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# The Influence of the Rapid Increase in the Number of Adverse Event Reports for COVID-19 Vaccine on the Disproportionality Analysis Using JADER

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**Abstract.** *Background/Aim: The COVID-19 prophylactic vaccine for the prevention of coronavirus infection was approved in Japan on February 14, 2021. Adverse event reports for the vaccine were collected from the Japan Adverse Drug Event Relief (JADER) database, similar to those for drugs. Reported odds ratios (RORs) and proportional reporting ratios (PRRs) are commonly used in disproportionality analysis to detect safety signals. Therefore, adverse event reports from the vaccinated population may affect the detection of safety signals for the registered drugs. This study determined the impact of adverse event reports on the detection of safety signals for a COVID-19 prophylactic vaccine by analyzing the JADER database using disproportionality analysis. Patients and Methods: We extracted data from the JADER dataset, in which the COVID-19 vaccine was reported as a suspected drug, and selected the top 10 adverse events in terms of the number of reports. We then extracted the top 30 drugs by the amount of information in the selected 10 adverse events and compared the changes in the number of signal detections with and without the COVID-19 vaccine report data. Results: The total number of adverse events reported in the JADER database during the study period was 2,002,564. Of the total number of reports, 85,489 (4.3%) reported adverse events related to the COVID-19 vaccine. Of the top 30 drugs reported in the 10 selected adverse events, the ROR and PRR were found to be lower with the inclusion of COVID-19 vaccine data than without. Detection by ROR excluded 23 out of 245 drugs, and detection by PRR excluded 34 out of 204 drugs. Conclusion: The rapid increase in the number of adverse event reports for the COVID-19 vaccine in JADER may affect the detection of safety signals by disproportionality analysis.*

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*Key Words:* COVID-19 prophylactic vaccine, Japanese Adverse Drug Event Report database, disproportionality Analysis, reported odds ratios, proportional reporting ratios.



In Japan, a special exception for the intramuscular vaccine for the prevention of coronavirus disease 2019 (COVID-19) was approved on February 14, 2021, and vaccination began simultaneously nationwide in mid-February (1, 2). Several studies have reported adverse events for the COVID-19 prophylactic vaccine in Japan (3, 4).

In the U.S., early data are accumulated in the Vaccine Adverse Event Reporting System (VAERS), a monitoring system that identifies immunization safety issues (5). Conversely, post-marketing adverse events for pharmaceuticals are collected in the FDA Adverse Event Reporting System (FAERS) (6). Therefore, there should be less mixing of vaccination and drug-related adverse events when using a methodology that uses a database of spontaneous adverse event reports to generate hypotheses about the possible relationships with unknown or potential adverse events.

In contrast, The Ministry of Health, Labour and Welfare of Japan requires medical institutions to report and collect reports of adverse reactions after vaccination with the new coronavirus vaccine following the Immunization Law (7). However, no system has been established to accumulate spontaneous reports of adverse events limited to vaccinations

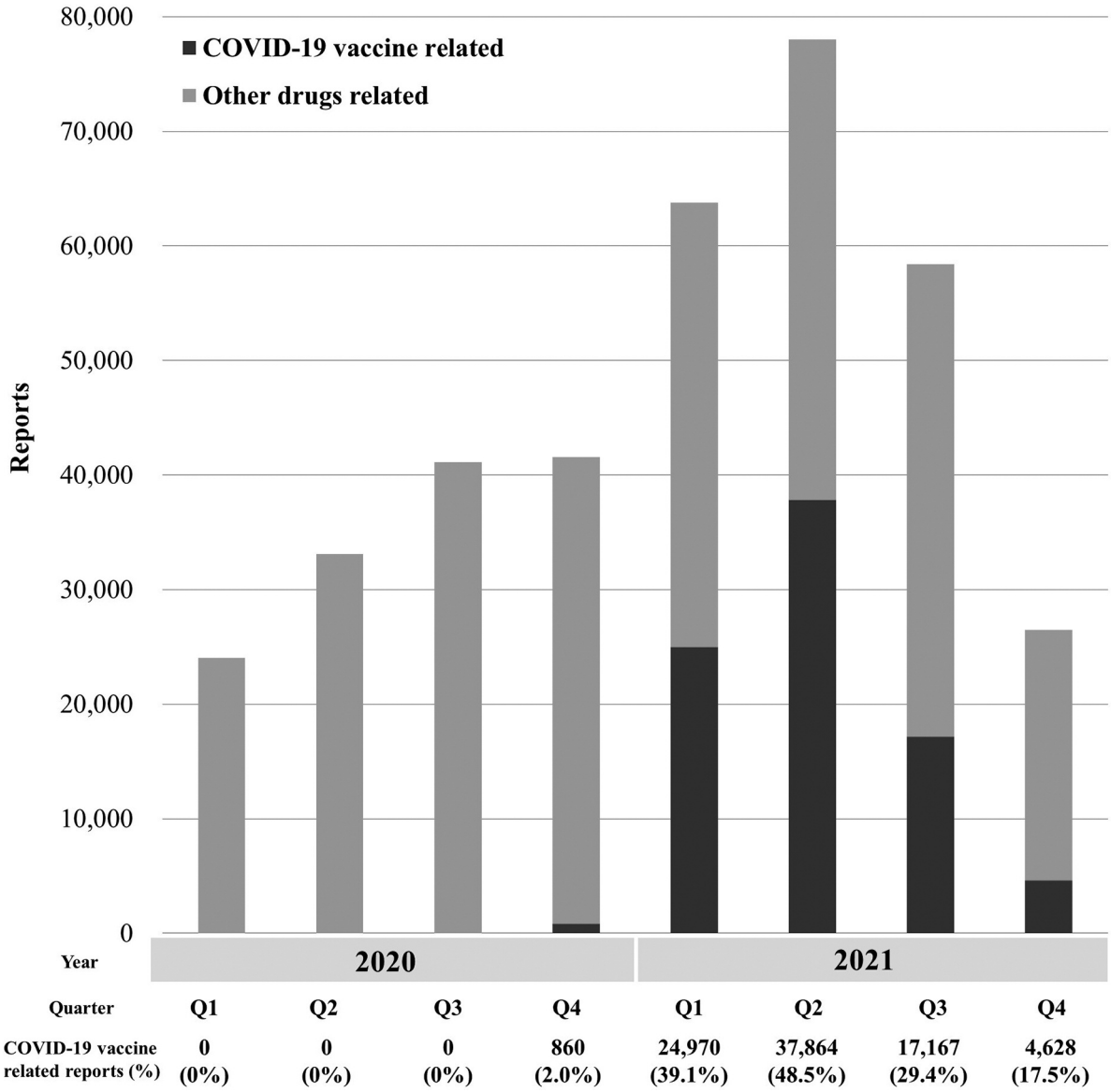


Figure 1. *Number of adverse events reported due to COVID-19 vaccine as a percentage of all reports in 2020-2021.*

Table I. *Number of reports and reported odds ratio (ROR), proportional reporting ratio (PRR), and $\chi^2$ of COVID-19 vaccine associated with adverse effects.*

| Variable | Cases (n) | Non-cases (n) | Rate (%) | ROR (95%CI) | PRR | $\chi^2$ |
|---|---|---|---|---|---|---|
| Anaphylactic reaction | 3,488 | 82,001 | 4.08 | 7.55 (7.26-7.85) | 7.28 | 14,349.65 |
| Pyrexia | 3,263 | 82,226 | 3.82 | 3.03 (2.91-3.14) | 2.95 | 3,761.57 |
| Nausea | 1,934 | 83,555 | 2.26 | 4.37 (4.16-4.59) | 4.29 | 4,118.26 |
| Dyspnoea | 1,858 | 83,631 | 2.17 | 6.09 (5.78-6.41) | 5.98 | 6,103.97 |
| Headache | 1,821 | 83,668 | 2.13 | 13.59 (12.82-14.41) | 13.32 | 13,033.37 |
| Malaise | 1,775 | 83,714 | 2.08 | 4.94 (4.69-5.20) | 4.85 | 4,485.73 |
| Blood pressure increased | 1,654 | 83,835 | 1.93 | 14.03 (13.19-14.92) | 13.78 | 12,159.96 |
| Pruritus | 1,562 | 83,927 | 1.83 | 11.99 (11.27-12.74) | 11.79 | 10,125.53 |
| Erythema | 1,457 | 84,032 | 1.70 | 4.66 (4.46-5.00) | 4.66 | 3,478.29 |
| Feeling abnormal | 1,425 | 84,064 | 1.67 | 28.18 (26.06-30.45) | 27.73 | 16,429.96 |

