.23			1.59	0.75	0.59		0.54		1.51	2.20
Problems after birth			0.69	0.91	0.31	0.38	0.64	0.64		0.74	
Subjective health status[1]	0.57	0.55	0.65	0.72	0.68	0.60	0.73	0.79	0.37	0.60	0.57
Parental allergies	0.47	0.69		0.87		0.74					0.75
Mother breastfeeding										0.79	
Mother smoker				0.88							
Mother smoked during nursing				1.18							
Mother smoked during pregnancy				0.85						0.70	
Father smoker											1.29

	Atopic Disease	Obstructive Bronchitis	Pneumonia	Otitis media	Heart disease	Anemia	Seizures	Thyroid disease	Diabetes	Scoliosis	Migraine
Smoking indoors	1.25									1.49	0.64
Social status			0.97	0.97			1.02			0.95	
Had pertussis			0.81	0.74							
Had measles					1.83						
Mad mumps					0.59						
Had chickenpox	1.25			0.59			0.71				
Had scarlatina		1.43	0.69	0.65	0.80						
Had herpes	1.21			0.77		0.60	0.77			0.80	
Had salmonella			0.75	0.72			0.49				
Had hepatitis				0.49							
Medications prescribed			0.68	0.83		0.64		0.11	0.16		0.60
Number of medications in the last 7 days	0.84	0.86					0.86		0.66	0.93	
Body mass index								0.95		1.08	
Number of vaccinations				0.98		0.98				0.97	

Table 8 presents the model fit statistics of the logistic regression models presented in Table 7. Note that a ratio of Chi^2 to DF close to 1 or below 1 is generally accepted as indicating good fit, as is a non-significant Chi^2-value in the Hosmer-Lemeshow adaptation test, which is true for most models. However, three models present with a significant Hosmer-Lemeshow test, indicating sub-optimal fit. Observe, though, that with such large numbers such adaptation tests are overpowered and often indicate a lack of fit because of a few outliers. The variance explained by the models is indicated by the R^2-Value and is between 1% and 8% at the most, i.e. quite small.

Table 8 – Model fit statistics for the logistic regression models given in Table 7: Ratio of Chi^2 statistics to degrees of freedom, Cox-Snell R^2, p-value of Hosmer-Lemeshow Chi^2 test of deviation of observed from predicted scores

	Atopic Disease Model Fit	**Obstructive Bronchitis** Model Fit	**Pneumonia** Model Fit	**Otitis media** Model Fit	**Heart disease** Model Fit	**Anemia** Model Fit	**Seizures** Model Fit	**Thyroid disease** Model Fit	**Diabetes** Model Fit	**Scoliosis** Model Fit	**Migraine** Model Fit
Chi^2 /DF (§)	1.02	0.78	0.68	1.33	0.24	0.22	0.31	0.14	0.02	0.37	0.21
Cox-Snell R^2 (%)	0.08	0.039	0.02	0.064	0.012	0.013	0.008	0.034	0.004	0.052	0.027
Hosmer Lemeshow Chi^2 associated p-value ($)	0.05	0.18	0.7	0.001	0.4	0.8	0.7	0.5	0.9	0.6	0.01

1: subjective health status 1 = very good, 5 very bad; § = goodness of fit description: if close to or below 1 the fit of the model is reasonable; % = gives the percent of variance explained by the model; $ = goodness of fit-Test: if not significant, there is little or no deviation from expectation (note that with large numbers such tests reach significance quickly and indicate a lack of fit, although the deviation from expectation might only be very small)

Fewer medications prescribed and fewer medications taken are good predictors for the absence of most diagnoses. Only heart disease is independent of number of medications prescribed or taken. In all other disease categories medications are associated with more diagnoses. Whether this is causal or a consequence of the disease is impossible to say.

Fewer vaccinations are associated with not having otitis media, anemia, and scoliosis. The effect size is small, and we see a 2 to 3 % reduction in incidence, after controlling for all other factors.

For those three diseases – otitis media, anemia, scoliosis - where number of vaccinations played a role, we explored which vaccinations might play a role by entering all the previously predictive variables into a logistic regression model, and instead of the summary variable "number of vaccinations", the number of single vaccinations received, especially the number of vaccinations against tetanus, diphtheria, pertussis, Hemophilus influenza, hepatitis B, polio, measles, mumps and rubella. We did the same for the overall Poisson model predicting morbidity, i.e. the sum of all diagnoses. Results are given in Table 9. It presents Odds Ratios for the single logistic regression models to explain otitis media, anemia and scoliosis, as well as the raw regression weights for the logistic regression model explaining the morbidity score.

