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Breakthrough Infection Signal In VAERS Corroborates IgG4-Mediated Increased Susceptibility To SARS-CoV-2

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Abstract

Background: Millions of individuals have reported adverse events (AEs) using the U.S. Centers for Disease Control (CDC) Vaccine Adverse Event Reporting System (VAERS) in the context of the COVID-19 injectable products. Tens of thousands have reported concurrent Breakthrough SARS-CoV-2 Infections (BTIs).

Methods: BTI reports from VAERS were extracted to determine if VAERS data corroborates multiple-COVID-19 modRNA product injection-related propensity toward IgG4-mediated increased susceptibility to SARS-CoV-2. The data was stratified according to numbers of doses in the "vaccine dose series" (up to dose 4), and the age of the individual reporting the BTI, and compared to scientific and medical literature-based findings indicating a shift to tolerizing (non-inflammatory) spike-specific IgG4 antibodies following third and fourth doses of the COVID-19 modRNA products.

Results: There are 68,504 BTI reports in VAERS U.S. data following administration of the COVID-19 modRNA products spanning 2020-2024. The highest percentage of dose-specific BTI reports of total BTI reports was seen following dose 4 (30%), followed by dose 3 (16%) and doses 1 and 2 (4% and 12%, respectively), despite absolute counts of reports per dose being the highest in the cases of doses 3 and 4 (N=11,330, N=31,739, N=14,999, N=10,436, doses 1-4, respectively). Importantly, an emergent pattern in dose 4 data was discovered which was not observed for dose 1-3 data. This pattern was observed for 55-77-year-olds whereby peak reporting far exceeded that for dose 1-3 data. Significant differences include weak correlation between BTI and doses 1 and 4 ($r(97) = .45$; $p < .001$) and strong correlation between BTI and doses 1 and 2 ($r(116) = .85$; $p < .001$) and doses 1 and 3 ($r(108) = .94$; $p < .001$). Normalized rates (BTI reports per 100,000 BTI reports/age/dose) demonstrated that dose 4 reports for 55-77-year-olds were significantly more frequent than for dose 1 (Area Under the Curve (AUC) of 1.00; $r(21) = .88$; $p < .001$), further validating the Pearson's correlation.

Conclusions: Increased rates of BTI reports could be due to conferred susceptibility to SARS-CoV-2 following multiple doses of COVID-19 modRNA products that align with a 19.27% rise in IgG4 following dose 3 published in the literature.

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Keywords

Area under curve (AUC), Breakthrough infection (BTI), COVID-19, IgG4, Lipid nanoparticle (LNP), modRNA, SARS-CoV-2, VAERS

Background

According to CDC data as of May 10, 2023, approximately 85% of the United States population has received at least one dose of the COVID-19 modRNA products and most of these were either the Pfizer or Moderna-branded products (BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna)) [1,2]. These products had not been fully licensed by the U.S. Food and Drug Administration (FDA) prior to August 23, 2021 [3], and were instead authorized for emergency use by the FDA under an Emergency Use Authorization (EUA) as "medical products" to prevent Coronavirus Disease 2019 (COVID-19) [4,5]. The shots were not approved to reduce transmission or the severity of infection with SARS-CoV-2, thus any emergent AEs temporally-associated with administration of these COVID-19 shots resulting in hospitalization and death tip the risk-benefit ratio toward risk, especially considering that SARS-CoV-2 did not itself pose a risk of death in healthy and young demographics as described in The Lancet in 2021 [Bhopal, Sunil S et al.] [6]. Tens of thousands of deaths have been reported to VAERS in association with the COVID-19 shots since the roll-out began in December of 2020 [7]. The bivalent versions of the Pfizer/BioNTech and Moderna COVID-19 injectable products were available and authorized for use in September 2022 [8].

The modRNA-LNP COVID-19 injectable products are gene-based prodrugs encased in LNPs that utilize a modified messenger RNA (modRNA) as the coding material for an engineered viral spike protein of SARS-COV-2 for manufacture of the antigen by transfected host cells. These types of gene therapies have never before been deployed on such a large scale in the context of a viral infection. Pharmacovigilance databases such as the CDC's VAERS reporting system are designed to detect safety signals in data submitted as voluntary reports of AEs in the context of pharmaceuticals or biologics, such as vaccines [9,10]. The primary purpose for maintaining the database is to serve as an early warning system for AEs not detected during pre-market testing. VAERS has been used historically to identify safety issues and prompt investigations which led to the withdrawal of specific vaccines from the market due to observed safety issues [11]. In addition, the National Childhood Vaccine Injury Act of 1986 (NCVIA) requires health care providers and vaccine manufacturers to report to the Department of Health and Human Services (DHHS) specific AEs following the administration of vaccines outlined in the Act [12]. If safety signals emerge in the context of a particular marketed or EUAed product, such as a sudden cluster of reports of sudden death, death following cardiac arrest without known etiology, or death of an infant, this would provide a reason to order and perform an autopsy. It is a criminal offense to submit a false VAERS report and can result in imprisonment [9,10].