Table II. *Comparison of number of signals detected with and without the COVID-19 vaccine*.

| Variable | Number of detected safety signals using ROR | | Number of detected safety signals using PRR | |
|---|---|---|---|---|
| | Includes COVID-19 vaccine | Excludes COVID-19 vaccine | Includes COVID-19 vaccine | Excludes COVID-19 vaccine |
| Anaphylactic reaction | 28/30 (93.3%) | 30/30 (100%) | 24/30 (80.0%) | 27/30 (90.0%) |
| Pyrexia | 22/30 (73.3%) | 22/30 (73.3%) | 14/30 (46.7%) | 14/30 (46.7%) |
| Nausea | 26/30 (86.7%) | 27/30 (90.0%) | 20/30 (66.7%) | 22/30 (73.3%) |
| Dyspnoea | 17/30 (56.7%) | 20/30 (66.7%) | 10/30 (33.3%) | 10/30 (33.3%) |
| Headache | 19/30 (63.3%) | 21/30 (70.0%) | 15/30 (50.0%) | 19/30 (63.3%) |
| Malaise | 22/30 (73.3%) | 24/30 (80.0%) | 14/30 (46,7%) | 19/30 (63.3%) |
| Blood pressure increased | 23/30 (76.7%) | 26/30 (86.7%) | 18/30 (60.0%) | 24/30 (80.0%) |
| Pruritus | 18/30 (60.0%) | 21/30 (70.0%) | 15/30 (50.0%) | 18/30 (60.0%) |
| Erythema | 28/30 (93.3%) | 28/30 (93.3%) | 23/30 (76.7%) | 26/30 (86.7%) |
| Feeling abnormal | 19/30 (63.3%) | 26/30 (86.7%) | 17/30 (56.7%) | 25/30 (83.3%) |

Table III. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported anaphylactic reaction*.

| Drugs | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 7.55 (7.26-7.85) | 7.28 | 14,349.65 | – | – | – |
| Carboplatin | 1.11 (0.93-1.33) | 1.11 | 1.14 | 1.41 (1.18-1.69) | 1.41 | 13.78 |
| Docetaxel | 1.19 (0.96-1.49) | 1.19 | 2.26 | 1.52 (1.22-1.90) | 1.52 | 13.30 |
| Loxoprofen sodium hydrate | 1.36 (1.13-1.63) | 1.35 | 10.58 | 1.73 (1.44-2.07) | 1.72 | 34.98 |
| Paclitaxel | 1.66 (1.41-1.96) | 1.65 | 37.53 | 2.12 (1.80-2.49) | 2.11 | 84.10 |
| Oxaliplatin | 1.84 (1.60-2.11) | 1.83 | 78.29 | 2.35 (2.05-2.69) | 2.33 | 157.82 |
| Acetaminophen | 1.94 (1.57-2.40) | 1.93 | 38.61 | 2.47 (2.00-3.06) | 2.45 | 74.20 |
| Levofloxacin hydrate | 4.36 (3.83-4.96) | 4.26 | 592.11 | 5.57 (4.89-6.34) | 5.43 | 852.87 |
| Propofol | 4.38 (3.64-5.27) | 4.28 | 290.25 | 5.58 (4.64-6.71) | 5.44 | 417.45 |
| Garenoxacin mesilate hydrate | 4.98 (4.08-6.06) | 4.84 | 309.88 | 6.34 (5.20-7.72) | 6.15 | 437.68 |
| Remifentanil hydrochloride | 5.04 (3.99-6.36) | 4.90 | 226.19 | 6.41 (5.08-8.09) | 6.23 | 318.96 |
| Ceftriaxone sodium hydrate | 5.28 (4.53-6.15) | 5.12 | 570.46 | 6.73 (5.78-7.84) | 6.53 | 800.07 |
| Pneumococcal 13-valent conjugate vaccine | 5.36 (4.59-6.27) | 5.20 | 553.56 | 6.84 (5.85-8.00) | 6.63 | 774.88 |
| Irradiated red blood cells | 5.48 (4.86-6.18) | 5.32 | 974.96 | 7.01 (6.22-7.91) | 6.79 | 1362.23 |
| Influenza HA vaccine | 5.56 (4.81-6.44) | 5.39 | 670.57 | 7.10 (6.13-8.21) | 6.87 | 934.92 |
| Haemophilus b conjugate vaccine (tetanus toxoid conjugate); Haemophilus influenzae type b conjugate vaccine | 5.90 (5.09-6.84) | 5.71 | 716.73 | 7.53 (6.50-8.73) | 7.27 | 992.97 |
| Red blood cells | 6.07 (4.85-7.59) | 5.86 | 317.73 | 7.72 (6.17-9.66) | 7.44 | 438.86 |
| Iohexol | 6.18 (5.14-7.44) | 5.96 | 482.02 | 7.88 (6.54-9.48) | 7.59 | 664.56 |
| Nafamostat mesilate | 6.48 (5.32-7.89) | 6.24 | 452.24 | 8.25 (6.77-10.06) | 7.93 | 620.78 |
| L-Asparaginase | 7.06 (5.61-8.88) | 6.77 | 373.53 | 8.99 (7.14-11.31) | 8.60 | 509.02 |
| General cold remedy (OTC) | 7.08 (5.75-8.71) | 6.79 | 458.11 | 9.01 (7.32-11.09) | 8.63 | 624.17 |
| Adsorbed diphtheria-purified pertussis-tetanus-Inactivated polio combined vaccine | 7.48 (6.09-9.18) | 7.15 | 507.03 | 9.52 (7.75-11.69) | 9.09 | 687.89 |
| Iomeprol | 7.52 (6.21-9.10) | 7.19 | 589.77 | 9.57 (7.91-11.59) | 9.14 | 799.85 |
| Cefazolin sodium | 8.26 (6.93-9.84) | 7.86 | 793.14 | 10.52 (8.83-12.54) | 10.00 | 1,068.65 |
| Iopamidol | 8.46 (7.53-9.50) | 8.04 | 1,851.29 | 10.82 (9.63-12.16) | 10.27 | 2,492.11 |
| Hepatitis b vaccine | 8.90 (7.49-10.58) | 8.43 | 894.13 | 11.34 (9.54-13.49) | 10.73 | 1,199.07 |
| Fresh-frozen human plasma | 9.93 (8.82-11.17) | 9.35 | 2,203.44 | 12.7 (11.28-14.30) | 11.94 | 2,938.31 |
| Antipyretic analgesic anti-inflammatory (OTC) | 11.01 (9.01-13.45) | 10.29 | 862.44 | 14.03 (11.48-17.14) | 13.08 | 1,143.55 |
| Irradiated platelet concentrate | 12.81 (11.78-13.92) | 11.85 | 5,951.67 | 16.52 (15.18-17.97) | 15.26 | 7,851.61 |
| Rocuronium bromide | 16.51 (14.58-18.69) | 14.90 | 3,608.21 | 21.11 (18.64-23.91) | 19.03 | 4,714.41 |
| Sugammadex sodium | 20.48 (17.63-23.78) | 18.02 | 3,159.47 | 26.14 (22.50-30.36) | 22.97 | 4,104.26 |