Table 9 – Significant Odds Ratios (95% confidence intervals) associated with specific vaccinations in logistic models predicting the *absence* of otitis media, anemia and scoliosis. The other predictors are omitted. Significant beta-weights from Poisson regression model predicting morbidity (i.e. sum of all diagnosis), when number of vaccinations is replaced by number of specific vaccinations. Only significant vaccinations, all other predictors omitted

	Otitis media	**Anemia**	**Scoliosis**	**Morbidity**
Tetanus		0.84 (0.74–0.95)§		
Hemophilus influenza	0.89 (0.86–0.92)**	0.92 (0.85–1.001)§		0.03 (0.02–0.05)**
Polio	1.08 (1.04–1.13)**			
Measles	1.21 (1.08–1.35)**		1.19 (1.01–1.4)§	- 0.05 (-0.09--0.01)§
Mumps	0.67 (0.60–0.76)**		0.81 (0.68–0.99)§	0.1 (0.05–0.15)**
Diphtheria			0.79 (0.72–0.87)**	
Hepatitis B				-0.01 (-0.02--0.001)§

** = $p < 0.0001$; §= significant, but not at a corrected level (i.e. $p > 0.006$)

As can be seen, while polio, measles and hepatitis B vaccination have a beneficial effect, i.e. are associated with less cases of otitis, scoliosis or less morbidity, tetanus vaccinations are associated with more cases of anemia, Hemophilus influenza vaccination is associated with more morbidity, more cases of anemia and otitis, and mumps vaccination is associated with more morbidity, more cases of otitis and scoliosis. Finally, also diphtheria vaccination is associated with more cases of scoliosis.

Discussion

The question to be answered by this analysis is, whether vaccinations are associated with better or worse health in children in very general terms. To answer this question, we utilized data from a large representative cross-sectional survey database of German children between the ages of 1 and 17 years. We found that the number of vaccinations is a significant positive predictor of morbidity, defined as the number of diagnoses given in a computer assisted interview by a doctor. This variable is a sum of altogether 11 potential diagnoses. Exploring these diagnoses separately in logistic regression models we saw that in three out of these 11 categories fewer number of vaccinations were predictive, namely of the absence of otitis media, anemia and scoliosis. An exploration of the types of vaccinations most frequently entering the models reveals tetanus vaccination, hemophilus influenza vaccination, mumps vaccination and diphtheria vaccination as potential negative predictors for morbidity or single diagnoses. Measles and polio vaccinations, as well as vaccination against hepatitis B seem to have a beneficial effect. These effects are incremental to the predictive effects of sociodemographic variables and other health variables explored and controlled for. This has to be seen against the overall background that the number of children having had infections is generally small, whether vaccinated or not, except for chickenpox which are contracted by 73% of all children. Unvaccinated children had a 50% lower likelihood to have contracted chickenpox, scarlatina or salmonella infection, while vaccinated children were less likely to have contracted pertussis, measles, mumps and rubella.

Measles and mumps, however, were only predictors for single diagnoses in the logistic regression models, while rubella never entered the models. In the overall morbidity model *not* having had pertussis, chickenpox, scarlatina, herpes and salmonella infections is associated with *higher* morbidity. As this overall model is our principal, predefined analysis and the logistic regression models are subsidiary, we tend to put more emphasis on this principal finding. It suggests that

experiencing some of these diseases, namely pertussis, chickenpox, scarlatina, herpes and salmonella infections, and having fewer vaccinations is associated with better overall health.

POTENTIAL EXPLANATIONS

Why could it be that vaccinations might even have a negative effect on health? One explanation could be that unvaccinated children come from such special households, such that the vaccination status is a proxy variable for an altogether different lifestyle, beneficial to health, for instance in terms of communicative culture, or psychological health, or care about environmental factors that were not captured by the variables used in this survey. Whether this is true could only be explored by longitudinal randomized studies. Another explanation could be that having some of the diseases naturally as a child, at least in advantaged settings as in Germany, is in general terms protective, as the immune system might be trained in a different way and hence autoimmune and other disease processes could be prevented.

Being exposed to some pathogens naturally might allow the immune system to mature and keep the Th1 and Th2 balance, such that a shift towards the more allergenic Th2-axis is avoided. This has been observed in children and generally people growing up in rural settings, where they are exposed to natural pathogens more often [50,51]. In the same sense, experiencing some of the diseases naturally might help children to generate a more robust immune response against other diseases as well. Currently, this explanation stems from observations of pediatricians only. To our knowledge, this area is understudied and would warrant some careful longitudinal studies. We see in our data that having had some of the childhood diseases, like pertussis, chickenpox, salmonella, scarlatina and herpes is protective for overall health.

