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Global burden of vaccine-associated kidney injury using an international pharmacovigilance database

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Global evidence on the association between vaccines and renal adverse events (AEs) is inconclusive. This pharmacovigilance study analyzed a total of 120,715,116 reports from VigiBase collected between 1967 and 2022. We evaluated the global reporting of acute kidney injury (AKI), glomerulonephritis (GN), and tubulointerstitial nephritis (TIN) and assessed disproportionate signals between vaccines and renal AEs using reporting odds ratios (ROR) and the lower limit of the 95% confidence interval of the information component (IC_{025}) in comparison with the entire database. The number and proportion of reports on AKI, GN, and TIN gradually increased, with a substantial increase after 2020. Disproportionate reporting of AKI was significant for COVID-19 mRNA vaccines (ROR, 2.38; IC_{025}, 1.09). Fourteen vaccines were significantly disproportionate for higher GN reporting, and the highest disproportionality for GN reporting was observed for COVID-19 mRNA (ROR, 13.41; IC_{025}, 2.90) and hepatitis B vaccines (ROR, 11.35; IC_{025}, 3.18). Disproportionate TIN reporting was significant for COVID-19 mRNA (ROR, 2.43; IC_{025}, 0.99) and human papillomavirus (ROR, 1.75; IC_{025}, 0.19) vaccines. Significant disproportionality in the reporting of AKI, GN, and TIN was observed in patients exposed to multiple vaccines, including COVID-19 mRNA vaccines, alongside increasing global reports of vaccine-associated renal AEs.

Keywords Acute kidney injury, Glomerulonephritis, Pharmacovigilance, Tubulointerstitial nephritis, Vaccines

Abbreviations

AKI	acute kidney injury
GN	glomerulonephritis
IQR	interquartile range
TIN	tubulointerstitial nephritis

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Vaccination is a crucial strategy for preventing life-threatening infectious diseases[1]. Vaccines protect not only the vaccinated individual but also contribute to the health of the wider community, including the unvaccinated[2,3]. This instrumental benefit has led to the introduction of vaccination programs on a global scale, and several countries have implemented compulsory vaccine programs to promote public health[4]. Vaccination is particularly critical for protecting individuals who cannot develop an adequate immune response, such as those receiving immunosuppressive therapies or living with impaired immune system. Achievement of widespread immunity ensures that these vulnerable populations are shielded from severe infectious disease[5,6]. The COVID-19 pandemic further highlighted the importance of vaccines, and the successful deployment of numerous vaccines has stimulated new technologies in vaccine development[7–9]. Overall, vaccines play a critical role in clinical practice as a means of reducing the burden of disease in both individuals and communities.

Despite the extensive evidence supporting the benefits of vaccines, numerous studies have reported that vaccines may be associated with several adverse reactions[7–9]. Subsets of these adverse reactions were unexpected and not included in the safety profiles of sequential clinical trials[10]. Reports indicate that immunologic response following vaccination can lead to myocarditis, arthritis, encephalomyelitis, autoimmune disease, and renal adverse events (AEs)[11–13]. Acute kidney injury (AKI), glomerulonephritis (GN), and tubulointerstitial nephritis (TIN) have been identified as representative manifestations of vaccine-associated renal injury[14–16]. However, renal AEs are often considered to be incidental or occasional findings. Uncertainty exists whether vaccinations are significantly associated with renal injury compared to other drugs and if vaccines are associated with a higher reporting of AKI, GN, and TIN.

Our study aimed to define and stratify vaccines with signals for renal injury using VigiBase, the World Health Organization (WHO) global pharmacovigilance database. To improve patient safety and facilitate monitoring guidelines after vaccination, we sought to identify which vaccines against several diseases have significant signals for AKI, GN, and TIN. In addition, we investigated global trends in reporting on vaccine-associated renal injury over time and across regions.

Materials and methods

Data sources

This global pharmacovigilance study examined adverse drug reactions reported in VigiBase, a WHO deduplicated database of individual case safety reports[17,18]. The database collects adverse drug reaction reports from over 150 countries, covering 25,000 drugs and vaccines, and contains 120,715,116 reports submitted from national pharmacovigilance centers starting from 1967. Physicians, pharmacists, healthcare professionals, and patients spontaneously submit reports, which are checked for quality, regularly reviewed, and analyzed based on predefined criteria[17,18]. AEs were coded into preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The data from Vigibase were anonymized, and this study was conducted in accordance with relevant guidelines and regulations. The institutional review board of the Kyung Hee University Medical Center approved the use of confidential and electronically processed patient information, and the need to obtain informed consent was waived by the institutional review board of the Kyung Hee University Medical Center.