Table IV. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported pyrexia.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 3.03 (2.91-3.14) | 2.95 | 3,761.57 | – | – | – |
| Prednisolone | 0.38 (0.33-0.43) | 0.38 | 212.94 | 0.41 (0.35-0.47) | 0.41 | 176.71 |
| Methotrexate | 0.50 (0.44-0.56) | 0.50 | 132.77 | 0.54 (0.48-0.61) | 0.54 | 102.37 |
| Bevacizumab | 0.61 (0.53-0.70) | 0.61 | 47.78 | 0.66 (0.57-0.76) | 0.66 | 33.09 |
| Oxaliplatin | 0.63 (0.54-0.74) | 0.64 | 30.73 | 0.68 (0.58-0.81) | 0.69 | 20.58 |
| Fluorouracil | 0.75 (0.64-0.87) | 0.75 | 14.38 | 0.81 (0.70-0.94) | 0.81 | 7.41 |
| Carboplatin | 0.75 (0.65-0.88) | 0.76 | 12.68 | 0.82 (0.70-0.95) | 0.82 | 6.33 |
| Irinotecan hydrochloride hydrate | 0.88 (0.75-1.03) | 0.88 | 2.46 | 0.95 (0.81-1.12) | 0.95 | 0.31 |
| Pembrolizumab | 0.99 (0.86-1.13) | 0.99 | 0.03 | 1.07 (0.93-1.23) | 1.07 | 0.83 |
| Nivolumab | 1.15 (1.04-1.27) | 1.15 | 7.81 | 1.25 (1.13-1.38) | 1.25 | 19.73 |
| Carbamazepine | 1.29 (1.12-1.48) | 1.28 | 12.08 | 1.39 (1.21-1.61) | 1.39 | 21.39 |
| Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusiani cells) | 1.42 (1.22-1.65) | 1.41 | 20.03 | 1.54 (1.32-1.79) | 1.53 | 30.67 |
| Ipilimumab | 1.43 (1.27-1.62) | 1.42 | 33.02 | 1.55 (1.38-1.76) | 1.54 | 50.10 |
| Peginterferon alfa-2b | 1.47 (1.30-1.67) | 1.46 | 38.63 | 1.60 (1.42-1.81) | 1.59 | 57.01 |
| Ribavirin | 1.51 (1.37-1.67) | 1.50 | 66.28 | 1.64 (1.48-1.81) | 1.63 | 95.92 |
| Sulfamethoxazole and trimethoprim | 1.65 (1.41-1.93) | 1.64 | 38.51 | 1.79 (1.53-2.10) | 1.77 | 52.50 |
| Sunitinib malate | 1.71 (1.48-1.98) | 1.69 | 52.47 | 1.85 (1.60-2.14) | 1.83 | 70.29 |
| Simeprevir sodium | 2.42 (2.08-2.81) | 2.37 | 139.93 | 2.62 (2.26-3.05) | 2.57 | 169.05 |
| Anti-human thymocyte immunoglobulin | 3.15 (2.74-3.64) | 3.06 | 279.12 | 3.42 (2.97-3.95) | 3.32 | 325.17 |
| Irradiated platelet concentrate | 3.30 (2.96-3.68) | 3.20 | 516.36 | 3.58 (3.21-3.99) | 3.47 | 599.09 |
| Lamotrigine | 3.89 (3.58-4.22) | 3.74 | 1,222.00 | 4.22 (3.89-4.59) | 4.06 | 1,399.50 |
| Irradiated red blood cells | 4.54 (4.13-4.99) | 4.33 | 1,163.70 | 4.93 (4.48-5.43) | 4.70 | 1,319.08 |
| Live attenuated human rota virus vaccine | 4.82 (4.22-5.49) | 4.57 | 667.27 | 5.23 (4.58-5.96) | 4.96 | 753.72 |
| Hepatitis b vaccine | 5.78 (4.96-6.75) | 5.42 | 635.25 | 6.28 (5.38-7.32) | 5.88 | 711.64 |
| Mesalazine | 5.80 (5.11-6.60) | 5.44 | 924.48 | 6.30 (5.54-7.16) | 5.90 | 1,035.59 |
| Influenza HA vaccine | 6.00 (5.41-6.66) | 5.61 | 1,478.48 | 6.52 (5.88-7.24) | 6.09 | 1,654.31 |
| Pneumococcal vaccine polyvalent | 6.13 (5.49-6.84) | 5.72 | 1,357.94 | 6.66 (5.96-7.43) | 6.21 | 1,518.19 |
| Pneumococcal 13-valent conjugate vaccine | 7.64 (6.92-8.44) | 7.00 | 2,238.33 | 8.31 (7.52-9.17) | 7.60 | 2,485.41 |
| Haemophilus b conjugate vaccine (tetanus toxoid conjugate); Haemophilus influenzae type b conjugate vaccine | 9.60 (8.77-10.50) | 8.58 | 3,667.28 | 10.43 (9.54-11.41) | 9.32 | 4,050.69 |
| Adsorbed diphtheria-purified pertussis-tetanus-Inactivated polio combined vaccine | 9.72 (8.47-11.15) | 8.66 | 1,574.29 | 10.55 (9.19-12.10) | 9.39 | 1,738.02 |
| Pneumococcal polysaccharide conjugate vaccine 0(adsorbed) | 17.88 (15.52-20.60) | 14.48 | 3,040.16 | 19.41 (16.85-22.36) | 15.70 | 3,327.34 |

in Japan. Hence, vaccine adverse event reports were collected from the Japanese Adverse Drug Event Report (JADER) database in the same manner as those for pharmaceutical drugs. The reported odds ratio (ROR) and proportional reporting ratio (PRR) are commonly used for disproportionality analysis to detect safety signals in databases of spontaneous adverse event reports (8, 9). These methods do not include the entire administered population, and rely only on adverse event reports for the drug. Therefore, adverse event reports from the total vaccinated population can affect the detection of safety signals for registered drugs (2).

This study determined the impact of COVID-19 prophylactic vaccine adverse event reporting on the detection

Table V. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported nausea.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 4.37 (4.16-4.59) | 4.29 | 4,118.26 | – | – | – |
| Methotrexate | 0.38 (0.31-0.47) | 0.38 | 87.64 | 0.43 (0.35-0.54) | 0.43 | 63.79 |
| Nivolumab | 0.46 (0.37-0.58) | 0.46 | 44.03 | 0.53 (0.42-0.67) | 0.53 | 29.57 |
| Cyclophosphamide | 0.78 (0.61-1.00) | 0.78 | 3.64 | 0.89 (0.70-1.14) | 0.89 | 0.71 |
| Bevacizumab | 1.08 (0.91-1.27) | 1.07 | 0.68 | 1.23 (1.04-1.45) | 1.23 | 5.88 |
| Carboplatin | 1.34 (1.12-1.60) | 1.34 | 10.32 | 1.53 (1.28-1.83) | 1.53 | 22.13 |
| Paclitaxel | 1.35 (1.11-1.64) | 1.34 | 8.55 | 1.54 (1.26-1.87) | 1.53 | 18.27 |
| Gemcitabine hydrochloride | 1.36 (1.08-1.72) | 1.36 | 6.43 | 1.56 (1.23-1.97) | 1.55 | 13.41 |
| Pregabalin | 1.64 (1.38-1.95) | 1.63 | 31.44 | 1.88 (1.58-2.23) | 1.87 | 51.45 |
| Doxorubicin hydrochloride | 1.79 (1.48-2.17) | 1.78 | 36.02 | 2.05 (1.69-2.48) | 2.04 | 55.24 |
| Ribavirin | 1.96 (1.71-2.23) | 1.94 | 99.56 | 2.24 (1.96-2.56) | 2.22 | 145.81 |
| Paroxetine hydrochloride hemihydrate | 2.20 (1.78-2.72) | 2.18 | 53.87 | 2.51 (2.03-3.11) | 2.49 | 75.09 |
| Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells) | 2.39 (1.99-2.86) | 2.37 | 93.66 | 2.73 (2.28-3.27) | 2.70 | 127.22 |
| Valacyclovir hydrochloride | 2.48 (2.08-2.95) | 2.46 | 108.55 | 2.83 (2.38-3.38) | 2.81 | 145.91 |
| Peginterferon alfa-2b | 2.51 (2.17-2.90) | 2.49 | 166.61 | 2.87 (2.49-3.32) | 2.84 | 223.35 |
| Tegafur, gimeracil and oteracil potassium | 2.51 (2.18-2.89) | 2.49 | 176.70 | 2.88 (2.50-3.31) | 2.85 | 236.82 |
| Irinotecan hydrochloride hydrate | 2.66 (2.31-3.06) | 2.63 | 197.35 | 3.04 (2.64-3.50) | 3.01 | 260.96 |
| Capecitabine | 3.00 (2.56-3.52) | 2.97 | 198.74 | 3.43 (2.93-4.03) | 3.39 | 256.29 |
| Oxaliplatin | 3.13 (2.79-3.51) | 3.09 | 415.96 | 3.58 (3.19-4.02) | 3.54 | 533.40 |
| Cisplatin | 3.48 (3.14-3.86) | 3.43 | 636.36 | 4.00 (3.61-4.44) | 3.94 | 803.32 |
| Telaprevir | 3.52 (2.99-4.15) | 3.47 | 252.58 | 4.03 (3.41-4.75) | 3.96 | 317.79 |
| Pemetrexed sodium hydrate | 3.64 (3.07-4.32) | 3.58 | 251.19 | 4.16 (3.51-4.94) | 4.09 | 314.68 |
| Melphalan | 3.67 (3.03-4.45) | 3.61 | 199.09 | 4.20 (3.46-5.09) | 4.13 | 249.10 |
| Tramadol hydrochloride | | | | | | |
| Acetaminophen | 3.71 (2.94-4.69) | 3.65 | 136.09 | 4.24 (3.36-5.36) | 4.17 | 170.05 |
| Fluorouracil | 3.98 (3.59-4.42) | 3.91 | 792.28 | 4.57 (4.12-5.07) | 4.49 | 983.74 |
| Calcium levofolinate hydrate | 4.03 (3.50-4.64) | 3.96 | 432.49 | 4.61 (4.00-5.32) | 4.53 | 535.64 |
| Enzalutamide | 4.73 (3.77-5.93) | 4.63 | 217.93 | 5.40 (4.31-6.77) | 5.28 | 265.75 |
| Crizotinib | 5.64 (4.50-7.07) | 5.49 | 281.46 | 6.44 (5.14-8.08) | 6.26 | 338.85 |
| Lapatinib tosilate hydrate | 5.91 (4.67-7.48) | 5.74 | 277.32 | 6.75 (5.33-8.55) | 6.56 | 332.88 |
| Oxycodone hydrochloride hydrate | 7.45 (5.94-9.34) | 7.18 | 413.55 | 8.52 (6.79-10.68) | 8.19 | 490.50 |
| Buprenorphine hydrochloride | 17.87 (13.98-22.84) | 16.23 | 999.82 | 20.42 (15.97-26.1) | 18.53 | 1,158.05 |

of safety signals by disproportionality analysis using the JADER database.

