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JYNNEOS vaccine safety surveillance in the Vaccine Safety Datalink during the 2022 mpox outbreak in the United States

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Abstract

Background: The JYNNEOS vaccine (two doses given 28 days apart) was recommended in the United States for people at high risk of exposure to monkeypox virus during the 2022 mpox outbreak. Our objective was to assess the safety of JYNNEOS using two complementary epidemiologic methods.

Methods: This observational cohort included patients of eight large integrated healthcare organizations who received JYNNEOS. Adverse events were identified using ICD-10 coded diagnoses assigned to medical visits. The first analysis used standardized incidence ratios (SIR) to compare the observed incidence of ten prespecified adverse events of special interest (AESI) during the 28 days after receipt of each dose of JYNNEOS to the expected incidence adjusted for several risk factors. The second analysis used tree-based data mining to identify temporal clustering of cases for more than 60,000 diagnoses and diagnosis groups within 70-days after JYNNEOS dose 1 administration.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Information about how to access data from the Vaccine Safety Datalink can be found at the following URL. <https://www.cdc.gov/vaccine-safety-systems/vsd/access-use.html>

Results: The SIR analysis included 53,583 adults who received JYNNEOS dose 1 and 38,206 who received dose 2. Males received 92% of the doses. There were no statistically significant elevated SIRs for any of the ten AESI. The tree-based data mining analysis included 36,912 vaccinees. Analysis of diagnoses in inpatient, emergency department, and outpatient settings identified statistically significant clusters of visits for rash and unspecified adverse effects.

Conclusions: No new or unexpected safety concerns were identified. AESI did not occur more frequently than expected by chance alone. Non-serious medically attended adverse events, such as rash, have been previously reported and occurred infrequently.

Keywords

mpox; smallpox vaccine; vaccine safety; adverse event; myocarditis

BACKGROUND

Mpox disease is caused by *Monkeypox virus*, which is in the genus *Orthopoxvirus* along with the *Variola virus* that causes smallpox [1]. A global mpox outbreak detected in May 2022 led to person-to-person virus transmission in the United States. Most cases occurred in men who have sex with men [1]. The U.S Centers for Disease Control and Prevention (CDC) recommended that people with higher potential for exposure to mpox be offered vaccination with JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating; Bavarian Nordic, Denmark) [2]. People at high risk for exposure were identified as men who have sex with men, transgender, and nonbinary people who had a new sexually transmitted disease or more than one sex partner in the prior six months; people who had sex at a commercial sex venue or in association with a large public event in the prior six months; sexual partners of people with the preceding risk factors; and people with HIV infection or other causes of immunosuppression who anticipated potential exposure [2].

JYNNEOS is a third-generation smallpox vaccine that is also indicated for the prevention of mpox [3]. JYNNEOS contains a live, non-replicating vaccinia virus (another orthopoxvirus) and is intended to have fewer serious adverse reactions compared to first- and second-generation smallpox vaccines, which contain live replicating vaccinia virus. JYNNEOS was licensed in the U.S. in 2019. Clinical trials included 7,859 adults who received at least 1 dose of JYNNEOS, including some people with HIV infection, but the vaccine had not had wider use prior to the 2022 outbreak [3]. The prelicensure trials did not identify risks of any serious adverse reactions. JYNNEOS is approved for administration of two 0.5mL doses given 28 days apart by subcutaneous injection into the upper arm. In August 2022, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) that allowed administration of 0.1mL doses by intradermal injection (preferably into the forearm) for adults in order to increase the number of doses available during the outbreak [4]. The EUA also allowed for vaccination of people <18 years of age using the 0.5mL subcutaneous dosing.

Our objective was to assess the safety of JYNNEOS in the Vaccine Safety Datalink (VSD) population using two different methods. The first method assessed several pre-specified

adverse events of special interest (AESI). The second method used a tree-based data mining approach to detect potential risk for any adverse event (AE).

METHODS

The VSD is a collaboration between the CDC and several integrated healthcare organizations (sites) [5]. Eight sites with a combined population of more than 12.5 million people contributed data to these analyses. The sites obtained records of JYNNEOS vaccine administration for their members from sources such as electronic health records and state immunization information systems. The number of JYNNEOS vaccine doses administered in the VSD population was monitored on a weekly basis. Statistical analyses were performed once after the cumulative number of doses administered had plateaued. Therefore, analyses were done using available data rather than being based on a priori sample size considerations. Adverse event outcomes were ascertained using International Classification of Diseases, Tenth Revision (ICD-10) codes assigned to healthcare encounters.