Vaccine-induced injuries or AEs can be defined as the onset of clinical symptoms that are temporally associated with vaccine/injection administration and in the absence of another known cause [13,14]. An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human study participant, including any abnormal physical exam or laboratory finding from autopsy, symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research. A serious or severe adverse event (SAE) is defined as any adverse event that results in death, is life threatening, or places the participant at immediate risk of death from the event as it occurred; requires, or prolongs hospitalization; causes persistent or significant disability or

incapacity; results in congenital anomalies or birth defects; or is another condition which investigators judge to represent significant hazards [9,15]. The VAERS Data Use Guide states that 10-15% of reported AEs are classified as severe for any given set of data [9].

The VAERS coding system uses an international coding system that is used worldwide called the Medical Dictionary for Regulatory Activities (MedDRA) [9, 16]. The MedDRA coding system uses key words representing the AEs described in the case report and converts them to standardized codes. The MedDRA codes provided in the VAERS dataset are called the "Preferred Terms." VAERS reports are primarily filed by medical professionals (67%) and can also be filed by family members [17]. Upon individual reporting of AEs, a temporary VAERS ID number is assigned to the individual to preserve confidentiality, and a detailed description of the side effects are transcribed along with the individual's age, residence by state, past medical history, laboratory data, allergies, sex, and other details. In addition, the vax lot number, place of injection, and manufacturer details are included in the report. If the VAERS report is "validated" following vetting, a permanent VAERS ID number is assigned, and the report is filed in the front-end data set available for download. VAERS is a prominent U.S.-based pharmacovigilance database that contains millions of reports of AEs in the context of the COVID-19 modRNA products.

A BTI is a case of illness in which a vaccinated individual becomes infected with the illness, because the vaccine has failed to provide complete immunity against the pathogen (currently only viruses) [18]. BTI reports are entered into VAERS as primary AEs when an individual succumbs to the vaccine-associated disease in the context of a pharmaceutical or biological intervention. In the case of COVID-19, a BTI is defined by the use of a SARS-CoV-2 test that returns a "positive" result (MedDRA code "SARS-CoV-2 test positive") reported concurrently with MedDRA codes "COVID-19," "Vaccination failure," "BT COVID-19," or "Vaccine BT infection." BTI have been reported in VAERS following all doses of the COVID-19 modRNA products, and for the purposes of this study, from doses 1-4.

Bivalent vaccines were developed and recommended for subsequent booster doses. The bivalent Pfizer COVID-19 shot uses the Omicron BA.4 and BA.5 subvariants and the bivalent Moderna COVID-19 shot, uses a mix of the original/Omicron BA.1 and Omicron BA.4 and BA.5 subvariants. Although these products have been reported in the literature to be associated with BTIs, it is not exclusive to the bivalent products and can depend on various factors, including the time since the last vaccine dose, the presence of new variants, and individual immune response [19,20,21].

Immunoglobulin 4 (IgG4), is a subclass of antibody that induces immune tolerance and is produced in response to repeated or long-term exposure to the same or similar antigens. IgG4 antibodies may become the dominant subclass of IgG, as a result of this repeated exposure, causing the body to fail to mount an immune response, rather than mounting a normal immune response in the presence of a foreign antigen [22]. Immunoglobulin class switching to IgG4 may be modulated by Interleukin-10 (IL-10) and thus links this subclass of antibody to tolerance induction [23]. IgG4 may also represent the dominant antibody subclass in immune responses to the essential blood clotting proteins: factor VIII and IX. This class switch has been found to be associated with a reduced capacity of the spike-specific antibodies to mediate antibody-dependent cellular phagocytosis and complement deposition. Irrgang et al. 2023 found

that individuals who were injected with three doses of the COVID-19 modRNA products, who also experienced a BTI, had the highest IgG4 levels amongst the 4 groups they examined [24].

The roll-out of COVID-19 injections are actively being monitored by regulatory agencies, but all of the risks are not yet known [46-49]. There are thousands of peer-reviewed articles documenting BTI emergence in the context of the COVID-19 injectable products, and these publications can be sought out by querying "vaccine-BT [infections] sars-cov-2" in PubMed [25-31].

It bears repeating that under-reporting is a known and serious limitation of the VAERS system with past estimates of less than 1% to 13% of total AEs actually being reported. Also, due to multiple additional reporting systems for these COVID-19 modRNA products including manufacturer and clinical trial reporting systems, along with V-SAFE, the VAERS system was less utilized than is typical for the COVID vaccines [9,10,32-37].