## Patients and Methods

We obtained JADER data from the PMDA website (10). The data were collected from April 2004 to April 2022. The JADER data consist of four files: “demo”, “drug”, “reac”, and “hist.” The “demo” contains basic patient information such as sex, age, and reporting year; “drug” contains information on the drug (generic name), trade name, route of administration, start date of administration, end date of administration, and drug involvement; “reac” contains information on the adverse event, including the name of the adverse event, the date of its occurrence, and the outcome; and “hist” contains information on the patient’s underlying disease (11). We based the adverse event names on the basic terms listed in the Japanese version of the International Conference on Harmonization’s International Glossary of Terms for Medicinal Products, version 25.0.

We extracted data from the JADER dataset, in which the COVID-19 vaccine was reported as a suspected drug, and selected the top 10 adverse events in terms of the number of reports. We then extracted the top 30 drugs by the amount of information in the selected 10 adverse events and compared the changes in the number of signal detections with and without COVID-19 vaccine report data.

Table VI. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported dyspnoea.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 6.09 (5.78-6.41) | 5.98 | 6,103.97 | – | – | – |
| Prednisolone | 0.19 (0.13-0.27) | 0.19 | 112.76 | 0.23 (0.16-0.32) | 0.23 | 83.57 |
| Methotrexate | 0.27 (0.20-0.36) | 0.27 | 89.08 | 0.33 (0.25-0.44) | 0.33 | 61.91 |
| Bevacizumab | 0.38 (0.27-0.52) | 0.38 | 38.06 | 0.46 (0.33-0.63) | 0.46 | 23.53 |
| Nivolumab | 0.40 (0.30-0.54) | 0.40 | 39.69 | 0.50 (0.36-0.70) | 0.50 | 16.93 |
| Ribavirin | 0.41 (0.30-0.57) | 0.41 | 28.72 | 0.49 (0.37-0.66) | 0.49 | 23.70 |
| Fluorouracil | 0.51 (0.37-0.71) | 0.51 | 16.76 | 0.63 (0.45-0.88) | 0.63 | 7.04 |
| Pembrolizumab | 0.52 (0.37-0.73) | 0.52 | 14.71 | 0.62 (0.45-0.86) | 0.62 | 8.17 |
| Carboplatin | 0.57 (0.42-0.78) | 0.57 | 12.05 | 0.69 (0.51-0.95) | 0.69 | 4.93 |
| Docetaxel | 0.82 (0.59-1.16) | 0.83 | 1.09 | 1.00 (0.71-1.40) | 1.00 | 0.01 |
| Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells) | 1.01 (0.73-1.39) | 1.01 | 0.00 | 1.23 (0.89-1.69) | 1.22 | 1.34 |
| Paclitaxel | 1.17 (0.91-1.49) | 1.17 | 1.38 | 1.44 (1.04-2.00) | 1.44 | 4.34 |
| Infliximab | 1.18 (0.85-1.64) | 1.18 | 0.85 | 1.46 (1.05-2.02) | 1.45 | 4.65 |
| Diclofenac sodium | 1.20 (0.86-1.66) | 1.20 | 0.99 | 1.42 (1.11-1.81) | 1.42 | 7.53 |
| Pregabalin | 1.33 (1.06-1.66) | 1.33 | 5.89 | 1.72 (1.24-2.39) | 1.71 | 10.01 |
| Loxoprofen sodium hydrate | 1.36 (1.08-1.71) | 1.35 | 6.50 | 1.67 (1.27-2.20) | 1.66 | 12.81 |
| Calcium levofolinate hydrate | 1.37 (1.04-1.81) | 1.37 | 4.73 | 1.61 (1.29-2.02) | 1.61 | 17.33 |
| Oxaliplatin | 1.38 (1.13-1.68) | 1.38 | 9.85 | 1.65 (1.31-2.08) | 1.65 | 18.00 |
| Cetuximab | 1.42 (1.02-1.97) | 1.41 | 3.94 | 1.87 (1.34-2.63) | 1.87 | 12.83 |
| Levofloxacin hydrate | 1.50 (1.14-1.96) | 1.49 | 8.11 | 1.68 (1.38-2.05) | 1.67 | 26.16 |
| Influenza HA vaccine | 1.54 (1.10-2.16) | 1.54 | 5.88 | 1.82 (1.39-2.38) | 1.81 | 18.42 |
| Nafamostat mesilate | 3.11 (2.19-4.41) | 3.08 | 42.95 | 3.78 (2.66-5.36) | 3.74 | 61.45 |
| Garenoxacin mesilate hydrate | 4.30 (3.29-5.60) | 4.23 | 134.87 | 5.22 (4.00-6.81) | 5.14 | 181.97 |
| Iohexol | 5.47 (4.28-6.99) | 5.37 | 229.57 | 6.66 (5.21-8.51) | 6.52 | 301.36 |
| Iopamidol | 6.87 (5.86-8.06) | 6.70 | 755.34 | 8.38 (7.15-9.83) | 8.17 | 973.81 |
| Fresh-frozen human plasma | 7.90 (6.72-9.29) | 7.67 | 875.43 | 9.86 (7.83-12.41) | 9.55 | 569.27 |
| Iomeprol | 8.10 (6.44-10.20) | 7.86 | 446.29 | 9.64 (8.19-11.33) | 9.35 | 1,118.60 |
| Red blood cells | 13.65 (11.24-16.58) | 12.94 | 1,179.27 | 16.62 (13.68-20.19) | 15.74 | 1,472.03 |
| Irradiated red blood cells | 15.93 (14.48-17.51) | 14.99 | 5,915.96 | 19.62 (17.83-21.60) | 18.46 | 7,361.14 |
| Platelet concentrate | 16.68 (11.82-23.52) | 15.60 | 464.03 | 20.26 (14.36-28.58) | 18.94 | 576.13 |
| Irradiated platelet concentrate | 17.55 (16.03-19.23) | 16.42 | 7,194.50 | 21.67 (19.77-23.75) | 20.26 | 8,931.48 |

This observational study was conducted in compliance with the ethical guidelines for epidemiological studies of the Ministry of Health, Labor, and Welfare. The study complied with the principles of the Declaration of Helsinki, used anonymized information from the JADER database, and did not involve therapeutic interventions or the collection of human samples. In addition, the ethics review committee of his institution deemed that the study did not require ethical approval.

## Results

The total number of adverse events reported in the JADER database during the study period was 2,002,564. Of the total number of reports, 85,489 (4.3%) reported adverse events related to the COVID-19 vaccine. The reporting periods were concentrated in the first three periods of 2021, with the second period of 2021 accounting for 48% of the total number of reports (Figure 1). The top 10 adverse events related to the COVID-19 vaccine were selected, with 4 in the 10% range, 2 in the 20% range, 4 in the 30% range, and 1 in the 50% range of the total number of adverse event reports. The number of cases in the 10% range, 2 in the 20% range, 4 in the 30% range, and 1 in the 50% range were identified (Table I). Furthermore, the aforementioned disproportionality analysis of the top 10 adverse events revealed a safety signal for all of the adverse events (Table I).