Pre-specified AESI analyses

JYNNEOS doses administered from May 1, 2022 through March 4, 2023 to individuals in the VSD population were included in the AESI analyses. The day of vaccination was defined as day 0. AESI were selected for evaluation because they are of interest for vaccines in general (e.g., anaphylaxis, Guillain-Barré syndrome), or based on adverse reactions that occurred with first- and second-generation smallpox vaccines (e.g., myocarditis and pericarditis), or based on AESI specified in the EUA (e.g., cardiac, thromboembolic, or neurovascular events). The AESI case definitions used are shown in Supplemental Table 1. Adverse reactions associated with older smallpox vaccines that are caused by replication of live vaccinia virus (e.g., progressive vaccinia) were not assessed for JYNNEOS because JYNNEOS contains a non-replicating virus.

A standardized incidence ratio (SIR) analysis was used to evaluate the risk for each of ten outcomes (all AESI except anaphylaxis) following each dose, including myocarditis or pericarditis, acute myocardial infarction, hemorrhagic stroke, ischemic stroke, venous thromboembolism, pulmonary embolism, acute disseminated encephalomyelitis, encephalitis, Guillain-Barré syndrome, and transverse myelitis. The SIR analysis was restricted to adults aged ≥ 18 years because the number of people aged < 18 years who received JYNNEOS was too small to be informative for these rare AESI (the number of people < 18 who received JYNNEOS is described separately). We did separate analyses for males and females because most JYNNEOS recipients were male. We compared the observed incidence rate for each outcome to the expected rate. An incident diagnosis of an AESI within 28 days after either dose of JYNNEOS was included. The expected rates were calculated using the background incidence in the VSD population from July 1, 2021 through June 30, 2022; this time period was chosen to most closely represent the conditions during the period of interest based on a prior evaluation of healthcare utilization in the VSD through 2023 which showed that by the later part of 2021, inpatient and ED visit rates returned to pre-pandemic levels.[6] The expected rates were adjusted for VSD site, age group

(18–49, 50–64, ≥65 years), and history of four categories of atherosclerotic cardiovascular disease risk factors (coronary heart disease equivalents, dyslipidemia, hypertension, HIV infection). These risk factors were assessed based on ICD-10 coded medical encounters (Supplemental Table 2). Due to the large number of strata already involved, no other variables were adjusted for, such as potential seasonal variation in background rates. The stratum-specific background population incidence rates were multiplied by the person-time for each corresponding stratum in the vaccinated population, and the weighted average of these values was used to calculate the expected number of cases for each outcome among the vaccinated. The SIR was calculated by dividing the observed incidence rate among the vaccinated by the expected incidence rate. Analysis was done using SAS version 9.4.

Independent of the SIR analysis, medical record abstraction was prespecified for two AESI, anaphylaxis and myocarditis/pericarditis, to calculate crude postvaccination incidence rates using chart verified cases. For anaphylaxis, cases diagnosed on days 0–1 were classified using the Brighton Collaboration case definitions [7, 8] and the clinical history was reviewed for any potential causes other than vaccination. Myocarditis and pericarditis were classified using CDC case definitions.[9] The incidence of myocarditis (with or without pericarditis) with onset within 30 days following each dose was calculated as an additional analysis because risk intervals up to 30 days post vaccination have been used in previous smallpox vaccine studies. Dose 1 follow-up time was censored upon receipt of dose 2.

Tree-based data mining analyses

This analysis evaluated ICD-10 coded medical encounters during the 70 days following vaccination with dose 1 to identify statistically significant temporal clustering of cases of any incident diagnosis following vaccination. The presence of temporal clustering could suggest a potential association between the vaccination and the medical condition. This method has been described previously.[10–12] Here we will summarize the method and state the specific parameters chosen for this analysis.