Selection of cases

The study examined vaccine-related case reports between 1967 and 2022, and vaccines were classified into 19 categories, namely, (1) diphtheria, tetanus, pertussis, polio, *Hemophilus influenzae* type b (DTaP-IPV-Hib), (2) hepatitis A, (3) hepatitis B, (4) rotavirus diarrhea, (5) pneumococcal, (6) influenza, (7) measles, mumps and rubella (MMR), (8) varicella zoster, (9) human papillomavirus (HPV), (10) meningococcal, (11) tuberculosis, (12) typhoid, (13) encephalitis, (14) anthrax, (15) cholera, (16) COVID-19 mRNA, (17) adenovirus type-5 (ad5)-vectored COVID-19, (18) inactivated whole virus COVID-19, and (19) other (brucellosis, plague, typhus, leptospirosis, rabies, yellow fever, smallpox, Ebola, dengue) vaccines. Vaccines were identified using the Level 4 Anatomical Therapeutic Chemical code in the WHO Drug Dictionary. Renal AEs were evaluated for AKI, GN, and TIN, and all reports of these AEs were retrieved using MedDRA 25.0 preferred terms level. MedDRA terms used to identify renal AEs are described in Supplementary Table S1. The vaccines are only considered as "suspected" for the calculation of disproportionate signals for renal AEs based on the WHO causality assessment recommendations.

Data collection

The study included cases in which vaccine-associated renal AE was suspected and required further identification. Individual case safety reports contained patient demographic data, including age and sex, and administrative information, including country of origin, reporter qualifications, date of report, and type of report. The reports also included drug information and reported reaction information, such as the date of onset of the reaction, MedDRA classification terms, nature and severity of the AE, and mortality. Time-to-onset refers to the number of days between the date of vaccination and the date when an AE presented. Each event was characterized as "serious" or "non-serious" based on the WHO definition[17,18]. Serious outcome encompassed not recovered/not resolved, recovered/resolved with sequelae, fatal, or died. Physicians who reported the case clinically determined the severity of the AE. Concurrent AEs reported with vaccine-associated renal AE were new onset events, which were associated with vaccine administration. The concurrent AEs were classified using MedDRA terms (Supplementary Table S2)[19].

Statistical analysis

The VigiBase dataset was divided into two groups, case and non-case, and the disproportionality signal was evaluated. Disproportionality analysis involves comparing the proportion of a specific AE reported for a single drug (vaccine in this study) with the proportion of the same AE reported for a control group of drugs (the entire database)[17,18]. The total number of reported AEs for each group of drugs served as the denominator in these analyses. If the proportion of cases with a certain AE is greater in patients taking the specific drug (case) than in patients exposed to any other drug in the entire database (non-case), a signal of disproportionality association (signal identification) between the drug and AE was identified.

The following two common pharmacovigilance measures of disproportionate analysis were introduced: the information component (IC) and reporting odds ratio (ROR). The IC was developed using a Bayesian confidence propagation neural network, and the Uppsala Monitoring Centre validated it as an indicator value for disproportionate reporting[17,18,20]. The statistical formula for calculating the IC was as follows: $IC = \log_2([N_{observed}+0.5] / [N_{expected}+0.5])$. $N_{expected}$ is the expected number of cases for the combination of drug and AE and was calculated as $[N_{drug} \times N_{effect}]/N_{total}$. $N_{observed}$ refers to the number of case reports for a certain AE associated with a specific drug, N_{drug} refers to the number of case reports for a specific drug regardless of AEs, N_{effect} refers to the number of case reports for a given reaction regardless of the drug, and N_{total} represents the total number of case reports in the database. IC_{025} is the lower limit of the 95% confidence interval for IC. A positive value of IC_{025} is the conventional threshold used to detect statistical signals.

Disproportionate signals were also evaluated using the ROR, which compares the probability of a specific AE occurring with a targeted drug to the probability of the same event occurring with all other drugs in the database. The formula for calculating the ROR is as follows: ROR = (a/b)/(c/d), where 'a' represents the number of cases for a certain AE, 'b' is the number of cases for all other AEs associated with a specific drug, 'c' is the number of all cases for a certain AE not related to a specific drug, and 'd' is the number of all cases not related to the specific AEs and drugs. The lower 95% confidence interval of the ROR greater than 1 indicates a significant signals between the drug and a certain AE[21,22].

To assess vaccine-associated renal AEs in age-specific subgroups, we classified the age groups based on the immunization schedules recommended in WHO and the US Centers for Disease Control and Prevention[23]. Characteristics of reports were described as median with interquartile ranges (IQR) for continuous variables, and numbers and proportions for categorical ones. The ANOVA and χ^2 test were used for comparisons, as appropriate[24]. A two-sided P value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

Results

Clinical characteristics of vaccine-associated renal AE

The number of vaccine-associated renal AE reports included 5,901 for AKI, 3,312 for GN, and 374 for TIN, out of the 120,715,116 reports in the complete database (Table 1). The age at onset of AKI was predominantly > 65