For the 10 selected adverse events, the number and percentage of drugs for which a safety signal was detected in the top 30 drugs in terms of the number of reports

Table VII. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported headache.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 13.59 (12.82-14.41) | 13.32 | 13,033.37 | – | – | – |
| Methotrexate | 0.17 (0.10-0.28) | 0.17 | 63.74 | 0.26 (0.16-0.43) | 0.26 | 32.73 |
| Prednisolone | 0.24 (0.16-0.36) | 0.24 | 54.37 | 0.37 (0.24-0.55) | 0.37 | 24.25 |
| Tacrolimus hydrate | 0.29 (0.18-0.47) | 0.29 | 27.43 | 0.44 (0.27-0.72) | 0.44 | 10.78 |
| Ciclosporin | 0.36 (0.21-0.61) | 0.36 | 14.99 | 0.55 (0.33-0.94) | 0.56 | 4.53 |
| Nivolumab | 0.41 (0.28-0.61) | 0.41 | 21.00 | 0.63 (0.43-0.93) | 0.63 | 5.14 |
| Aspirin | 0.54 (0.34-0.86) | 0.54 | 6.41 | 0.83 (0.52-1.32) | 0.83 | 0.45 |
| Ipilimumab | 0.65 (0.42-0.99) | 0.65 | 3.65 | 0.99 (0.65-1.52) | 0.99 | 0.01 |
| Loxoprofen sodium hydrate | 0.69 (0.45-1.06) | 0.69 | 2.57 | 1.07 (0.68-1.68) | 1.07 | 0.03 |
| Carbamazepine | 0.70 (0.44-1.09) | 0.70 | 2.19 | 1.06 (0.69-1.63) | 1.06 | 0.02 |
| Lamotrigine | 1.13 (0.81-1.60) | 1.13 | 0.40 | 1.74 (1.23-2.45) | 1.74 | 9.53 |
| Pregabalin | 1.26 (0.93-1.71) | 1.26 | 1.92 | 1.93 (1.42-2.63) | 1.93 | 17.28 |
| Ribavirin | 1.53 (1.21-1.94) | 1.53 | 12.29 | 2.36 (1.86-2.99) | 2.35 | 52.73 |
| Peginterferon alfa-2b | 1.53 (1.15-2.04) | 1.53 | 8.30 | 2.36 (1.77-3.14) | 2.35 | 35.52 |
| Temozolomide | 1.57 (0.94-2.60) | 1.56 | 2.51 | 2.40 (1.44-3.99) | 2.39 | 10.77 |
| Etizolam | 1.99 (1.27-3.12) | 1.98 | 8.29 | 3.04 (1.94-4.79) | 3.04 | 23.82 |
| Paroxetine hydrochloride hydrate | 2.07 (1.47-2.92) | 2.07 | 17.03 | 3.18 (2.25-4.48) | 3.17 | 46.36 |
| Valaciclovir hydrochloride | 2.37 (1.80-3.14) | 2.37 | 37.82 | 3.65 (2.76-4.83) | 3.64 | 91.54 |
| Pneumococcal vaccine polyvalent | 2.44 (1.66-3.60) | 2.44 | 20.53 | 3.75 (2.54-5.52) | 3.73 | 48.93 |
| Mesalazine | 2.58 (1.68-3.96) | 2.57 | 18.50 | 3.95 (2.57-6.07) | 3.93 | 42.71 |
| Alprazolam | 2.73 (1.64-4.54) | 2.72 | 14.59 | 4.18 (2.51-6.95) | 4.16 | 32.74 |
| Cilostazol | 2.76 (1.88-4.07) | 2.75 | 27.19 | 4.24 (2.88-6.24) | 4.21 | 60.14 |
| Influenza HA vaccine | 2.89 (2.07-4.03) | 2.87 | 40.66 | 4.43 (3.17-6.19) | 4.40 | 87.82 |
| Venlafaxine hydrochloride | 2.94 (1.82-4.73) | 2.92 | 19.59 | 4.50 (2.79-7.25) | 4.47 | 42.22 |
| Simeprevir sodium | 3.02 (2.20-4.15) | 3.01 | 50.08 | 4.64 (3.38-6.38) | 4.62 | 105.74 |
| Eculizumab | 5.20 (3.07-8.81) | 5.14 | 42.66 | 7.95 (4.69-13.49) | 7.87 | 76.96 |
| Teriparatide acetate | 5.35 (3.54-8.08) | 5.29 | 75.69 | 8.20 (5.42-12.39) | 8.11 | 135.43 |
| Epoprostenol sodium | 6.18 (3.92-9.72) | 6.10 | 75.87 | 9.46 (6.00-14.90) | 9.33 | 132.55 |
| Polyethylene glycol treated n human normal immunoglobuli | 7.56 (4.74-12.05) | 7.44 | 93.83 | 11.57 (7.25-18.47) | 11.38 | 159.50 |
| Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells) | 14.07 (12.42-15.93) | 13.65 | 2,986.34 | 22.27 (19.61-25.28) | 21.59 | 4,824.03 |
| Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) | 20.02 (16.67-24.04) | 19.15 | 2,049.98 | 31.06 (25.83-37.36) | 29.69 | 3,251.20 |

counting or excluding COVID-19 vaccine reports (Table II) were recorded. ROR and PRR showed lower values when the COVID-19 vaccine data were included (Table III, Table IV, Table V, Table VI, Table VII, Table VIII, Table IX, Table X, Table XI, Table XII). In the detection of safety signals using ROR, the COVID-19 vaccine eliminated the detection of safety signals for 23 out of 245 drugs, including carboplatin in anaphylaxis (Table III) and bevacizumab in nausea (Table V). In addition, PRR-based signal detection eliminated the signals of 34 of 204 drugs, including paclitaxel (Table III) for anaphylaxis and ribavirin (Table V) for nausea.

## Discussion

The number of COVID-19 vaccine reports accounted for 4.2% of all JADER reports up to the time of analysis, suggesting a high occupancy rate for a single agent. The reports were concentrated in the first three periods of 2021, when vaccination began, and were extremely high in the second period at 48% of the total number of reports. In addition, of the top 10 adverse events reported by the COVID-19 vaccine, the COVID-19 vaccine accounted for 30% or more of all reports in 5 of the events. These results suggest that the number of reports may have increased

Table VIII. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported malaise.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 4.94 (4.69-5.20) | 4.85 | 4,485.73 | – | – | – |
| Methotrexate | 0.42 (0.34-0.52) | 0.42 | 63.74 | 0.49 (0.39-0.61) | 0.49 | 42.19 |
| Pembrolizumab | 0.82 (0.64-1.06) | 0.82 | 2.09 | 0.96 (0.75-1.24) | 0.96 | 0.06 |
| Dexamethasone | 0.91 (0.71-1.17) | 0.91 | 0.49 | 1.06 (0.82-1.36) | 1.06 | 0.14 |
| Carboplatin | 0.92 (0.73-1.17) | 0.92 | 0.37 | 1.08 (0.85-1.36) | 1.08 | 0.31 |
| Bevacizumab | 0.96 (0.79-1.16) | 0.96 | 0.15 | 1.12 (0.93-1.35) | 1.12 | 1.23 |
| Lamotrigine | 1.08 (0.84-1.38) | 1.08 | 0.27 | 1.26 (0.98-1.61) | 1.25 | 3.04 |
| Cisplatin | 1.09 (0.90-1.32) | 1.09 | 0.65 | 1.30 (1.03-1.63) | 1.30 | 4.66 |
| Pregabalin | 1.11 (0.88-1.40) | 1.11 | 0.71 | 1.27 (1.05-1.55) | 1.27 | 5.56 |
| Nivolumab | 1.49 (1.29-1.72) | 1.48 | 28.62 | 1.82 (1.43-2.31) | 1.81 | 23.36 |
| Oxaliplatin | 1.52 (1.27-1.81) | 1.51 | 20.77 | 1.77 (1.48-2.11) | 1.76 | 39.81 |
| Gemcitabine hydrochloride | 1.56 (1.22-1.98) | 1.55 | 12.58 | 1.74 (1.50-2.01) | 1.73 | 56.39 |
| Ipilimumab | 1.76 (1.46-2.11) | 1.75 | 35.96 | 2.05 (1.70-2.47) | 2.04 | 59.52 |
| Tegafur, gimeracil and oteracil potassium | 1.77 (1.48-2.12) | 1.76 | 38.24 | 2.07 (1.72-2.48) | 2.06 | 62.96 |
| Fluorouracil | 1.81 (1.54-2.13) | 1.80 | 51.06 | 2.12 (1.80-2.50) | 2.11 | 82.69 |
| Irinotecan hydrochloride hydrate | 1.92 (1.60-2.30) | 1.91 | 50.47 | 2.29 (1.83-2.85) | 2.27 | 55.52 |
| Sorafenib tosilate | 1.96 (1.57-2.44) | 1.95 | 35.95 | 2.24 (1.87-2.68) | 2.23 | 78.92 |
| Calcium levofolinate hydrate | 2.08 (1.69-2.58) | 2.07 | 47.10 | 2.43 (1.97-3.01) | 2.42 | 70.53 |
| Capecitabine | 2.18 (1.78-2.67) | 2.17 | 57.51 | 2.54 (2.07-3.12) | 2.53 | 84.50 |
| Palbociclib | 2.70 (2.12-3.44) | 2.68 | 68.51 | 3.15 (2.47-4.01) | 3.12 | 94.02 |
| Simeprevir sodium | 3.25 (2.62-4.03) | 3.21 | 126.80 | 3.79 (3.06-4.70) | 3.75 | 167.36 |
| Sunitinib malate | 3.32 (2.78-3.95) | 3.28 | 198.84 | 3.87 (3.25-4.62) | 3.83 | 261.56 |
| Axitinib | 3.41 (2.63-4.42) | 3.37 | 94.25 | 3.98 (3.07-5.16) | 3.93 | 123.39 |
| Pneumococcal vaccine polyvalent | 3.44 (2.73-4.33) | 3.40 | 122.62 | 4.02 (3.19-5.06) | 3.96 | 160.31 |
| Ribavirin | 3.66 (3.28-4.08) | 3.61 | 612.91 | 4.29 (3.84-4.79) | 4.23 | 795.87 |
| Peginterferon alfa-2b | 4.03 (3.55-4.57) | 3.97 | 540.76 | 4.72 (4.15-5.36) | 4.64 | 692.56 |
| Telaprevir | 4.48 (3.81-5.27) | 4.40 | 395.09 | 5.24 (4.46-6.16) | 5.15 | 499.54 |
| Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells) | 4.71 (4.08-5.44) | 4.62 | 539.48 | 5.51 (4.77-6.36) | 5.41 | 678.94 |
| Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) | 6.22 (4.98-7.77) | 6.06 | 336.45 | 7.26 (5.81-9.07) | 7.07 | 414.02 |
| Lenvatinib Mesilate | 6.81 (5.66-8.19) | 6.62 | 548.59 | 7.95 (6.61-9.57) | 7.73 | 671.47 |
| Enzalutamide | 10.66 (8.99-12.64) | 10.18 | 1,146.75 | 12.46 (10.50-14.78) | 11.88 | 1,376.65 |