ICD-10 codes have a hierarchical tree-like structure with 21 broad categories of diagnoses which successively branch into more specific sub-categories, culminating in highly specific diagnosis codes. ICD-10 codes have up to seven digits, and the ICD-10 “tree” branches out into seven levels, with level 1 corresponding to the 21 broad categories, level 2 to blocks of related diagnoses within each of the 21 categories, level 3 to 3-character ICD-10 codes, level 4 to 4-character codes, and so on out to level 7. We excluded ICD-10 codes for neoplasms, external causes of morbidity, and factors influencing health status and contact with health services, because these conditions seem biologically implausible to be caused by vaccination during the follow-up period assessed. Pregnancy, perinatal conditions, and congenital malformations were excluded because the vaccinated population consisted mostly of adult males. The remaining tree contained more than 60,000 diagnoses and diagnosis groups for evaluation.

Temporal clustering of diagnoses was assessed using the tree-temporal scan statistic with a self-controlled design, which looks for a statistically higher incidence of each outcome during each potential post-vaccination risk interval compared to the person time outside of the interval [11, 12]. We assessed case clustering during post-vaccination days 1 through

70 following dose 1. The day of vaccination (day 0) is excluded because the coded data may not clearly distinguish between conditions with onset before versus after vaccination. We evaluated all potential risk intervals with lengths from 2 through 35 days within the 70 days of follow-up time. Monte Carlo simulation was used to adjust for the multiple scanning of the thousands of different diagnoses and the hundreds of different time intervals. The log likelihood ratio is calculated for each node on the tree and then is compared to the maximum log likelihood ratio distribution developed under the null hypothesis. The *P*-value is determined based on that distribution. We chose a statistical significance threshold of $P < 0.01$ a priori but show all outcomes with $P < 0.05$ in the results to provide additional context. The statistical analyses were conducted using TreeScan software version 2.0 [13].

VSD members who received dose 1 of JYNNEOS from May 1, 2022 through April 30, 2023 were included in this analysis if they were continuously enrolled during the period from 400 days prior to vaccination through 70 days after receipt of dose 1. This allowed for exclusion of prevalent diagnoses which had been documented prior to vaccination and allowed for six weeks of follow-up time after dose 2 when this was administered at the recommended interval.

The primary analysis evaluated incident diagnoses recorded for inpatient or emergency department (ED) visits; incident diagnoses were defined as those where no instance of the same three-character code (level 3 of the tree) occurred in any setting in the patient's record in the prior 400 days. Secondary analysis included incident diagnoses recorded for any healthcare visit (including outpatient); incident diagnoses were defined as those where no instance of a diagnosis in the same block of codes (level 2 of the tree) occurred in any setting in the patient's record in the prior 400 days. Clustering was evaluated in levels 3–6 of the tree in the primary analysis and in levels 2–6 of the tree in the secondary analysis, because the highest and lowest levels of the tree were considered, respectively, too broad or too specific to be clinically meaningful. Analyses were done for all ages combined, and age-stratified analyses were done for the following age groups: <18, 18–39, 40–64, ≥65 years.

Human Subjects Determination

These studies were reviewed and approved by the Institutional Review Board at each participating VSD site. These activities were reviewed by CDC and were conducted consistent with applicable federal law and CDC policy [14].

RESULTS

Pre-specified AESI analyses

As of March 4, 2023, in the VSD population there were 53,583 adults who received JYNNEOS dose 1, of whom, 38,206 also received dose 2. Males received 92% of the doses (Table 1). The prevalence of HIV infection among males was 16% in the vaccinated cohort compared to 0.5% in the VSD population, and among females was 4% compared to 0.06%. The two-dose vaccine series completion rate for males was 73% and for females was 51%. The anatomic sites of vaccine administration were forearm (19%), upper arm (5%), arm not

otherwise specified (56%), unknown (19%), and other (<1%). Most doses were given during the summer of 2022, with 75% of doses given from July through September. JYNNEOS was administered alone (without other vaccines on the same day) for 90% of doses; the most common vaccines simultaneously administered with JYNNEOS were influenza (6.4%) and COVID-19 (2.7%).

The SIR analyses did not find statistically significant elevated SIRs for any AESI among either males or females (Table 2).

Medical records were abstracted for two patients identified by myocarditis ICD-10 codes within 30 days postvaccination. Both met the CDC case definition for “probable” myocarditis (without pericarditis). The two cases occurred in males aged between 30–50 years. One patient was hospitalized and the other was treated in the ED. One case had symptom onset 24 days after dose 1 and the other had onset 13 days after dose 2. The incidence rate of myocarditis among males within 30 days following JYNNEOS dose 1 was 20 cases per million doses administered (95%CI: 0.52, 114) and following dose 2 was 28 cases per million doses administered (95%CI: 0.71, 156).