	AKI (*n* = 5901)	GN (*n* = 3312)	TIN (*n* = 374)
Age, yr			
0–1	99 (1.7)	91 (2.8)	8 (2.1)
2–11	33 (0.6)	317 (9.6)	4 (1.1)
12–17	105 (1.8)	226 (6.8)	39 (10.4)
18–64	1767 (29.9)	1335 (40.3)	181 (48.4)
≥65	3092 (52.4)	566 (17.1)	54 (14.4)
Unknown	805 (13.6)	777 (23.5)	88 (23.5)
Sex			
Female	2566 (43.5)	1634 (49.8)	196 (52.6)
Unknown	19 (0.3)	28 (0.7)	1 (0.3)
Study-relation			
Study related	48 (0.8)	46 (1.4)	2 (0.5)
Non-study related	5852 (99.2)	3263 (98.5)	372 (99.5)
Unknown	1 (0.0)	3 (0.1)	0 (0.0)
Median (IQR) time-to-onset, d	3.9 (3.1–4.7)	9.5 (7.2–11.8)	9.1 (4.5–13.8)
Fatal outcomes			
Non-serious	1427 (24.2)	797 (24.1)	149 (39.8)
Serious	821 (13.9)	958 (28.9)	77 (20.6)
Unknown	3653 (61.9)	1557 (47.0)	148 (39.6)
Single drug suspected	5876 (99.6)	3312 (100.0)	374 (100.0)

Table 1. Patient characteristics of reports on vaccine-associated renal adverse reaction. Note: Values are reported as n (%), or *median (IQR)*.Abbreviations: AKI, acute kidney injury; GN, glomerulonephritis; IQR, interquartile range; TIN, tubulointerstitial nephritis.

years, and the onset of GN and TIN was most prevalent between 18 and 64 years of age. More than 99% of reports originated from the standard of care. The median time (IQR) to onset was 3.9 (3.1–4.7) days for AKI, 9.5 (7.2–11.8) days for GN, and 9.1 (4.5–13.8) days for TIN ($P < 0.001$). Serious clinical outcomes were reported in 13.9%, 28.9%, and 20.6% of patients with AKI, GN, and TIN, respectively ($P < 0.001$).

Figure 1 shows temporal changes in the reported counts and proportions of vaccine-associated renal AEs relative to all drug-associated renal AEs. The number of reported vaccine-associated AEs for AKI, GN, and TIN gradually increased over time. The proportions of vaccine-associated AKI, GN, and TIN cases among all drug-related AEs also increased. Notably, there was a remarkable increase in the number and proportion of vaccine-associated AEs after 2020. The Americas had the highest reporting of AKI, GN, and TIN, followed by European regions.

Vaccines and number of reported cases of renal AEs

Figure 2 illustrates the cumulative numbers of AKI, GN, and TIN cases according to the different vaccines. AKI cases were reported for all vaccines, and GN and TIN cases were reported for 18 and 15 vaccines, respectively. Before 2020, influenza vaccines had the highest cumulative AKI counts, whereas, after 2020, AKI was most reported after administration of COVID-19 mRNA vaccines. GN was most commonly reported for influenza, DTaP-IPV-Hib, hepatitis B, and HPV vaccines, and TIN was most commonly reported for influenza and HPV vaccines, before 2020, while after 2020 the highest proportion of cases of GN and TIN were reported for COVID-19 mRNA vaccines. A similar pattern was observed when the proportion of reported vaccines for each renal AE was analyzed (Fig. S1).

Vaccines and disproportionate signals of renal AEs

Fifteen of the 19 vaccines were associated with significant disproportionality reporting of renal AEs (Table 2). COVID-19 mRNA vaccines showed higher reporting of AKI compared with the entire database (ROR, 2.38, 95% CI 2.30–2.46; IC_{025}, 1.09). In the age-specific subgroup analysis, disproportionate signals of COVID-19 mRNA vaccines for AKI reporting were significant in individuals aged 2 years and older (Table S3).

Significant signals for GN reporting was observed with 14 vaccines. Among them, the highest disproportionate signal for GN reporting was with COVID-19 mRNA (ROR, 13.41, 95% CI 12.62–14.26; IC_{025}, 2.90), and hepatitis B vaccines (ROR, 11.35, 95% CI 9.69–13.30; IC_{025}, 3.18). In the age-specific subgroup analysis, COVID-19 mRNA vaccines showed higher reporting of GN in individuals aged 2 years and older, and hepatitis B vaccines were associated with significant disproportionality of GN reporting in those aged less than 65 years (Table S4). Multiple vaccines also showed significant disproportionate signals in several age subgroups: age-specific disproportionality was highest in DTaP-IPV-Hib vaccines among babies aged 0–1 y and persons aged 65