Methods

To analyze the VAERS data, the Language and Environment for Statistical Computing R was used. Excel was also used to generate the figures, to perform Pearson Correlation Coefficient calculations (significance level 0.05) and for AUC calculations. AUC was calculated using Riemann Sum. The VAERS data was downloaded as three separate comma separated values (csv) files representing i) general data for each report; ii) the reported AEs or "symptoms"; and iii) injection data including injection manufacturer and lot number for each VAERS ID. In order to maximize the input variables per individual for analysis, the three files were merged using the VAERS ID as a linking variable.

For the purposes of comparing potential differences in BT infection rates with respect to doses 1 through 4, a master file was first generated containing only VAERS reports of BT infection with complete age data for the Moderna and Pfizer COVID-19 products. This was done by filtering according to "vaccine" manufacturer (VAX_MANU) (MODERNA or PFIZER\\BIONTECH), filtering by vaccine dose series to ensure only data containing one of dose 1 through 4 was included (VAX_DOSE_SERIES <=4), filtering by MedDRA codes ("COVID-19," "SARS-CoV-2 test positive," "Vaccination failure," "BT COVID-19," and "Vaccine BT infection"), and then finally filtering out the VAERS_IDs that did not contain age data (AGE_YRS != "NA"). Of note, to ensure that doses were not counted twice/included in sequential dose counts, only the maximum dose reported per VAERS_ID was included in the master file. In doing so, a complete data set containing only modRNA, age-complete, dose 1-4 data was created. From this master file, four data subsets were created; each one corresponding to doses 1 through 4, by filtering by the vaccine dose series (VAX_DOSE_SERIES == 1; VAX_DOSE_SERIES ==2; VAX_DOSE_SERIES ==3; VAX_DOSE_SERIES ==4). Relevant variables were selected for each subset including VAERS ID, AEs, age, state, vaccine dose series, vaccine manufacturer, and symptoms.

For each subset, the total number of BTI reports was calculated and used to normalize the data according to each age. That is, for each specific age/per dose data set, the number of BTIs was divided by the total number of BTIs per dose, and multiplied by 100,000 to obtain the normalized rate per 100,000 BTIs per age/per dose. These rates were plotted for each dose and superimposed to demonstrate potential differences in trajectories according to the number of reports per age. Pearson correlation calculations were done to

determine potential significant differences between doses, and AUC calculations were done specifically to demonstrate the large difference between dose 1 and dose 4 curves.

Results

BT AE reports associated with modRNA COVID-19 injectable products

As of November 2024, a total of 925,420 individuals have reported being injected with COVID-19 modRNA products. Of these, 702,468 have complete age data and have received either 1, 2, 3, or 4 doses. Of these, there are 93,379 (13%) U.S. VAERS reports of BTIs. Of these, 68,504 (73%) have been injected with one of doses 1-4, and have age-complete data. For the purposes of this study, the data used for analysis comprised the modRNA, dose 1-4 age-complete U.S. BTI data (N=68,504). The distributions of the absolute numbers of reports per dose and the percentage of each dose per total modRNA reports is shown in Table 1. The greatest number of BTI reports is associated with dose 2 (31,739), however 30% of all AEs reported for dose 4 are BTI reflecting the highest percentage of BTI reports with respect to doses 1 - 4.

When the normalized dose data is plotted and superimposed, a clear picture of the difference in the reporting per age emerges in the context of dose 4 as shown in Figure 1. The data for doses 1 through 3 are very consistent in terms of who is filing BTI reports in terms of age. Dose 1 is significantly-correlated to dose 2 ($r(116) = .85$, $p < .001$) and significantly-correlated to dose 3 ($r(108) = 0.94$, $p < .001$). Dose 2 is likewise significantly-correlated to dose 3 ($r(108) = .68$, $p < .001$). However, dose 1 is weakly correlated to dose 4 ($r(97) = .45$; $p < .001$) and dose 2 is not correlated to dose 4 at all ($r(97) = .19$; $p = .06$). Dose 3 and 4 also significantly-correlated ($r(97) = .58$; $p < .001$), even though they do not appear to from Figure 1. What is exceedingly notable from this graph - in addition to the difference in the ages reporting BTIs in the context of dose 4 - is the specificity of the ages in the yellow peak: individuals between the ages of 55 and 77 reported BTI far more frequently following dose 4, than for doses 1-3. In general, reporting rates of BTI in elderly individuals are higher as per VAERS data, however, this only partially accounts for the dose 4 peak as will be discussed in the Discussion section of this study. Safe to say, a proportionality reporting ratio (PRR) analysis revealed that there is an indication of a stronger association of BTI reports in the 55-77 age group (PRR = (A/(A+B))/(C/(C+D)) where A = specific AE (BTI) for specific age group (55-77) and B = all other AEs for specific age group and C = specific AE (BTI) for all age groups and D = all other AEs for all age groups; PRR > 1) suggesting that the signal is real and not merely based on reporting bias.