Two potential cases of anaphylaxis identified by ICD-10 codes were evaluated by medical record abstraction. In one patient, the ICD-10 code was used due to a history of allergic reaction and did not represent a new event following vaccination. The other patient was a male who had acute onset of hives, dyspnea, and throat closing sensation three minutes after receiving JYNNEOS dose 1 (without any other vaccines). This allergic event met the original 2007 Brighton Collaboration case definition for anaphylaxis with diagnostic certainty level 2; however, using the updated 2022 Brighton Collaboration case definition, this was not a case of anaphylaxis. Using the 2007 case definition gives an incidence rate of 19 cases per million doses (95%CI: 0.47, 104).

Among children aged <18 years in the VSD, 88 received JYNNEOS dose 1 and 33 received dose 2. The age range among this group was 1 to 17 years. There were no AESI identified in this age group.

Tree-based data mining analyses

After applying the enrollment criteria, this analysis included 36,912 people who received JYNNEOS dose 1, of which 33,685 (91%) were male and 26,377 (71.5%) went on to receive dose 2 (Table 3). Table 4 shows the temporal clustering results. The primary analysis, which included inpatient and ED visits, did not identify statistically significant clusters for any outcome overall or in any age subgroup. The secondary analysis, which included inpatient, ED, and outpatient visits, identified statistically significant clusters for rash and several codes for unspecified adverse events; age group-specific analyses also identified a non-significant grouping of “pain in ankle and joints of foot” in the ≥65-year age group.

DISCUSSION

The VSD population from the eight sites participating in this study represented about 3.6% of the U.S. population. Among all JYNNEOS vaccine doses administered in the United

States from May 2022 through March 4, 2023 as reported to CDC, 7.6% were administered to members of the VSD. This VSD JYNNEOS vaccinated cohort was more than five times larger than the number of people who received JYNNEOS in the pre-licensure clinical trials. We did not identify any new safety concerns in our evaluation of medically attended adverse events in the VSD population. Several cases of pre-specified AESI occurred following vaccination, but the number of cases was consistent with what was expected to occur by chance alone.

There was one case of anaphylaxis according to the original 2007 Brighton Collaboration anaphylaxis case definition, which we used in order to compare the rate observed here to a previous VSD study of anaphylaxis after other types of vaccines that also used the same definition [15]. The rate we observed after JYNNEOS [19 (95%CI: 0.47, 104) per million doses] has a wide confidence interval that overlaps with previous estimates for routinely recommended vaccines [1.31 (95%CI: 0.90, 1.84)] [15]. Immediate type hypersensitivity reactions such as anaphylaxis, although rare, might occur after any type of vaccine, so vaccine providers should be prepared to treat these uncommon allergic reactions.

The tree-based data mining analysis identified statistical clustering only in the secondary analysis that included outpatient clinic visits. Two clusters involved ICD-10 codes for unspecified adverse effects of vaccines (T88.1 and T50) which have been detected in previous studies for other types of vaccines and have been found to be used to indicate common, expected types of AEs such as injection site reactions or systemic symptoms such as fever or myalgia [12]. The other cluster was for rash. Rash is not a commonly expected AE but was one of the AEs after JYNNEOS most frequently reported to the Vaccine Adverse Event Reporting System, which is a separate U.S. vaccine safety surveillance system.[16] Therefore, we did not investigate rash further in the VSD. The grouping of “pain in ankle and joints of foot” detected only in the oldest age group did not meet our prespecified level of statistical significance and based on the small number of cases and the narrow risk interval later during postvaccination follow-up time is likely a random occurrence. We do not interpret any of these data-mining findings as suggesting a new safety signal.