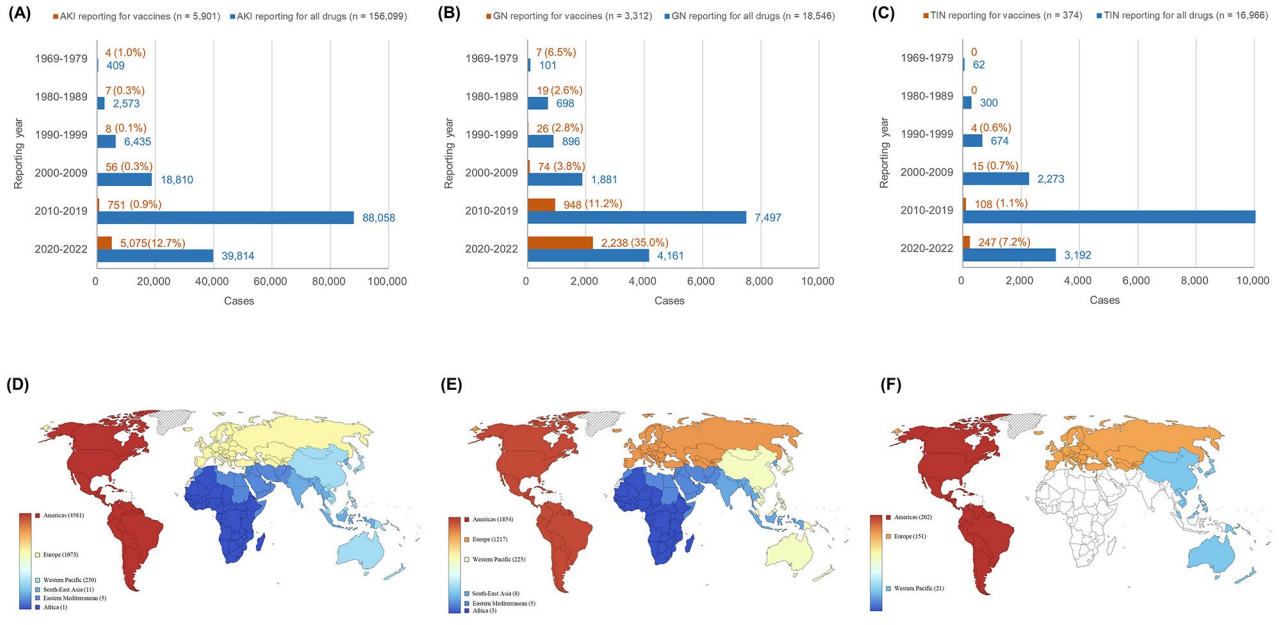

Fig. 1. Temporal changes in the reported counts of vaccine- and drug-associated renal adverse events, and a world map showing reported cases across continents. The reported counts of AKI (**A**), GN (**B**), and TIN (**C**) are presented over timeframe. The number of each renal AE for vaccines (red bars) and all drugs (blue bars) is listed, and the proportions of renal AEs among all drug-related AEs are displayed as percentages adjacent to the red bars. Globally reported counts of AKI (**D**), GN (**E**), and TIN (**F**) are shown across continents. Regions with higher counts are indicated in red, while those with lower counts are marked in blue. AKI, acute kidney injury; GN, glomerulonephritis; TIN, tubulointerstitial nephritis.