Table IX. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported blood pressure increased.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 14.03 (13.19-14.92) | 13.78 | 12,159.96 | – | – | – |
| Prednisolone | 0.23 (0.15-0.36) | 0.23 | 49.07 | 0.36 (0.23-0.56) | 0.36 | 21.57 |
| Tacrolimus hydrate | 0.32 (0.20-0.53) | 0.32 | 21.93 | 0.50 (0.31-0.82) | 0.50 | 7.44 |
| Paclitaxel | 0.73 (0.47-1.13) | 0.73 | 1.79 | 1.13 (0.72-1.75) | 1.13 | 0.17 |
| Bevacizumab | 0.79 (0.58-1.09) | 0.79 | 1.89 | 1.23 (0.90-1.69) | 1.23 | 1.45 |
| Diclofenac sodium | 1.08 (0.66-1.77) | 1.08 | 0.03 | 1.67 (1.02-2.74) | 1.67 | 3.66 |

Table IX. *Continued*

Table IX. *Continued*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| Etanercept | 1.21 (0.77-1.89) | 1.20 | 0.47 | 1.87 (1.19-2.94) | 1.87 | 6.76 |
| Celecoxib | 1.38 (0.87-2.19) | 1.37 | 1.48 | 2.13 (1.34-3.39) | 2.13 | 9.62 |
| Irradiated platelet concentrate | 1.62 (1.11-2.36) | 1.62 | 5.71 | 2.77 (1.67-4.60) | 2.76 | 15.08 |
| Propofol | 1.79 (1.08-2.97) | 1.78 | 4.41 | 2.51 (1.72-3.67) | 2.51 | 22.74 |
| Methylprednisolone sodium succinate | 1.82 (1.14-2.89) | 1.82 | 5.81 | 2.82 (1.77-4.49) | 2.81 | 19.17 |
| Clozapine | 1.87 (1.19-2.93) | 1.86 | 6.73 | 2.89 (1.84-4.55) | 2.89 | 21.43 |
| Sunitinib malate | 1.87 (1.32-2.66) | 1.87 | 12.04 | 2.91 (2.05-4.13) | 2.90 | 37.63 |
| Amlodipine besilate | 2.08 (1.45-2.98) | 2.07 | 15.51 | 3.22 (2.25-4.63) | 3.21 | 43.16 |
| Pregabalin | 2.12 (1.65-2.73) | 2.12 | 34.34 | 3.31 (2.56-4.26) | 3.30 | 93.24 |
| Pazopanib hydrochloride | 2.34 (1.49-3.68) | 2.33 | 13.13 | 3.63 (2.31-5.70) | 3.61 | 33.15 |
| Irradiated platelet concentrate | 3.12 (2.37-4.12) | 3.11 | 70.07 | 4.86 (3.68-6.42) | 4.83 | 148.61 |
| Ciclosporin | 3.20 (2.64-3.88) | 3.19 | 154.76 | 5.03 (4.14-6.10) | 5.00 | 325.28 |
| Tramadol hydrochloride | | | | | | |
| Acetaminophen | 3.25 (2.15-4.90) | 3.23 | 33.14 | 5.04 (3.34-7.60) | 5.01 | 69.33 |
| Red blood cells | 3.36 (1.98-5.69) | 3.34 | 20.67 | 5.20 (3.07-8.81) | 5.17 | 42.88 |
| Darbepoetin alfa | 3.61 (2.41-5.40) | 3.59 | 42.08 | 5.60 (3.74-8.38) | 5.56 | 84.62 |
| Ledipasvir acetonate | | | | | | |
| Sofosbuvir | 4.71 (2.92-7.60) | 4.67 | 45.38 | 7.30 (4.52-11.79) | 7.24 | 84.81 |
| Vildagliptin | 4.93 (3.60-6.74) | 4.88 | 118.84 | 7.66 (5.60-10.48) | 7.59 | 219.26 |
| Axitinib | 5.27 (3.83-7.23) | 5.22 | 127.88 | 8.19 (5.96-11.25) | 8.11 | 232.77 |
| Teriparatide | 5.96 (3.91-9.09) | 5.90 | 84.42 | 9.25 (6.06-14.11) | 9.14 | 150.46 |
| Venlafaxine hydrochloride | 6.67 (4.75-9.37) | 6.59 | 154.80 | 10.36 (7.37-14.57) | 10.23 | 270.94 |
| Iomeprol | 7.88 (5.69-10.92) | 7.77 | 210.01 | 12.25 (8.83-16.99) | 12.06 | 359.81 |
| Valsartan | 8.89 (7.29-10.83) | 8.74 | 676.68 | 13.95 (11.42-17.03) | 13.70 | 1145.21 |
| Mirabegron | 9.29 (6.50-13.28) | 9.13 | 215.26 | 14.43 (10.09-20.63) | 14.17 | 362.59 |
| Aliskiren fumarate | 19.09 (12.32-29.56) | 18.37 | 326.83 | 29.60 (19.10-45.87) | 28.46 | 525.95 |
| Nicotine | 21.97 (13.49-35.77) | 21.01 | 303.80 | 34.05 (20.90-55.47) | 32.54 | 486.31 |

Table X. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and χ2 in the top 30 drugs in terms of reported pruritus*.