A further point to take into account is that various vaccines are produced with different antigens: some with attenuated live pathogens, some with incapacitated pathogens, some with dead ones. Over the years, different strains and types of vaccines might have been used, and due to the cross-sectional nature of our study, this factor cannot be further analyzed.

A point often neglected, it seems to us, is the fact that in nature an immune system normally has to deal with only one pathogen at a time, if a child falls ill. But nowadays many vaccinations are applied at the same time and are only available as triple- or even manifold vaccines, as is the case with measles-mumps-rubella or diphteria-tetanus-pertussis vaccines. It has been observed that children who had received an influenza vaccine were four times more likely to contract another virologically verified respiratory disease. This might have to do with the fact that vaccinations might impact non-specific immunity, according to the authors of the study.[24] Also, so called virus interference might happen: during the time when a vaccine is given there is a higher susceptibility to other pathogens, as Cowling and colleagues have shown.[52] Thus, when multiple pathogens are applied at the same time in a triple-vaccine, it might be conceivable that natural immunity is too weak to deal with other, naturally occurring processes. To our knowledge, this is also an understudied area.

Finally, one should bear in mind that the age at which children are being vaccinated is reducing over the years. If mothers have a strong specific immunity against the so called “childhood diseases” from their own disease history, they pass on this immunity to their children, if they are nursing, such that children are protected, while their own immune system matures. If this maturation process is interrupted or there is not sufficient protection, because mothers have not enough antibodies themselves, then early vaccinations might cause a problem, also, because the potential negative effects of adjuvants, see next paragraph, might be much more severe in younger children.

Note that vaccination did not protect fully against childhood infections, and in some cases vaccinated children had more of these diseases than unvaccinated children. Finally, another explanation could be that some vaccines are produced with problematic adjuvants. As our sample was cross-sectional, and very likely different types of vaccines had been given over the years this cannot be explored any further. However, safety studies that unravel potential hazards are often conducted in large enough populations only at later stages, and there is a track record of adjuvants being called safe, while getting retracted years later as they have been associated with negative effects, such as thiomersal, i.e. methyl mercury [53]. Thiomersal is nowadays only contained in multi-vaccine doses of influenza vaccine in the US, which is recommended for children from age 6 months (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/thimerosal-and-vaccines, accessed 6th June 2026), but has been banned otherwise in the US for vaccines for children under six years of age [54-56]. In fact, more autism cases were seen in children that had received an MMR vaccine before age three [57]. In the same vein, current adjuvants could contain problematic substances which might only be discovered in the future.

It might also be the case that the sheer load of different vaccines that have been accumulated over the years is one of the potential problems. An indirect hint is the fact that in the single analyses hemophilus influenza and mumps vaccines are most frequently seen as carrying potentially damaging effects, and those vaccines are comparatively recent additions to the vaccination portfolio of children in industrialized countries. The negative impact of pediatric hemophilus influenza vaccinations is consistent with their apparent effect of increasing the risk for type I diabetes that was shown in Finnish children and NOD mice [20].

It is very important to take note of the fact that our findings have no bearings whatsoever on public health campaigns in developing countries, where large campaigns against measles and other diseases have been largely beneficial [3,4]. But they do call into question the generalized stance that vaccinations are always beneficial for everyone under all circumstances. At least in an advantaged health care system as in Germany being unvaccinated might confer a health benefit on children. This is of course only true for the small minority of 1,2% of all German children that are unvaccinated, and we have no way of knowing what would happen if a larger part of the children population were to go unvaccinated. Historical comparisons are not viable, as they confound different social, political and economic situations with present or future epidemiological data.

Our findings should be taken as preliminary and should prompt more thorough prospective, randomized studies. These should by all means be three armed, controlling also for the adjuvants in a zero-control arm that receives only saline to study the differential effect of the full vaccine and the adjuvants against no treatment. Our findings certainly question political campaigns for compulsory vaccination campaigns.

Clearly, this is a finding running counter to prevailing beliefs and hence needs careful and critical scrutiny. Therefore, the following limitations should be borne in mind:

LIMITATIONS

This dataset is a natural, representative sample without any experimental intervention and hence allows only tentative conclusions. It is always difficult to say whether a variable is causal or not in such models. For instance, number of medications prescribed or taken in the last 7 days, which is a robust predictor in the main model and in many logistic

regression models, might be causal for a worse health status and higher morbidity, or it might be a consequence. In the same sense, experiencing some of the childhood infections might be the consequence of a disease, or the cause. Only vaccinations, not being consequent on diseases but meant as a causal preventive measure, can be legitimately interpreted as causal, at least in theory.

