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Int. J. Environ. Res. Public Health2020,17, 8674; doi:10.3390/ijerph17228674 [www.mdpi.com/journal/ijerph](http://www.mdpi.com/journal/ijerph) Article Relative Incidence of Office Visits and Cumulative Rates of Billed Diagnoses Along the Axis of Vaccination James Lyons-Weiler1,\* and Paul Thomas21The Institute for Pure and Applied Knowledge, Pittsburgh, PA 15101, USA2Integrative Pediatrics, Portland, OR97225, USA; paulthomasmd@drpaul.md\* Correspondence: jim@ipaknowledge.orgReceived: 23 October 2020; Accepted: 18 November 2020; Published: 22 November 2020Abstract:

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-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. Key words: pediatrics; vaccines; adverse events; relative incidence of office visit1. 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

Int. J. Environ. Res. Public Health2020,17, 8674 2 of 25outcomes. 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 VS. There are serious limitations inherent to long-term vaccine safety studies as currently implemented. Post-licensure studies on vaccine safety typically employ an “Nvs.N+ 1” design of analysis, meaning they compare fully vaccinated children with fully vaccinated children missing online 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 (Jorgensen 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 armhole 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 Methods2.1. Data Source and Provenance A detailed proposal for a retrospective study was submitted to an Institutional Review Board(IRB), and was approved (Pro00031853 letter dated7 May 2019). The data source for this study was all billing and medical records of Integrative Pediatrics, a private pediatric practice located in

Int. J. Environ. Res. Public Health2020,17, 8674 3 of 25Portland, 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 Criterial 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 1.2.3. Study Population The inclusion/exclusion criteria lead to 3324 patients, of which 2763 were variably vaccinated, having received 1 to 40 vaccines (Figure 1).Figure 1.Inclusion criteria diagram.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.

Int. J. Environ. Res. Public Health2020,17, 8674 4 of 25Table 1.Demographic variables in the analyzed data set. Category Unvaccinated (N = 561) Vaccinated (N = 2763)Χ2pMale (N,%)279 (49.7%)1432 (51.8%)0.8190.365Female (N,%) 282 (50.3%) 1331 (48.2%)Breastfed (N,%) 550 (98%) 2670 (96.6%) 3.037 0.081T-testFHA (any) 174 (31%) 695 (25.16%) 28.239<0.00001Mean DOC 741 1525 17.69 <0.00001DOC matched 741 741 (N = 561) 0 1.0Mean BW (kg)unmatched3.3 3.28 0.509 0.305DOC = “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 mo, mean age 2 y 1 mo, and max age 10 y 1 mo; vaccinated: manage 2 mo, mean age 4 y 3 mo, and max age 10 y 6 mo; after DOC matching, average age in the vaccinated was also 2 yr 1 mo). The difference in DOC between the vaccinated and unvaccinated groups was highly significant prior to DOC matching (Student’st, 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’st)).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.

Int. J. Environ. Res. Public Health2020,17, 8674 5 of 252.6. 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 no 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 (OVV) and unvaccinated(OVUV) 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”. They-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 (OVV/OVUV). 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. 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(OVV/OVUV) 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.

Int. J. Environ. Res. Public Health2020,17, 8674 6 of 252.6.2. 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).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 ith diagnosis were calculated as the standard ratio of the rate of exposure in those with the diagnosis (p1,i) to the rate of exposure in those without diagnosis (p2,i), i.e.,ܴܱ௜=௜,ଵ݌൫1 − ݌ଵ,௜൯൘௜,ଶ݌൫1 − ݌ଶ,௜൯൘(1)Relative risk ratios for each of the ith conditions with n1ivaccinated in D1diagnosed and n2ivaccinated among D2without diagnosis was calculated as௜=݊ଵ,௜ܦ൫ଵ,௜൯൘݊ଶ,௜ܦ൫ଶ,௜൯൘(2)Z-tests of proportion were conducted to provide-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. Foreach 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

Int. J. Environ. Res. Public Health2020,17, 8674 7 of 25graphical 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 xi) and OR on incidence (xi> 0). For the simulation, 1000 measurement sets X ={x1,x2,x3...xn}drawn from a Poisson distribution of 400,000random 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(λ= 1) were used to represent the unvaccinated with no effect. We simulated an increased effect of vaccines on office visits by increasing from 1.01 to 1.1 (step0.01), with 400,000 values at each level ofλ. Increased levels ofλ 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 xi> 0 as a positive diagnosis and again using RIOV, leaving the generated values of xi 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 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 10We 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 theχ2test.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.