	Dose 1 (% Total)	Dose 2 (% Total)	Dose 3 (% Total)	Dose 4 (% Total)	Total
BT	11330 (17)	31739 (46)	14999 (22)	10436 (15)	68504
Total	315766 (45)	256017 (36)	95945 (14)	34740 (5)	702468
%BT/Total	4	12	16	**30**	

Table 1. Absolute counts for each dose (doses 1-4) in the context of all modRNA BTI reports and modRNA total AE reports (Total). Percentages of each row total are shown in brackets. Also shown, are the percentages of each dose as per total reports of AEs (%BTI/Total).

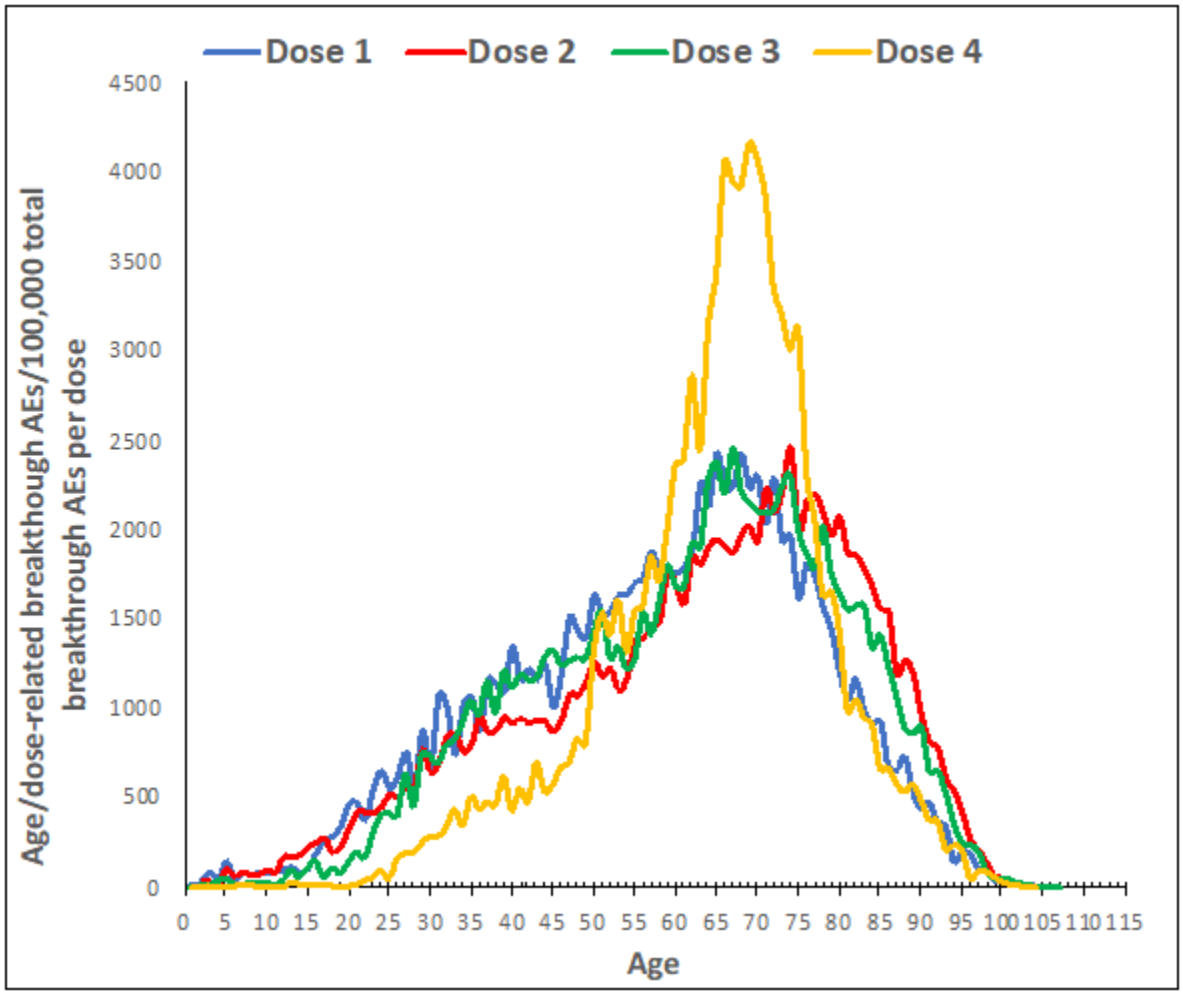

Figure 1. BTI reports from VAERS U.S. data according to dose (by color) and age (x-axis) - AE count per age normalized to number of reports 100,000 BTI reports/per dose (y-axis).