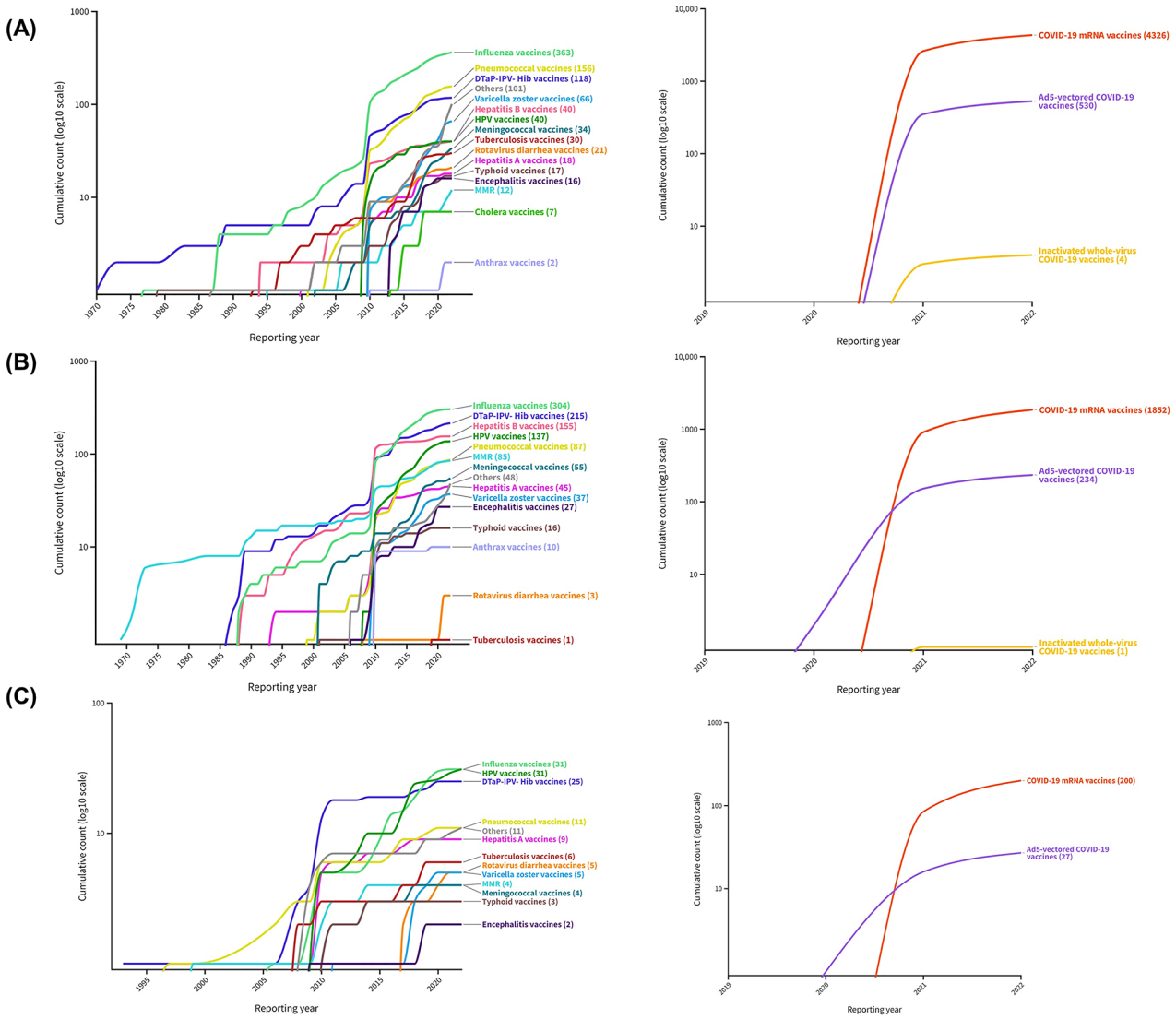

Fig. 2. Cumulative counts of AKI (A), GN (B), and TIN (C) reports per year in association with different vaccines. Other vaccines included brucellosis, plague, typhus, leptospirosis, rabies, yellow fever, smallpox, Ebola, and dengue vaccines. The COVID-19 vaccine is illustrated separately within the same row because of its distinct temporal distribution. Ad5, adenovirus type-5; DTaP-IPV-Hib, diphtheria, tetanus, pertussis, polio, and *Hemophilus influenzae* type b; HPV, human papillomavirus; MMR, measles, mumps, and rubella. AKI, acute kidney injury; GN, glomerulonephritis; TIN, tubulointerstitial nephritis

years and older, influenza vaccines among children aged 2–11 y, HPV and COVID-19 mRNA vaccines among adolescents aged 12–17 y, and hepatitis B vaccines among adults aged 18–64 y.

Significant disproportionality in TIN reporting was found for COVID-19 mRNA (ROR, 2.43, 95% CI 2.11–2.81; IC_{025}, 0.99), HPV (ROR, 1.75, 95% CI 1.23–2.48; IC_{025}, 0.19), and other vaccines (ROR, 2.37, 95% CI 1.26–4.10; IC_{025}, 0.08). Age-specific subgroup analysis showed that COVID-19 mRNA and HPV vaccines had significantly disproportionate signals of TIN reporting among adolescents aged 12–17 y (Table S5).

Clinical characteristics and concurrent renal AEs in vaccines with significant disproportionate signals of renal AEs

Figure 3 illustrates the overlap between vaccine-associated AKI, GN, and TIN. The highest number of cases ($n = 228$) were observed with overlapping AKI and GN, followed by overlapping AKI and TIN ($n = 82$) and overlapping GN and TIN ($n = 35$). COVID-19 mRNA vaccines were the most commonly reported vaccines in cases where there was an overlap in renal AEs.

The median (IQR) time-to-onset for AKI in association with COVID-19 mRNA vaccines was 1.9 (1.4–2.4) days, and the associated rate of serious outcomes was 8.9% (Table S6). Neurological events were the most frequently reported concurrent serious outcome (38.6%), followed by cardiovascular events (coronary, 15.2%; arrhythmia, 22.9%; heart failure, 28.5%; other cardiac disease, 12.8%) and pulmonary events (33.4%). The median time-to-onset of GN reporting was 7.2 (4.6–9.9) days for COVID-19 mRNA vaccines and 6.3 (2.0-