There were no cases of myocarditis or pericarditis observed in the JYNNEOS prelicensure clinical trials, but a theoretical concern remained that these conditions might occur at a lower rate than could be detected in the prelicensure studies. Our SIR analysis did not find an elevated incidence of myocarditis following JYNNEOS (or any cases of pericarditis). The VSD previously assessed the myocarditis incidence rate within 30 days after each dose of JYNNEOS using data through October 21, 2022 [17]. The current analysis included data through March 4, 2023, which included more than twice as many JYNNEOS doses compared to the earlier analysis, with no additional cases of myocarditis; therefore, the incidence rates decreased compared to the earlier estimate. However, the confidence intervals for the myocarditis incidence rates remain wide and the upper bounds still encompass the myocarditis rate observed in an early study of first-generation smallpox vaccines, which was 78 cases per million doses [18]. While our surveillance does not suggest an increased risk of myocarditis following JYNNEOS, we think that the possibility of a small risk still cannot be excluded. The incidence of myocarditis that we observed

following JYNNEOS is much lower than the rate observed with second-generation smallpox vaccine in more recent U.S. military cohorts, which was as high as 5,230 cases per million doses [19, 20]. However, the cohorts in these different studies may not be directly comparable due to different distribution of myocarditis risk factors such as age or pre-existing medical conditions.

We did not specifically evaluate the safety of coadministration of JYNNEOS with other vaccines because the relatively small number of doses co-administered with other vaccines would not be sufficient to evaluate risks for rare AESI. CDC has recommended caution when co-administering JYNNEOS with COVID-19 vaccines because of the potential risk of myocarditis with both vaccines, particularly for adolescent and young adult males [2].

During the 2022 mpox outbreak, JYNNEOS was authorized to be given to adults by either subcutaneous or intradermal routes of administration, which should elicit a similar immune response. The frequency or severity of injection site reactions might differ between the two routes, but VSD is not suited to evaluate that because most people do not seek medical care for injection site reactions. Furthermore, we did not do any route-of-administration-specific analyses in this surveillance because information about route of administration was not captured by VSD and the available information about anatomic site of vaccine administration was not specific enough for most patients to be a reliable proxy.

This analysis was subject to several limitations. The total number of people who received JYNNEOS in the VSD was relatively small compared to vaccines with more broad recommendations, so there was limited ability to assess the risk of very rare AESI that had a small number of expected cases. JYNNEOS was received by relatively few VSD members who were female or who were <18 years of age, which was expected based on the population at risk that was recommended to be vaccinated, but post-licensure safety data about uncommon AEs remains limited for these groups. The source data for the sex variable may represent sex assigned at birth or other definitions, but does not differentiate them, potentially leading to an unknown amount of misclassification. The relatively small sample size also means that the tree-based data mining analysis does not rule out the possibility that an increased risk could exist for other outcomes that were not identified as significant clusters. Also, temporal clustering analysis in general is not suited to detect AEs that have wide variation in time of symptom onset or timing of seeking healthcare.

In summary, no new or unexpected safety concerns were identified. The risk of rare AEs could be re-evaluated in the future with a larger sample size if more people receive JYNNEOS. CDC will continue to provide up to date recommendations for the use of JYNNEOS to prevent mpox infection in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Characteristics of JYNNEOS vaccine recipients included in the standardized incidence ratio (SIR) analysis for pre-specified adverse events of special interest (AESI), Vaccine Safety Datalink (VSD) population, May 01, 2022 – March 04, 2023

	Dose 1		Dose 2		Total doses	
Sex / age in years	n	%	n	%	n	%
Male	48,858	91.2	35,812	93.7	84,670	92.2
18–49	33,782		23,727		57,509	
50–64	11,731		9,350		21,081	
≥65	3,345		2,735		6,080	
Female	4,725	8.8	2,394	6.3	7,119	7.8
18–49	3,956		2,004		5,960	
50–64	598		306		904	
≥65	171		84		255	
Total	53,583	100	38,206	100	91,789	100

Table 2.

Standardized incidence ratio (SIR) analysis^a for pre-specified adverse events of special interest (AESI) following JYNNEOS vaccination among people aged ≥18 years, Vaccine Safety Datalink (VSD), May 1, 2022 - March 4, 2023