Many of the reports of BTIs, regardless of dose, appear to be made for individuals age 50 and older (49%, 52%, 58%, and 79% for doses 1-4, respectively). This will be expanded upon in the next section. This likely has to do with incentivization strategies to "vaccinate the elderly" first, and also due to the availability of products based on EUA and approval status, and to which age group these products were made available for, and when.

In order to determine the degree to which the dose 4 reports outnumber the dose 1 reports for BTIs, the AUC was calculated for dose 1 and dose 4 for the 55-77-year-old age group, and subtracted. Dose 1 and 4 were chosen as comparatives in that they are the most disparate. Figure 2 shows that the AUC is far greater for the dose 4 reports (orange), and that the difference in the AUCs between dose 4 and dose 1 when considering individuals between 55 and 77 is very large (AUC of 1.00; $r(21) = .88$; $p < .001$). This age range was selected since these ages represented the greatest discrepancy between dose 4 and dose 1. For a different perspective, there were 3,767 more reports of BTI following dose 1 when compared to dose 4 for the 55-77 age range, however, when considering *rates* as per total BTIs reported per 100,000 doses, there are 20,478 more reports per 100,000 doses for dose 4 in the 55-77 age range.

Effect of bivalent products and age on BTI rates

13% of dose 4 COVID-19 modRNA product-associated reports filed to VAERS were bivalent products. This indicates that many people got the monovalent original product versions - even as fourth doses - and this *could* lead to BTI depending on the variants circulating at the time. The percentages of bivalent product reports to VAERS for doses 1, 2 and 3 are 4.6%, 0.1%, and 1.2%, respectively, as shown in Table 2.

It is possible that the bivalent products had an effect on BTIs since the highest percentage of reports were associated with dose 2 and 13% of the doses were bivalent products. It is interesting that the BTI reports associated with bivalent products following dose 4 have two major peaks according to age in the 50s and 70s that do not occur for dose 1 as shown in Figure 3.

The absolute counts and percentages of individuals over 50 who reported modRNA COVID-19 product-associated AEs following one of doses 1 through 4 are shown in Table 3, with the first row indicating the absolute counts and percentages of individuals who reported BTI (per dose), and the second row indicating the absolute counts and percentages of individuals who reported any AE (per dose).

The majority of individuals who succumbed to and reported a COVID-19 modRNA product-associated BTI were over 50 years of age, regardless of dose and mono versus bi-valent (Table 2). However, 88% of the individuals who reported a COVID-19 modRNA product-associated BTI following dose 4 were 50 plus, as opposed to 73% following dose 3, and 69% and 74% for doses 1 and 2, respectively. Also, 79% of the individuals who reported a COVID-19 modRNA product-associated general AE following dose 4 were 50 plus, as opposed to 58% following dose 3, and 49% and 52% for doses 1 and 2, respectively. The dose 4 rates in both the “All reports” group and the “BT infection reports” group, are higher in the dose 4 context meaning that either most who received dose 4 were 50 plus and/or most succumbed to BTIs. In fact, there is a 22% and a 49% increase in reporting rate of BTIs and all AEs, respectively, when comparing dose 4 to the averages for doses 1-3.

	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)	Dose 4 (%)
Monovalent	10806 (95)	31711 (99.9)	14814 (98.8)	9083 (87)
Bivalent	524 (4.6)	28 (0.1)	185 (1.2)	1353 (13)
Total	11330	31739	14999	10436

Table 2. Percentages of mono- and bivalent modRNA COVID-19 products reported in the context of BT infections in VAERS.

	Dose 1 N(%)	Dose 2 N(%)	Dose 3 N(%)	Dose 4 N(%)
BT infection reports >=50y/o	7774 (69)	23608 (74)	10960 (73)	9176 (88)
All reports >=50y/o	155446 (49)	132761 (52)	55265 (58)	27350 (79)

Table 3. Absolute counts (doses 1-4) and percentages in the context of two groups: i) all COVID-19 modRNA product-associated BTI reports (BT infection reports) and ii) all COVID-19 modRNA product-associated reports (All reports). The percentages of individuals 50 years of age or older in each group are shown in brackets.