Int. J. Environ. Res. Public Health2020,17, 8674 8 of 25Table 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 Zp Fever 759 17 9.065 8.801 12.476 <0.0001“Well Child” Visits 32826 49871.336 1.149 6.540 <0.0001Ear Pain 269 16 3.414 3.232 5.310 <0.0001Otitis media 3105 216 2.919 2.518 23.441 <0.0001Conjunctivitis 1018 87 2.376 1.935 9.783 <0.0001Eye Disorders (Other) 277 31 1.814 1.586 3.350 0.0008Asthma 336 13 5.248 5.065 6.693 <0.0001Allergic Rhinitis 405 12 6.853 6.662 8.158 <0.0001Sinusitis 107 5 4.345 4.240 3.566 0.00036Breathing Issues 621 44 2.866 2.561 7.898 <0.0001Anemia 979 36 5.522 5.181 13.603 <0.0001Eczema 512 23 4.520 4.281 8.479 <0.0001Urticaria 174 17 2.078 1.908 3.027 0.00244Dermatitis 742 105 1.435 0.992 4.034 <0.0001Behavioral Issues 343 17 4.097 3.900 6.087 <0.0001Gastroenteritis 688 30 4.656 4.374 6.543 <0.0001Weight/Eating Disorders 1115 90 2.515 2.056 10.264 <0.0001Seizure 43 8 1.091 0.985 0.229 0.8181RIOVs 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 clustering 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

Int. J. Environ. Res. Public Health2020,17, 8674 9 of 25significant (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 on the test of proportions from 9.98 to18 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.

Int. J. Environ. Res. Public Health2020,17, 8674 10 of 25Figure 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 561unvaccinated groups for each percentile of vaccine uptake on the x-axis. (A) Autoimmune respiratoryillnesses; (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 socialinteractions and autism spectrum disorder.

Int. J. Environ. Res. Public Health2020,17, 8674 11 of 25Table 3.RIOV analysis of outcomes of the vaccinated vs. unvaccinated groups, matched for Days of Care (DOC) matched comparison (N1 = 561 and N2 = 561).Test of Proportions Condition Vaxxed Unvaxxed RIOV 95thCI 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 0.0307Ear Pain 18 16 1.127 1.022 0.354 0.726Otitis media 355 216 1.646 1.001 8.312 <0.00001Conjunctivitis 113 87 1.301 1.023 2.042 0.04136Eye Disorders—Other 38 31 1.228 1.076 0.877 0.3788Asthma 20 13 1.541 1.437 1.317 0.186Allergic Rhinitis 21 12 1.753 1.649 1.600 0.1096Sinusitis 6 5 1.202 1.143 0.306 0.756Breathing Issues 75 44 1.708 1.502 3.015 0.00252Anemia 130 36 3.618 3.361 7.912 <0.00001Eczema 64 23 2.788 2.613 4.581 <0.00001Urticaria 14 17 0.825 0.925−0.541 0.5892Dermatitis 86 105 0.821 1.090−1.459 0.1443Behavioral Issues 54 17 3.182 3.026 4.452 <0.00001Gastroenteritis 89 30 2.972 2.763 5.728 <0.00001Weight/EatingDisorders147 92 1.601 1.288 4.023 <0.00001Seizure 10 8 0.798 0.067 0.874 0.6312Respiratory Infection 703 382 2.682 1.134 51.85 <0.00001The 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.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 Table4. 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).

Int. J. Environ. Res. Public Health2020,17, 8674 12 of 25Table 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 4.4793.587 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’st, p= 0.919). Average age at last office visit was also not significantly different (= 0.95). The average age of first office visit differed only by 2 days (6 days vs. 8 days, Student’st, p< 0.001).3. Student’st, p 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 external, 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).

Int. J. Environ. Res. Public Health2020,17, 8674 13 of 25Table 5.Analysis 4: DOC-matched incidence analysis. Outcome OR RR 95th 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 1.4521.44 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 0.4980.499 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) 95thCI 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.

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