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 11.99 (11.27-12.75) | 11.79 | 10,125.53 | – | – | – |
| Pembrolizumab | 0.47 (0.29-0.77) | 0.47 | 8.76 | 0.69 (0.42-1.13) | 0.69 | 1.85 |
| Oxaliplatin | 0.48 (0.30-0.76) | 0.48 | 9.69 | 0.70 (0.44-1.11) | 0.70 | 2.01 |
| Nivolumab | 0.72 (0.53-0.98) | 0.72 | 4.20 | 1.06 (0.78-1.44) | 1.06 | 0.08 |
| Loxoprofen sodium hydrate | 0.74 (0.49-1.14) | 0.75 | 1.58 | 1.09 (0.71-1.68) | 1.09 | 0.08 |
| Paclitaxel | 0.77 (0.50-1.17) | 0.77 | 1.34 | 1.12 (0.74-1.71) | 1.12 | 0.18 |
| Carbamazepine | 0.83 (0.54-1.28) | 0.83 | 0.56 | 1.22 (0.79-1.87) | 1.22 | 0.60 |
| Pregabalin | 0.96 (0.66-1.38) | 0.96 | 0.02 | 1.40 (0.97-2.02) | 1.40 | 2.92 |
| Carboplatin | 1.03 (0.74-1.43) | 1.03 | 0.01 | 1.51 (1.09-2.10) | 1.51 | 5.67 |
| Lansoprazole | 1.05 (0.65-1.69) | 1.05 | 0.00 | 1.53 (0.95-2.47) | 1.53 | 2.60 |
| Acetaminophen | 1.10 (0.67-1.79) | 1.10 | 0.06 | 1.61 (0.98-2.63) | 1.61 | 3.06 |
| Diclofenac sodium | 1.17 (0.73-1.85) | 1.17 | 0.27 | 1.71 (1.07-2.71) | 1.71 | 4.54 |
| Ipilimumab | 1.20 (0.87-1.67) | 1.20 | 1.01 | 1.76 (1.27-2.45) | 1.76 | 10.95 |
| Levofloxacin hydrate | 1.48 (1.01-2.16) | 1.48 | 3.71 | 2.17 (1.49-3.17) | 2.17 | 15.69 |
| Allopurinol | 1.63 (1.10-2.42) | 1.63 | 5.41 | 2.39 (1.61-3.54) | 2.38 | 18.56 |
| Irradiated red blood cells | 1.86 (1.32-2.64) | 1.86 | 11.82 | 2.73 (1.93-3.87) | 2.73 | 32.95 |
| Peginterferon alfa-2a | 2.14 (1.45-3.18) | 2.14 | 13.98 | 3.14 (2.12-4.66) | 3.13 | 33.92 |

Table X. *Continued*

Table X. *Continued*

| Drugs | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| Garenoxacin mesilate hydrate | 2.35 (1.44-3.85) | 2.35 | 11.05 | 3.45 (2.11-5.64) | 3.43 | 25.12 |
| Rebamipide | 2.51 (1.66-3.78) | 2.50 | 19.18 | 3.68 (2.44-5.55) | 3.66 | 41.60 |
| Ribavirin | 3.34 (2.82-3.95) | 3.32 | 220.13 | 4.96 (4.19-5.88) | 4.93 | 418.19 |
| Peginterferon alfa-2b | 3.39 (2.77-4.15) | 3.37 | 156.61 | 5.01 (4.09-6.14) | 4.98 | 295.35 |
| Celecoxib | 3.71 (2.80-4.91) | 3.69 | 94.34 | 5.45 (4.12-7.22) | 5.41 | 172.81 |
| Sulbactam sodium, ampicillin sodium | 3.71 (2.41-5.71) | 3.69 | 38.43 | 5.44 (3.53-8.37) | 5.40 | 70.56 |
| Lamotrigine | 4.09 (3.38-4.96) | 4.07 | 241.27 | 6.06 (5.00-7.35) | 6.01 | 430.77 |
| Nafamostat mesilate | 4.16 (2.73-6.33) | 4.13 | 48.90 | 6.09 (3.99-9.28) | 6.04 | 87.05 |
| Fresh-frozen human plasma | 4.16 (3.08-5.63) | 4.14 | 98.38 | 6.12 (4.52-8.28) | 6.07 | 174.70 |
| Iomeprol | 4.24 (2.76-6.52) | 4.21 | 48.10 | 6.21 (4.03-9.56) | 6.16 | 85.22 |
| Iohexol | 5.76 (4.14-8.01) | 5.70 | 134.10 | 8.45 (6.07-11.77) | 8.36 | 223.53 |
| Iopamidol | 6.64 (5.32-8.30) | 6.56 | 365.70 | 9.80 (7.83-12.25) | 9.67 | 597.58 |
| Irradiated platelet concentrate | 6.88 (5.71-8.28) | 6.79 | 553.40 | 10.19 (8.45-12.28) | 10.05 | 900.98 |
| Simeprevir sodium | 8.04 (6.54-9.87) | 7.91 | 550.33 | 11.87 (9.65-14.61) | 11.68 | 880.17 |

Table XI. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported erythema.*

| Drugs | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 4.72 (4.46-5.00) | 4.66 | 3,478.29 | – | – | – |
| Nivolumab | 0.48 (0.36-0.62) | 0.48 | 29.30 | 0.55 (0.42-0.72) | 0.55 | 18.46 |
| Carboplatin | 0.80 (0.61-1.04) | 0.80 | 2.52 | 0.92 (0.70-1.21) | 0.92 | 0.28 |
| Ribavirin | 1.59 (1.34-1.90) | 1.59 | 27.01 | 1.85 (1.55-2.20) | 1.84 | 47.65 |
| Loxoprofen sodium hydrate | 1.71 (1.38-2.10) | 1.70 | 24.83 | 1.98 (1.60-2.44) | 1.97 | 41.14 |
| Sodium valproate | 1.76 (1.33-2.34) | 1.76 | 15.28 | 2.04 (1.54-2.71) | 2.04 | 24.71 |
| Lansoprazole | 1.86 (1.43-2.42) | 1.85 | 20.95 | 2.15 (1.65-2.80) | 2.14 | 32.75 |
| Sulfamethoxazole and trimethoprim | 1.87 (1.43-2.45) | 1.87 | 20.83 | 2.17 (1.66-2.84) | 2.16 | 32.39 |
| Levofloxacin hydrate | 2.10 (1.66-2.65) | 2.09 | 38.95 | 2.43 (1.92-3.07) | 2.42 | 57.17 |
| Acetaminophen | 2.15 (1.66-2.78) | 2.14 | 33.83 | 2.49 (1.92-3.22) | 2.47 | 49.18 |
| Peginterferon alfa-2b | 2.23 (1.86-2.67) | 2.22 | 78.22 | 2.59 (2.16-3.10) | 2.57 | 112.05 |
| Clarithromycin | 2.41 (1.84-3.18) | 2.40 | 40.99 | 2.80 (2.13-3.68) | 2.78 | 57.17 |
| Rebamipide | 2.70 (2.01-3.61) | 2.68 | 46.62 | 3.12 (2.33-4.18) | 3.10 | 63.11 |
| Carbamazepine | 2.89 (2.44-3.43) | 2.87 | 159.39 | 3.36 (2.83-3.98) | 3.33 | 212.41 |
| Salazosulfapyridine | 3.13 (2.35-4.17) | 3.10 | 66.22 | 3.63 (2.72-4.82) | 3.59 | 86.88 |
| Vancomycin hydrochloride | 3.27 (2.53-4.24) | 3.24 | 88.98 | 3.79 (2.93-4.91) | 3.75 | 115.83 |
| Irradiated red blood cells | 3.35 (2.76-4.06) | 3.32 | 167.69 | 3.88 (3.20-4.71) | 3.84 | 217.51 |
| Pneumococcal vaccine polyvalent | 3.61 (2.83-4.61) | 3.57 | 119.19 | 4.18 (3.28-5.34) | 4.14 | 152.86 |
| Allopurinol | 3.69 (3.03-4.48) | 3.65 | 195.54 | 4.28 (3.52-5.20) | 4.23 | 250.08 |
| Iopamidol | 3.83 (3.10-4.74) | 3.79 | 174.78 | 4.44 (3.59-5.50) | 4.39 | 222.37 |
| Telaprevir | 3.87 (3.21-4.66) | 3.82 | 230.58 | 4.49 (3.72-5.41) | 4.43 | 293.08 |
| Iohexol | 3.94 (2.94-5.27) | 3.89 | 95.71 | 4.56 (3.40-6.11) | 4.50 | 121.39 |
| Irradiated platelet concentrate | 4.37 (3.69-5.18) | 4.31 | 346.01 | 5.07 (4.28-6.01) | 5.00 | 433.85 |
| Amoxicillin hydrate | 4.39 (3.40-5.67) | 4.33 | 149.73 | 5.08 (3.93-6.57) | 5.01 | 187.61 |
| Celecoxib | 5.07 (4.25-6.06) | 4.99 | 393.74 | 5.89 (4.93-7.04) | 5.79 | 486.96 |
| Iomeprol | 5.13 (3.84-6.86) | 5.05 | 148.25 | 5.95 (4.45-7.94) | 5.84 | 183.15 |
| Red blood cells | 6.15 (4.63-8.17) | 6.02 | 199.65 | 7.12 (5.36-9.46) | 6.96 | 243.50 |
| Rocuronium bromide | 6.52 (5.16-8.24) | 6.37 | 323.85 | 7.56 (5.98-9.54) | 7.38 | 393.58 |
| Lamotrigine | 7.50 (6.74-8.36) | 7.31 | 1,858.95 | 8.76 (7.86-9.76) | 8.52 | 2,245.67 |
| Fresh-frozen human plasma | 7.56 (6.39-8.95) | 7.36 | 764.62 | 8.78 (7.42-10.39) | 8.54 | 922.26 |
| Sugammadex sodium | 11.01 (8.66-14.01) | 10.57 | 594.48 | 12.76 (10.03-16.24) | 12.24 | 706.75 |