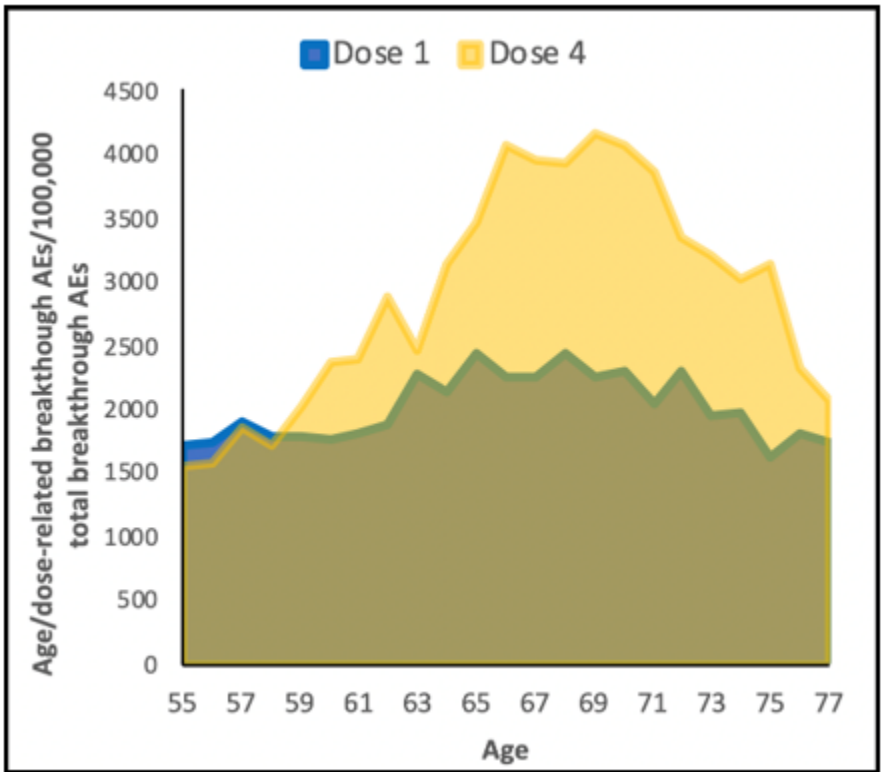

Figure 2. Visualization of the AUCs for dose 1 and dose 4 BTI reports between the ages of 55 and 77.

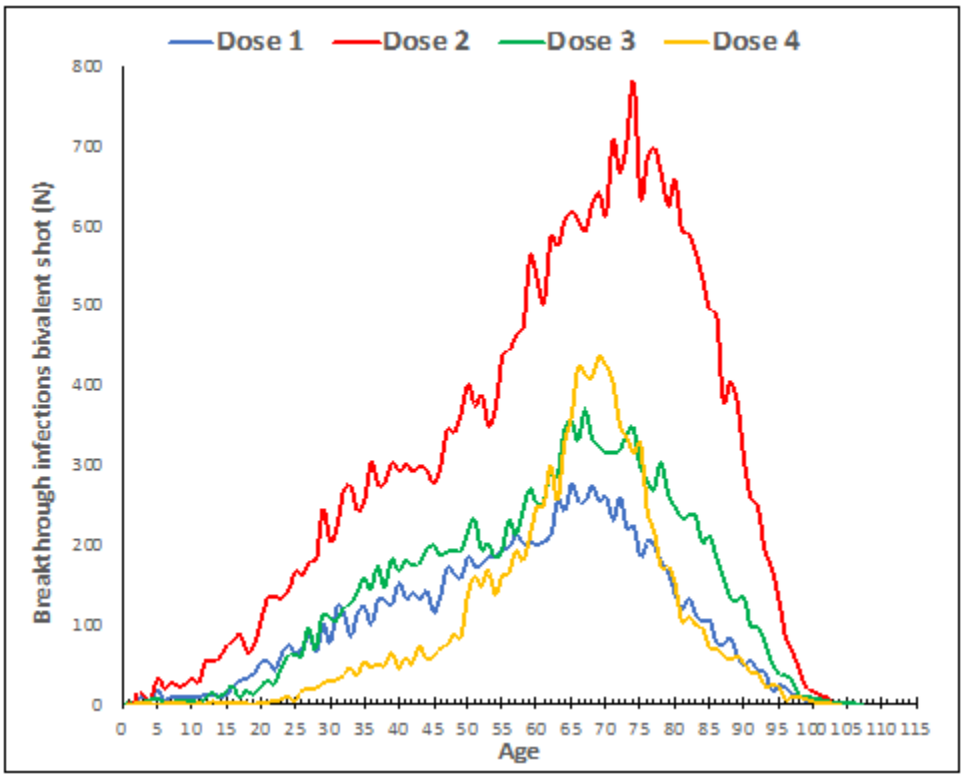

Figure 3. Absolute number of reports of BTI in context of bivalent products according to age showing tri-modal pattern for dose 2 with peaks at ages 30, 50 and 75.