The models explain between 0.5 and 8% of the variance, i.e. only a very small part of the variation can be grasped by the variables studied here, including vaccinations. Vaccination status has been entered into the models last. That means, if it shows up as a significant predictor, this is in addition to all other variables that can be controlled for. Especially hemophilus influenza, mumps and diphtheria vaccinations stand out as predictors of higher morbidity. While it is difficult to interpret this finding, it might have to do with the fact that hemophilus influenza and diphtheria are vaccines using inactivated pathogens, which seem to be generally less beneficial than those from live attenuated pathogens according to Aaby and colleagues [3,5]. However, if this were the sole explanation, mumps vaccine should not be in this group.

This points to a potential problem with data-quality: We used the data-set provided by the Robert-Koch-Institut (RKI). RKI is the owner and curator of the data. Since the data were collected in the field by various doctors and other personnel, systematic coding errors might be present that cannot be detected. An indirect hint is the fact that we detected implausibly high numbers of measles vaccinations in some cases. This is another reason why our data should be replicated in an independent study, preferably with a longitudinal design.

There are certainly many more variables, such as food, psychological health of families, genetic factors, environmental factors that play a role in modeling disease incidence which were not captured by our study. However, it was not our goal to explain morbidity in full, but to explore, whether vaccinations have a beneficial effect on health, in addition to what can be explained by sociodemographic and disease factors.

One might argue that already this restricted data-set had too many variables to be reliably modelled. We do not think that this is the case. Our data-set was large enough to provide enough power. Our modeling strategy was parsimonious, and we adjusted for multiple comparisons, following our predefined analytical protocol. This procedure guaranteed that only really important variables were taken up in the regression models, and we would argue that the content and interpretability of the models testify to the success of this strategy. Although effect sizes are generally very small and cover at the most 8% of the variance, it is intriguing that vaccination as an additional incremental predictor added to the explanatory power of the models. The fact that we had only 202 children who were unvaccinated, compared with more than 15'000 that were vaccinated would, if anything, work against such a clearcut finding, because it is usually the smallest group that determines statistical power, or in that case the power to differentiate. The fact that our analysis could differentiate shows that there is indeed a systematic difference between those groups and this difference speaks for a better health of unvaccinated children. Our model fit statistics and residual diagnostics showed that the models fitted comparatively well.

It should be noted, however, that these findings relate to well cared for children in Germany and can therefore not necessarily be extrapolated to children growing up in other countries or under different conditions.

However, by analyzing national survey data from the US, Hurwitz and Morgenstern reached similar conclusions regarding diphtheria-tetanus-pertussis or tetanus vaccination and found an increased risk for vaccinated children of developing allergies or allergy-related respiratory symptoms [58]. Data from Africa also raise doubts about the benefits of some vaccinations, as a significant increase in mortality has been reported after the introduction of diphtheria-tetanus-pertussis vaccinations in young children despite vaccinated children having had better nutritional status [59,60].

Conclusion

Meanwhile we conclude from our analysis that vaccinated children are not healthier than unvaccinated children. On the contrary, being unvaccinated is associated with lower morbidity and with a reduced risk for otitis media and scoliosis. The vaccinations that need to be scrutinized further are those against Hemophilus influenza, mumps, tetanus and diphtheria, while those against measles, polio, and hepatitis B seem to be beneficial. These findings come from a natural, representative cohort in Germany and are only partially generalizable to other settings or countries. Most importantly, they should give rise to thorough, longitudinal three-armed randomized studies that do not only study the immediate effects on the prevention of infections, but also on the overall health benefits long term.

Supplementary Material

Supplementary material can be accessed **here**

Declarations

ETHICS: Not applicable, as this was a secondary analysis of an anonymized data set.

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ROLE OF THE FUNDING SOURCE: The funding source asked for an independent evaluation of the KIGGS data after the first report had been published [39], but made no concrete design- or analysis proposals and requested an independent publication which the analysis of this study is supposed to supply.

CONFLICT OF INTEREST: None of the authors have a conflict of interest.

AUTHOR CONTRIBUTIONS

HW designed the study, wrote the protocol, conducted the analyses, interpreted the data and wrote the first draft of the paper. AM checked the original data, provided a database for analysis, checked the analyses, critically contributed to the interpretation of the data and to the writing of the paper.

DATA AVAILABILITY STATEMENT

The data belong to the Robert-Koch-Institut which releases them under special request as a public use file to qualified researchers who are willing to sign a data-use contract. The exact source of the data is indicated in the Methods section of the paper. If the RKI consents, we are happy to make our analysis data-set available to researchers but require a written permission statement of the RKI.

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