Table XII. *Reported odds ratio (ROR), proportional reporting ratio (PRR) and $\chi^2$ in the top 30 drugs in terms of reported feeling abnormal.*

| | Includes COVID-19 vaccine | | | Excludes COVID-19 vaccine | | |
|---|---|---|---|---|---|---|
| Drugs | ROR (95%CI) | PRR | $\chi^2$ | ROR (95%CI) | PRR | $\chi^2$ |
| COVID-19 mRNA vaccine (nucleoside-modified) | 28.18 (26.07-30.47) | 27.73 | 16,429.96 | – | – | – |
| Methotrexate | 0.16 (0.08-0.32) | 0.16 | 33.98 | 0.35 (0.17-0.69) | 0.35 | 9.16 |
| Carboplatin | 0.40 (0.20-0.80) | 0.40 | 6.55 | 0.86 (0.43-1.73) | 0.86 | 0.07 |
| Lamotrigine | 0.58 (0.30-1.12) | 0.58 | 2.26 | 1.26 (0.65-2.42) | 1.25 | 0.24 |
| Aspirin | 0.69 (0.39-1.21) | 0.69 | 1.40 | 1.48 (0.84-2.62) | 1.48 | 1.40 |
| Loxoprofen sodium hydrate | 0.81 (0.47-1.40) | 0.81 | 0.39 | 1.75 (1.01-3.02) | 1.75 | 3.41 |
| Irradiated red blood cells | 1.12 (0.62-2.03) | 1.12 | 0.05 | 2.42 (1.33-4.38) | 2.41 | 7.67 |
| Amlodipine besilate | 1.16 (0.62-2.16) | 1.16 | 0.09 | 2.50 (1.34-4.66) | 2.50 | 7.48 |
| Pneumococcal vaccine polyvalent | 1.60 (0.83-3.07) | 1.59 | 1.44 | 3.43 (1.78-6.62) | 3.43 | 13.03 |
| Cilostazol | 1.60 (0.80-3.21) | 1.60 | 1.25 | 3.44 (1.72-6.90) | 3.44 | 11.42 |
| Influenza HA vaccine | 1.71 (0.94-3.09) | 1.70 | 2.53 | 3.67 (2.03-6.66) | 3.67 | 18.58 |
| Rebamipide | 1.72 (0.89-3.31) | 1.72 | 2.03 | 3.70 (1.92-7.13) | 3.69 | 14.98 |
| Paroxetine hydrochloride hydrate | 1.78 (1.07-2.96) | 1.78 | 4.33 | 3.84 (2.30-6.39) | 3.83 | 28.24 |
| Valaciclovir hydrochloride | 1.97 (1.30-3.00) | 1.97 | 9.47 | 4.27 (2.80-6.51) | 4.26 | 50.68 |
| Candesartan cilexetil | 2.28 (1.18-4.38) | 2.27 | 5.18 | 4.89 (2.54-9.44) | 4.88 | 23.86 |
| Sertraline hydrochloride | 2.30 (1.15-4.61) | 2.30 | 4.62 | 4.95 (2.47-9.93) | 4.94 | 21.18 |
| Rosuvastatin calcium | 2.52 (1.35-4.70) | 2.52 | 7.66 | 5.42 (2.91-10.12) | 5.41 | 31.41 |
| Tramadol hydrochloride, acetaminophen | 2.61 (1.44-4.72) | 2.60 | 9.29 | 5.62 (3.10-10.18) | 5.60 | 36.78 |
| Iopamidol | 3.15 (2.07-4.80) | 3.14 | 29.84 | 6.83 (4.47-10.42) | 6.80 | 101.22 |
| Ranitidine hydrochloride | 4.11 (1.95-8.64) | 4.09 | 13.38 | 8.83 (4.19-18.59) | 8.79 | 40.59 |
| Etizolam | 3.18 (1.94-5.20) | 3.17 | 21.54 | 6.86 (4.19-11.25) | 6.84 | 73.02 |
| Pregabalin | 3.31 (2.54-4.32) | 3.30 | 85.72 | 7.29 (5.57-9.54) | 7.26 | 281.93 |
| Alprazolam | 3.79 (2.09-6.86) | 3.78 | 19.71 | 8.16 (4.50-14.80) | 8.13 | 61.26 |
| Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) | 4.06 (2.40-6.88) | 4.05 | 29.00 | 8.76 (5.16-14.86) | 8.72 | 87.07 |
| Triazolam | 4.28 (2.22-8.25) | 4.26 | 19.30 | 9.21 (4.77-17.78) | 9.17 | 57.14 |
| Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells) | 4.82 (3.66-6.35) | 4.80 | 149.80 | 10.60 (8.02-14.01) | 10.54 | 420.04 |
| Teprenone | 5.00 (2.49-10.03) | 4.97 | 21.53 | 10.75 (5.35-21.59) | 10.68 | 60.47 |
| Varenicline tartrate | 5.16 (2.92-9.11) | 5.13 | 35.75 | 11.11 (6.28-19.66) | 11.04 | 98.80 |
| Zanamivir hydrate | 5.43 (3.07-9.59) | 5.40 | 38.59 | 11.70 (6.61-20.70) | 11.62 | 105.08 |
| Teriparatide acetate | 7.93 (4.98-12.64) | 7.86 | 100.50 | 17.14 (10.74-27.37) | 16.98 | 251.09 |
| Clotiazepam | 8.87 (4.89-16.09) | 8.78 | 68.04 | 19.09 (10.51-34.69) | 18.89 | 167.40 |

rapidly because healthcare providers closely monitored the adverse events associated with the administration of the COVID-19 vaccine (2).

In addition, we examined the impact of the rapid increase in adverse event reports for the COVID-19 vaccine on the detection of safety signals for other drugs, using disproportionality analysis. The ROR and PRR were lower for the condition that included the number of COVID-19 vaccine reports than for the condition that did not. The denominator in the calculation of ROR and PRR includes the number of reports of specific adverse events other than the targeted suspected drug. Therefore, for adverse events in which the COVID-19 vaccine had a large share of reported adverse events, the ROR and PRR values for the other drugs were lower than when the number of reports of the vaccine was not included (8, 9).

Furthermore, the top 30 drugs for each of the 10 adverse events, for a total of 300 drug safety signals, 23 (9.4%) were lost in the ROR and 34 (16.7%) in the PRR when vaccine data were included compared to when they were not. The results suggest that the inclusion of a drug may induce important oversight in generating hypotheses of associations between the drug and known or unexpected adverse events. Therefore, researchers may need to consider

whether it is appropriate to include COVID-19 vaccine adverse event reports when conducting a drug-focused disproportionality analysis.

This study has several limitations. First, it focused only on the presence or absence of reports on the COVID-19 vaccine and did not consider other vaccine effects reported to JADER. Second, the 10 adverse events examined for safety signals based on the presence/absence of vaccine data were adverse events in which COVID-19 vaccine reports accounted for a large proportion. Therefore, it cannot be ruled out that the number of drugs for which the safety signal disappears is likely to be higher when vaccine data are available.

## Conclusion

This report demonstrates that the rapid increase in the number of adverse event reports for the COVID-19 vaccine in JADER has affected the detection of safety signals by disproportionality analysis. The establishment of a vaccine-specific adverse event reporting system, such as VAERS, is beginning to be discussed in Japan. However, the establishment of such a system is presumed to take time. Hypothesis-generating research on the relationship between drugs and adverse events using voluntary adverse event reporting databases will continue to play an important role as a safety measure for post-marketing drugs. To this end, the establishment of reporting systems specific to vaccines and drugs may reduce the likelihood of missing safety signals for unknown adverse events.

## Conflicts of Interest

All Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

Mr. Yamaoka, Mr. Fujiwara, and Dr. Shimizu had full access to study data and were responsible for data integrity and the accuracy of data analysis. Conception and design: Dr. Shimizu. Acquisition, analysis, and interpretation of data: All Authors. Preparation of manuscript: Mr. Yamaoka and Dr. Shimizu. Critical revision of the manuscript for important intellectual content: All Authors. Statistical analysis: Mr. Yamaoka, Mr. Fujiwara, Dr. Uchida, and Dr. Shimizu. Funding: Dr. Shimizu. Administrative and technical support: Dr. Uesawa. Supervision: Dr. Shimizu.

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