	Male						Female					
	Dose 1			Dose 2			Dose 1			Dose 2		
	Obs, n	Exp, n	SIR (95% CI)	Obs, n	Exp, n	SIR (95% CI)	Obs, n	Exp, n	SIR (95% CI)	Obs, n	Exp, n	SIR (95% CI)
AESI												
Myocarditis or Pericarditis	1	1.23	0.81 (0.02, 4.54)	1	0.92	1.09 (0.03, 6.06)	0	0.06	0	0	0.03	0
Acute Myocardial Infarction	8	9.00	0.89 (0.38, 1.75)	2	7.18	0.28 (0.03, 1.01)	0	0.35	0	1	0.17	6.02 (0.15, 33.54)
Stroke, hemorrhagic	2	2.86	0.70 (0.08, 2.52)	0	2.26	0	0	0.15	0	0	0.07	0
Stroke, ischemic	9	8.36	1.08 (0.49, 2.04)	3	6.68	0.45 (0.09, 1.31)	1	0.51	1.95 (0.05, 10.86)	0	0.25	0
Venous thromboembolism	4	9.25	0.43 (0.12, 1.11)	4	7.24	0.55 (0.15, 1.42)	1	0.59	1.68 (0.04, 9.39)	0	0.30	0
Pulmonary Embolism	1	4.58	0.22 (0.01, 1.22)	1	3.60	0.28 (0.01, 1.55)	1	0.29	3.49 (0.09, 19.47)	0	0.14	0
Acute Disseminated Encephalomyelitis	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00	0
Encephalitis	0	0.30	0	0	0.23	0	0	0.02	0	0	0.01	0
Guillain-Barré syndrome	0	0.25	0	0	0.19	0	0	0.02	0	0	0.01	0
Transverse Myelitis	0	0.11	0	0	0.08	0	0	0.02	0	0	0.01	0

Abbreviations: Obs=observed, Exp=expected, SIR= standardized incidence ratio.

^a SIR was adjusted for VSD site, age group (18–49, 50–64, ≥65 years), and history of four categories of atherosclerotic cardiovascular disease risk factors.

Table 3.

Characteristics of JYNNEOS dose 1 recipients included in the tree-based data mining analysis, Vaccine Safety Datalink (VSD) population, May 01, 2022 – April 30, 2023^a

	n	%
Received dose 1	36,912	100
Received dose 2	26,377	71.5
Age, years		
<18	64	0.2
18–39	16,338	44.3
40–64	17,226	46.7
≥65	3,284	8.9
Sex		
Male	33,685	91.3
Female	3,182	8.6
Unknown	45	0.1
Race		
American Indian/Alaska Native	147	0.4
Asian	4,394	11.9
Black	2,343	6.3
Native Hawaiian/Pacific Islander	219	0.6
White	18,445	50.0
Unknown	11,364	30.8
Ethnicity		
Hispanic or Latino Origin	9,044	24.5
Not Hispanic or Latino Origin	14,986	40.6
Unknown	12,882	34.9
Year of Vaccination		
2022	35,836	97.1
2023	1,076	2.9

^aThis analysis required continuous patient enrollment during the period from 400 days prior to vaccination through 70 days after receipt of dose 1.

Table 4.

Tree-based data mining temporal clusters ($P \leq 0.01$) and groupings ($0.01 < P \leq 0.05$) of incident adverse event cases found in the 70 days after JYNNEOS dose 1 administration, Vaccine Safety Datalink (VSD) population, May 01, 2022 – April 30, 2023.

Analysis	ICD-10 Code	ICD-10 Code description	Total Number of Cases	Risk Interval Start Day	Risk Interval End Day	Number of Cases in Risk Interval	Attributable Risk per Million Doses	Log Likelihood Ratio Test Statistic	P value
Primary: inpatient and ED visits, ICD-10 code level 3 ^a									
No groupings with $p \leq 0.05$ for any outcome in any age grouping									
Secondary: inpatient, ED, and outpatient visits, ICD-10 code level 2 ^a									
All ages	T88.1	Other complications following immunization, not elsewhere classified	29	2	8	22	570	24.48	0.0001
	T50	Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances	57	1	8	30	710	21.22	0.0001
	R21	Rash and other nonspecific skin eruption	247	3	16	95	1,500	14.67	0.0006
No groupings with $p \leq 0.05$ for any outcome									
18–39 years	T88.1	Other complications following immunization, not elsewhere classified	17	2	8	13	760	13.66	0.0006
40–64 years	T50	Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances	27	7	8	9	490	12.39	0.0056
≥65 years	M25.57	Pain in ankle and joints of foot	6	46	47	5	1,500	10.84	0.0126

^aLevel indicates (a) the highest level of the tree in which clustering was looked for, and also (b) the level used to determine the incidence of cases.