Discussion

A large number of BTIs were caused by the Omicron variant which indicates that COVID-19 modRNA product injection regimens did not confer sterilizing protection, as reported by Irrgang et al. in 2022 [24]. As reported in this pivotal study, IgG4 levels sharply increased and became detectable in almost all Comirnaty vaccinees following dose 3. They also report that anamnestic IgG4 responses were seen when BTIs occurred, and were robustly detectable in the context of triple dosing before infection. It appears from their investigation that the switch is a consequence of ongoing germinal center maturation since it took a few months for the IgG4-class-switched memory B cells to appear. Their results indicate that following third and fourth doses, a class switch to a tolerizing antibody occurs and this could increase susceptibility to a subsequent SARS-CoV-2 infection with a new variant. The authors show that the observed class switch was associated with *a reduced capacity of the spike-specific antibodies to mediate antibody-dependent cellular phagocytosis and complement deposition*.

If one was to speculate how this might manifest with respect to pharmacovigilance reporting in a similar "real world" context, one might expect increased reports of BTIs in the context of third and fourth doses if a class-switch had occurred. Of course, this will depend on immune status at the time of injection and also previous exposures to various SARS-CoV-2 variants. It would be very interesting to know what percentage of people had prior exposure to SARS-CoV-2 in the context of BTIs. Interestingly, according to the findings of this study, increased BTIs in the context of dose 4 is precisely what was observed in VAERS. Walmsley et al. 2023 recently reported as part of a study *to determine predictors of BT SARS-CoV-2 infection after vaccination*, that older-aged cohorts were less likely to have BTIs at all time-points including during the Omicron BA.4/5 and XBB waves due to establishment of hybrid immunity induced by earlier versions of the injections [38]. They concluded that the receipt of an original/Omicron vaccine was anti-correlated with BTI, meaning that older individuals were less prone to BTIs due to the establishment of this hybrid immunity.

My findings are contradictory to the Walmsley group's findings in that VAERS data in this study indicate a preponderance of BTI reporting in older age groups, and it is likely that many of these individuals did get injected with earlier versions (i.e.: monovalent products) initially, and VAERS data confirms this. In fact, 88% of the over 50 age group who experienced BTI reported receiving dose 4 (modRNA product) in 2022, and the most prominently administered COVID-19 modRNA products in 2022 were the Pfizer and Moderna monovalent products and furthermore, according to VAERS reports, 83% of these individuals reported being injected prior to September 2022 - before the bivalent products were available. Additionally, only 11% of these individuals (50+/BTI/dose 4) reported being injected with a bivalent product, according to VAERS.

Also, considering that 70%, 97%, and 84% of the 50 plus BTI groups following doses 1, 2 and 3, respectively, were injected in 2021, it is safe to say that most of the elderly population were consistently injected with monovalent products. Only 0.05%, 0.03%, and 0.18% of this group reported being injected with bivalent products following doses 1, 2 and 3, respectively. It is important to remember that because the Janssen product was used in a heterologous way - as booster to Pfizer and/or Moderna products - it would be very difficult to predict BTI outcomes in heterologous dosing contexts – especially using VAERS data.

The administration timeframe, and likely the BTI

incidence and higher reporting rates in the elderly, are likely due to the preponderance of availability of COVID-19 modRNA products to older aged individuals at earlier (and all subsequent) time points during the COVID-19 injectable product roll-out, and of course, due to age-related factors such as cellular senescence and existing co-morbidities. Immunosenescence in the older age groups and its association with IgG4 predisposition to antigen will be an interesting topic to research in the future. The fact that a higher proportion of individuals who reported BTI to VAERS had taken a fourth dose could be the result of IgG4 class-switching. It is interesting that VAERS data appears to contradict the statement made in the Walmsley et al. publication "*that older individuals [are] less prone to BT infections due to the establishment of hybrid immunity induced by the earlier versions of the injections.*" Again, 88% of all BTI that were reported were made by individuals 50 years of age or more following dose 4, and 87% of these individuals reported receiving a monovalent modRNA product. In general, most of the follow-up doses were the earlier versions of the COVID-19 injectable products (monovalent), according to VAERS data. Walmsley et al. also reported "an association between higher antibody levels and protection from BTI observed during the Delta and Omicron BA.1/2 waves of infection no longer existed during the Omicron BA.4/5 wave" [38].