	N	AKI			GN			TIN		
	total	N observed	IC (IC_{025})[a]	ROR (95% CI)[b]	N observed	IC (IC_{025})[a]	ROR (95% CI)[b]	N observed	IC (IC_{025})[a]	ROR (95% CI)[b]
DTaP-IPV-Hib vaccines	7,77,222	118	-3.03 (-3.33)	0.12 (0.10-0.15)	215	**1.13 (0.90)**	**2.21 (1.93-2.53)**	25	-2.07 (-2.74)	0.23 (0.16-0.34)
Hepatitis A vaccines	60,558	18	-2.04 (-2.83)	0.24 (0.15-0.38)	45	**2.48 (1.99)**	**5.91 (4.41-7.91)**	9	0.11 (-1.03)	1.08 (0.56-2.08)
Hepatitis B vaccines	1,09,304	40	-1.75 (-2.28)	0.29 (0.22-0.40)	155	**3.44 (3.18)**	**11.35 (9.69-13.3)**	0	NA	NA
Rotavirus diarrhea vaccines	78,971	21	-2.20 (-2.93)	0.21 (0.14-0.33)	3	-1.58 (-3.65)	0.30 (0.10-0.93)	5	-1.05 (-2.61)	0.46 (0.19-1.11)
Pneumococcal vaccines	2,64,284	156	-1.07 (-1.34)	0.47 (0.40-0.55)	87	**1.37 (1.01)**	**2.62 (2.12-3.23)**	11	-1.68 (-2.7)	0.30 (0.17-0.55)
Influenza vaccines	3,46,453	363	-0.25 (-0.42)	0.84 (0.76-0.93)	304	**2.78 (2.59)**	**7.08 (6.32-7.93)**	31	-0.61 (-1.21)	0.65 (0.46-0.93)
MMR	2,20,053	12	-4.46 (-5.43)	0.04 (0.02-0.08)	85	**1.60 (1.24)**	**3.07 (2.48-3.8)**	4	-2.77 (-4.54)	0.13 (0.05-0.35)
Varicella zoster	2,03,900	66	-1.93 (-2.34)	0.26 (0.20-0.33)	37	0.52 (-0.03)	**1.44 (1.04-1.99)**	5	-2.37 (-3.94)	0.18 (0.07-0.43)
HPV vaccines	1,29,318	40	-1.99 (-2.52)	0.25 (0.18-0.34)	137	**3.03 (2.75)**	**8.47 (7.16-10.02)**	31	**0.79 (0.19)**	**1.75 (1.23-2.48)**
Meningococcal vaccines	1,44,492	34	-2.39 (-2.96)	0.19 (0.13-0.26)	55	**1.57 (1.12)**	**3.02 (2.32-3.94)**	4	-2.18 (-3.94)	0.20 (0.08-0.54)
Tuberculosis vaccines	33,415	30	-0.46 (-1.07)	0.72 (0.50-1.03)	1	-1.65 (-5.44)	0.24 (0.03-1.68)	6	0.35 (-1.06)	1.31 (0.59-2.91)
Typhoid vaccines	16,578	17	-0.27 (-1.09)	0.82 (0.51-1.33)	16	**2.67 (1.83)**	**7.66 (4.69-12.51)**	3	0.33 (-1.74)	1.32 (0.42-4.08)
Encephalitis vaccines	19,976	16	-0.62 (-1.46)	0.64 (0.39-1.05)	27	**3.19 (2.54)**	**10.74 (7.36-15.67)**	2	-0.38 (-2.97)	0.73 (0.18-2.91)
Anthrax vaccines	9,923	2	-2.36 (-4.95)	0.16 (0.04-0.65)	10	**2.58 (1.51)**	**8.00 (4.30-14.87)**	0	NA	NA
Cholera vaccines	2,310	7	1.15 (-0.15)	**2.44 (1.16-5.12)**	0	NA	NA	0	NA	NA
COVID-19 mRNA vaccines	32,30,266	4,326	**1.14 (1.09)**	**2.38 (2.30-2.46)**	1,852	**2.98 (2.90)**	**13.41 (12.62-14.26)**	200	**1.22 (0.99)**	**2.43 (2.11-2.81)**
Ad5-vectored COVID-19 vaccines	10,73,625	530	-0.30 (-0.44)	0.81 (0.74-0.88)	234	**1.58 (1.36)**	**3.12 (2.73-3.56)**	27	-0.07 (-0.71)	0.95 (0.65-1.39)
Inactivated whole-virus COVID-19 vaccines	35,287	4	-2.28 (-4.05)	0.19 (0.07-0.50)	1	-1.03 (-4.81)	0.39 (0.05-2.77)	0	NA	NA
Others[c]	1,78,902	101	-1.14 (-1.47)	0.45 (0.37-0.55)	48	0.01 (-0.47)	1.01 (0.76-1.34)	11	**1.10 (0.08)**	**2.27 (1.26-4.1)**

Table 2. Disproportionality analysis of vaccine-associated renal adverse reaction. Note: The numbers in bold indicate a statistical significance. Abbreviations: Ad5, adenovirus type-5; AKI, acute kidney injury; CI, confidence interval; COVID-19, coronavirus disease 2019; DTaP-IPV-Hib, diphtheria, tetanus, pertussis, polio and *Hemophilus influenzae* type b; GN, glomerulonephritis; HPV, human papillomavirus; IC, information component; Ntotal, number of case reports for a specific vaccine; Nobserved, number of case reports for a certain adverse reaction associated with a specific vaccine; MMR, measles, mumps and rubella; NA, non-available; ROR, reporting odds ratio; TIN, tubulointerstitial nephritis. [a]A positive value of the IC_{025} was considered significant. [b]A lower end of the ROR 95% CI ≥ 1 was considered significant.[c]Other vaccines included brucellosis, plague, typhus, leptospirosis, rabies, yellow fever, smallpox, Ebola, and dengue vaccines

12.3) days for hepatitis B vaccines. Reported cases of COVID-19 mRNA and hepatitis B vaccine-associated GN frequently showed concurrent neurological, osteoarticular and rheumatological manifestations. The rate of serious outcomes was 25.0% for the COVID-19 mRNA vaccines and 16.8% for the hepatitis B vaccines. The median onset time for TIN reporting with COVID-19 mRNA vaccines was 2.0 (1.0–2.0) days, and the serious outcome rate was 23%. Neurological (13.0%) and hyperthermic events (10.5%) were the most common serious outcomes in these cases. In HPV vaccine-associated TIN reporting, the median time-to-event was 9.7 (4.2–52.1) days after vaccine administration, with a serious outcome rate of 6.5%. Hyperthermia and ophthalmologic manifestations were frequently reported in these cases.

Discussion

In this global pharmacovigilance dataset from 1967 to 2022, we observed a gradual increase in the number of reports of vaccine-associated renal AE over the years, with a sudden increase after 2020. Our analysis identified 15 vaccines with significant disproportionality in the reporting of vaccine-associated renal AEs. COVID-19 mRNA vaccines were associated with significant disproportionality of AKI reporting. Moreover, we detected multiple vaccines, including DTaP-IPV-Hib vaccines, Hepatitis A vaccines, Hepatitis B vaccines, Pneumococcal vaccines, Influenza vaccines, MMR vaccines, HPV vaccines, Meningococcal vaccines, Typhoid vaccines, Encephalitis vaccines, and Anthrax vaccines, with significant disproportionate signals for GN and TIN reporting.

We determined that the proportional reporting of vaccine-associated renal AEs and proportional reporting of renal AEs in all pharmacovigilance reports increased over time, highlighting the importance of continuous

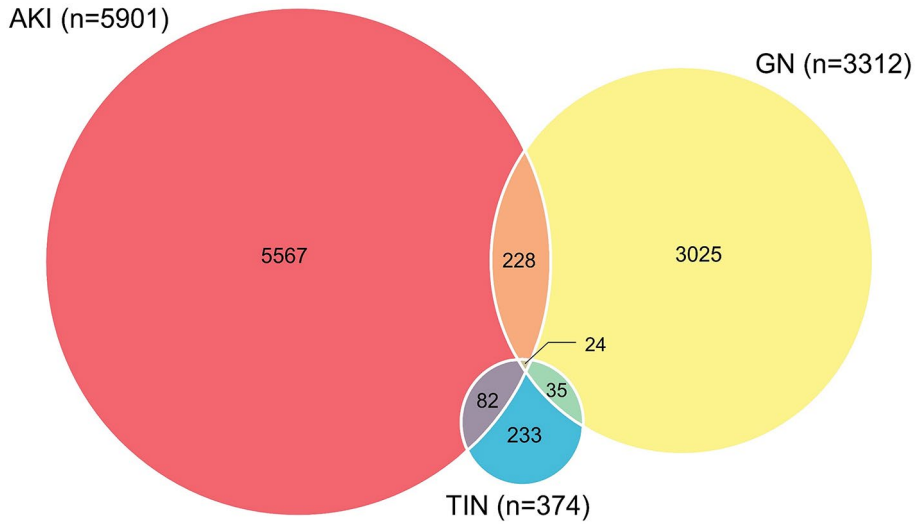

Fig. 3. The overlap between vaccine-associated AKI, GN, and TIN. A total of 228 cases overlapped between AKI and GN, 82 cases between AKI and TIN, and 35 cases between GN and TIN. In addition, 24 cases were reported to overlap across all three renal AEs. AKI, acute kidney injury; GN, glomerulonephritis; TIN, tubulointerstitial nephritis.

pharmacovigilance to detect vaccine-associated and other drug-associated renal AEs. In addition, our study revealed a substantial increase in vaccine-associated renal AEs after 2020, suggesting a link between global COVID-19 vaccination and occurrence of renal AEs. The Americas reported the highest number of vaccine-associated renal AEs, followed by Europe. While this study cannot definitively determine the reasons for disparities in renal AE reporting across regions, these differences may reflect variations in vaccine accessibility and uptake, leading to differences in opportunities for AE occurrence and detection, as well as variations in awareness and practices related to AE reporting[25,26]. The disparity may also be attributable to variations in racial differences, population demographics, patterns of vaccine deployment, and the types of vaccines administered across regions[27,28].

We identified several characteristic findings in the reports of vaccine-associated AKI, GN, and TIN. Most reports on renal AEs are not related to investigational studies, suggesting that vaccine users may not be pre-notified of the potential relationship between vaccines and renal AEs[29]. Our study also found that the median time from vaccination to onset of renal AEs was 4–10 days, indicating a delay in occurrence of the adverse effects. In addition, the presence of a 14–29% serious outcome rate in association with vaccine-associated renal AEs indicates that the importance of managing such events should not be underestimated.