Interestingly, in the Irrgang et al. study, induction of IgG4 antibodies was not observed for a non-modRNA COVID-19 injectable product (adenoviral vectors – they used Vaxzevria to examine heterologous effects; Comirnaty and the adenoviral vector–based vaccine ChAdOx1 (Vaxzevria)). As part of this study, BTI rates were determined in the context of the Janssen COVID-19 injectable product as per VAERS reports, but since 94% of the reports (N=40,530) filed to VAERS in the context of these products were following dose 1, there isn't much that can be said for subsequent dosing, or for subsequent dose BTI reports. Janssen is a single dose product *but* it has been used as part of heterologous regimens, and indeed, AE (BTI-inclusive) reports for non-COVID-19 modRNA products following a second, third, and fourth dose have been filed to VAERS. There were a total of 4,157 reports of BTI filed to VAERS following this non-COVID-19 modRNA injection (Janssen doses 1-4 with age complete data), whereby 90%, 9%, 0.7%, and 0.3% reports were filed following doses 1 through 4, respectively.

Based on the total number of BTI reports filed to VAERS as of November 2024 (N=100,545) (this is for all COVID-19 injectable products in the domestic data set), using an under-reporting factor of 31 [33], it is estimated that the actual number of COVID-19 injectable product-associated BTI in the United States is 3,116,895.

It is clear that the high incidences of BTI in multiply-injected individuals is due to the lack of/waning efficacy of the products in the face of new SARS-CoV-2 variants [39,40,41]. In fact, it was shown in a recent study by Dutra et al. 2022 that the estimated vaccine effectiveness (VE) of the BNT162b2 2-dose primary series against symptomatic infection with the Omicron variant decreased over time reaching negative efficacy after 4.5 months [42]. It is exceedingly important to note that in the face of increased IgG4 synthesis and tolerance induction due to repeat COVID-19 modRNA product injections, individuals will experience high unopposed antigen concentration and subsequent deleterious effects of both SARS-CoV-2 and the spike protein itself, and thus will likely experience autoimmune disease occurrence, cancer promotion, and other adverse events [43].

It should be noted that it could be possible that the spike protein presented on host cells as per immunological responses increases the propensity

for induction of immune tolerance either by IgG4 or perhaps other mechanisms. It is also possible that there is a thymic shift due to the aging process that occurs in as part of Immunosenescence that influences the IgG4 tolerance shift.

The age group most impacted with regard to BTI according to VAERS data is the 55-77-year old age group, but it is possible that this is *partially* due to the fact that they may simply be more likely to report into VAERS. The proportional reporting ratio (PRR) is a metric that compares the ratio of specific AEs to total AEs for vaccine products, and in this case, the specific AEs are the reports of BTI in the 55-77-year-old age group. This was done to determine whether reporting bias was contributing to the BTI signal in this age group [44,45]. The PRR was calculated and yielded a value greater than 1, suggesting that the signal is real and not merely based on reporting bias [44]. In spite of the limitations of VAERS data, these findings prompt future deeper investigations into actual impacts of IgG4 tolerizing effects using non-passive databases. It is important to note that it has been shown recently that repeat COVID-19 modRNA injection results in IgG4 class switching in older adults [46]. It has also been shown recently that IgG antibody responses are significantly higher in elderly individuals injected four times with a COVID-19 modRNA product [47].

Because of the spontaneous reporting of events to VAERS, we can assume that the cases reported thus far are not rare, but rather, just the tip of the iceberg. As aforementioned, under-reporting is a known and serious disadvantage of the VAERS system. Thus, VAERS alone without adjustment cannot be used to estimate population incidence. It is important to note that older age group reports of BTI might be due to higher testing in these age groups (aka: "SARS-CoV-2 test positive") or possibly that this age group may have age-related weakened immune systems.

Limitations of this study are acknowledged and are based on use of a pharmacovigilance database where reporting of AEs is voluntary. VAERS data are grossly under-reported due to many reasons, including the lack of clinical recognition of injury in the context of the COVID-19 injectable products, frustration with the VAERS online system, and fear of professional reprisal.

Conclusion

A possible link between BTI associated with the COVID-19 modRNA products and class switching toward non-inflammatory, spike-specific IgG4 antibodies following a third (and fourth dose according to this study) dose was investigated using VAERS U.S. data. The rates of BTI reporting in the contexts of COVID-19 modRNA products in VAERS are significantly higher following dose 4. This is a compelling finding, and corroborates evidence that class switching toward noninflammatory, spike-specific IgG4 antibodies confers susceptibility to SARS-CoV-2, and could be precisely why VAERS reveals a proportionally higher rate of BTI reporting following dose 4, especially in older age groups. VAERS does come with limitations, but it is designed to emit safety signals and in the case of BTI in the context of the modRNA shots, these signals are loud and clear. Once again, this pharmacovigilance database is functioning efficiently to reveal the signal of BTI in the context of the COVID-19 injectable products by demonstrating – strictly via data exposure – that repeat dosing is correlated to BTI. This subject matter bears further investigation and perhaps if these safety signals had been addressed earlier, fewer individuals would have succumbed to BTI potentiated by IgG4 class switching and immunological tolerance from repeated COVID-19 modRNA product administration.

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