COVID-19 mRNA vaccines were associated with the highest reporting of renal AEs, compared to other vaccines, as evidenced by significant disproportionality for AKI, GN, and TIN reporting, and the strongest signal. Additionally, the highest counts of overlapping reporting between AKI, GN, and TIN were observed in recipients of COVID-19 mRNA vaccines compared to other vaccines, providing valuable insight into potential drugs to combat renal AEs. Nevertheless, a total of 6,378 renal AEs reported for COVID-19 mRNA vaccines from VigiBase needs to be considered in the context of more than 13 billion individuals vaccinated[30]. The absolute risk of renal AEs associated with COVID-19 mRNA vaccines is very small, and recent clinical studies demonstrated that administering multiple doses of COVID-19 vaccines is beneficial in populations with suboptimal immune responses[5,31–33]. It is necessary, therefore, to recognize the significant benefits of COVID-19 vaccines, while the identification of populations at high-risk of renal AEs remains crucial to enhancing vaccine safety.

We showed that AKI was frequently reported in conjunction with serious neurological and cardiovascular outcomes following COVID-19 mRNA vaccination. These findings suggest that AKI frequently occurs in the context of a multi-system disease. Previous reports have also indicated the increased risk of organ injuries, including myocarditis, arrhythmia, encephalomyelitis, and Guillain-Barré syndrome, from vaccination[34–37]. Our study revealed significant disproportionality of TIN reporting with COVID-19 mRNA and HPV vaccines, especially among individuals aged 12–17 years. These findings imply that COVID-19 mRNA and HPV vaccines could have immunostimulatory properties that lead to a hypersensitivity reaction in the renal interstitium, and that adolescents are more susceptible. Our results indicate the need for research to evaluate vaccine-associated TIN and immunostimulatory properties, focusing on these specific vaccines.

While some reports have suggested the occurrence or relapse of GN after vaccination[14,38–41], the rare incidence of these events failed to provide reliable evidence for an association between vaccination and GNs[42–44]. We revealed a significant disproportionate signal for GN reporting across multiple vaccines, and that more vaccines were associated with disproportionality of GN reporting than with AKI and TIN reporting. These findings suggest that GN is a clinical manifestation with most diverse signals for multiple vaccines and highlights the emerging role of vaccines in secondary GN[45]. Our study, together with previous reports, reinforce the

association between vaccines and GN, indicating the need to assess the risks and benefits of vaccinations in patients with pre-existing GN or genetic susceptibility to GN.

Our study has several limitations. First, VigiBase lacks laboratory tests or radiological findings relevant to the reported cases. Therefore, we did not have access to extensive clinical information for vaccine-associated AEs. Second, it is conceivable that some suspected cases of vaccine-related renal AEs were not reported to VigiBase because of the observational and discretionary nature of the reporting system. Third, cases where vaccination did not result in any AEs were not reported in VigiBase, making it challenging to determine the actual incidence of renal AEs among people receiving vaccinations. To address this limitation, we included extensive reports of drug-related adverse events aggregated from over 130 countries across a span of more than 50 years, as the denominator. Furthermore, we employed Bayesian methodology, a validated approach in pharmacovigilance studies for signal detection, to enhance our analysis[22,46]. Finally, the disproportionality analysis allows clinicians to concentrate on the probability that a drug causes a specific adverse event. This evaluation requires additional validation and confirmation to determine a causal relationship. In addition, the inclusion of renal AEs in the package insert or the decrease in the perceived benefits of the vaccine based solely on this study could pose a significant risk.

Conclusions

In conclusion, our analyses of a global database revealed that the number and proportion of vaccine-associated renal AE reporting dramatically increased after 2020 and several vaccines were identified that were associated with significant disproportionality of AKI, GN, and TIN reporting. The COVID-19 mRNA vaccines showed noticeable signals for AKI, GI, and TIN reporting. We provide a list of vaccines potentially associated with renal AEs. Further validation studies would improve our understanding of the risk of vaccine-associated renal AEs.

Data availability

All data may be accessible after a detailed request from the Uppsala Monitoring Center, Sweden, following privacy requirements. The data underlying this article will be shared on reasonable request to the corresponding author.

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Author contributions

Drs. HSH and DKY had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript before submission. Study concept and design: HL, HSH, and DKY; Acquisition, analysis, or interpretation of data: HL, HSH, and DKY; Drafting of the manuscript: HL, HSH, and DKY; Critical revision of the manuscript for important intellectual content: all authors; Statistical analysis: HL, HSH, and DKY; Study supervision: HL, HSH, and DKY. HSH and DKY supervised the study and were guarantors. HSH and HL contributed equally as first authors. DKY and HSH contributed equally as corresponding authors. The corresponding authors attest that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Competing interests
The authors declare no competing interests.

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