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Erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis reported after vaccination, 1999–2017

John R. Su[a,*], **Penina Haber**[a], **Carmen S. Ng**[a,1], **Paige L. Marquez**[a], **Graça M. Dores**[b], **Silvia Perez-Vilar**[b,2], **Maria V. Cano**[a]

[a]Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States

[b]Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, United States

Abstract

Background: Since the last review of vaccine safety surveillance data for erythema multiforme (EM), Stevens Johnson syndrome (SJS), SJS/TEN, and toxic epidermal necrolysis (TEN) (EM/SJS/TEN), over 37 new vaccines have been introduced in the United States. We sought to describe reported EM/SJS/TEN after vaccines during 1999–2017.

Methods: We identified U.S. reports of EM/SJS/TEN received by the Vaccine Adverse Event Reporting System (VAERS) during 1999–2017. We stratified analysis by condition (EM, SJS, or TEN), and analyzed reports by serious or non-serious status, sex, age group, time from vaccination to symptom onset, exposure to known causes of EM/SJS/TEN, and vaccines administered. We used Empirical Bayesian data mining to detect vaccine-AE pairs reported more frequently than expected.

[*]Corresponding author at: Immunization Safety Office, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS V18-4, Atlanta, GA 30329, United States. ezu2@cdc.gov (J.R. Su).

[1]Currently at Division of Health Economics, Policy and Management, Hong Kong University School of Public Health, Hong Kong.

[2]Currently at Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, United States.

CRediT authorship contribution statement

John R. Su: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Penina Haber:** Conceptualization, Formal analysis, Investigation, Writing – review & editing. **Carmen S. Ng:** Data curation, Methodology, Validation, Writing – review & editing. **Paige L. Marquez:** Data curation, Methodology, Validation, Writing – review & editing. **Graça M. Dores:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Silvia Perez-Vilar:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Maria V. Cano:** Conceptualization, Investigation, Writing – review & editing.

5. Note

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

6. **Publisher's Disclaimer:** Disclaimer

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Results: Of 466,027 reports to VAERS during 1999–2017, we identified 984 reports of EM, 89 reports of SJS, 6 reports of SJS/TEN, and 7 reports of TEN. Few reports of EM (9%), and most reports of SJS (52%), SJS/TEN (100%), and TEN (100%) were serious. Overall, 55% of reports described males, 48% described children aged < 4 years; 58% of EM/SJS/TEN occurred ≤ 7 days after vaccination. Few reports (≤5%) described exposure to known causes of EM/SJS/TEN. Overall, childhood vaccines (e.g., combined measles, mumps, and rubella vaccine) were most commonly reported. We identified 6 deaths; 4 were exposed to medications associated with EM/SJS/TEN. EM after smallpox vaccine was reported disproportionately among people aged 19–49 years.

Conclusions: EM/SJS/TEN were rarely reported after vaccination; data mining identified a known association between EM and smallpox vaccine.

Keywords

Erythema multiforme; Stevens Johnson syndrome; Toxic epidermal necrolysis; Vaccine; VAERS; Vaccine safety; Surveillance; Data mining

1. Introduction

Dermatologic adverse events (AEs) are among the most frequently reported AEs after vaccination. The most common dermatologic AEs are redness, swelling, and tenderness at the injection site [1], which can occur in up to 90% of persons receiving vaccinations [2]. At the other extreme are AEs, such as Henoch-Schönlein purpura after the combined measles, mumps, and rubella (MMR) vaccine, for which only isolated case reports exist [3]. While some dermatologic AEs can be common to many vaccines (such as tenderness at the injection site), other dermatologic AEs can be specific to a particular vaccine, such as vesicular lesions after varicella vaccine.

Some dermatologic AEs that have been reported to occur after vaccination involve hypersensitivity reactions, such as an allergy to the aluminum in some adjuvanted vaccines [4], or lichen planus after hepatitis B vaccine [5]. Erythema multiforme (EM) is a hypersensitivity reaction characterized by papules, classically with a ringed, target-like appearance often involving the palms of the hands and soles of the feet [1]. More severe hypersensitivity reactions include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), both of which involve blistering and sloughing of skin. [6] SJS and TEN also typically involve lesions on mucosal surfaces. SJS and TEN are thought to be related conditions of varying severity, depending upon percentage of body surface area involved: <10% for SJS, 10–30% for combined SJS/TEN, and >30% of body surface area for TEN [7]. Fortunately, EM, SJS, and TEN are rare, occurring with a rate of 4.2 hospitalizations per million person-years after exposure to an associated medication [8]; rates after vaccinations, as of this writing, are unavailable.

Ball et al previously identified 99 reports of SJS, TEN, and serious reports of EM after vaccination received by the Vaccine Adverse Event Reporting System (VAERS) during July 1990 through September 1999 [9]. Since 1999, over 37 vaccines have been approved for use in the United States [10]. Thus, we searched and described reports of EM, SJS, SJS/TEN,

and TEN after vaccination (these specific dermatologic AEs will be referred to collectively as EM/SJS/TEN) reported to VAERS during 1999–2017, and compared the relative frequency of EM/SJS/TEN reported to VAERS by vaccine, to better understand if there are any concerning patterns of reported EM/SJS/TEN (e.g., after a specific vaccine, or among a particular age group) or other emerging safety concerns.

2. Methods

2.1. Data source

AEs occurring after vaccination can be reported to VAERS, a national spontaneous reporting system established in 1990 to monitor AEs that is jointly administered by the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration [11,12]. VAERS receives reports from healthcare providers, vaccine manufacturers, vaccine recipients, and other persons. Reported symptoms and diagnoses are coded using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) [13]. MedDRA PTs are not necessarily medically confirmed diagnoses, and multiple MedDRA PTs can be assigned to a VAERS report. Federal regulations define a serious report as a report in which one or more of the following conditions is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, congenital anomaly, or birth defect [14]. A report might therefore not be classified as serious, despite describing a clinically severe presentation. VAERS personnel routinely request medical records for non-manufacturer serious reports. Vaccine manufacturers that directly receive reports of AEs typically request and review medical records per regulatory processes [12]; these records are not always available to manufacturers. Serious reports from vaccine manufacturers therefore often do not contain medical records that VAERS personnel can review.

2.2. Descriptive analysis

We searched the VAERS database for U.S. reports of EM/SJS/TEN following vaccination received by VAERS during October 1, 1999, through December 31, 2017 (among reports received by CDC and FDA through April 27, 2018); reports specifying a vaccination date outside the analytic period were excluded. We searched for reports that included the PTs “erythema multiforme,” “Stevens Johnson Syndrome,” and “toxic epidermal necrolysis.” We also searched text fields for the following terms: “skin ulcer,” “blister,” “blister, infected,” and/or “blister, rupture,” where “multiforme,” “John son,” and/or “necrolysis” was also present. We combined results from both searches, then deduplicated records.

We reviewed the resulting reports for reports of EM/SJS/TEN that were diagnosed by physicians (reported by a physician, or a physician’s diagnosis was documented in available medical records). For reports of symptoms consistent with EM/SJS/TEN, but without a physician’s diagnosis, we defined (1) EM as papular lesions, classically with a ringed (“targetoid”) appearance, usually beginning peripherally and then spreading to the torso, that could involve the palms of the hands and/or soles of the feet, without mucosal lesions; (2) SJS as peeling or blistering of the skin with lesions on mucosal membranes that involved <10% of total body surface area (BSA); (3) SJS/TEN as signs and symptoms consistent with

SJS, but involving between 10 and 30% BSA; and (4) TEN as signs and symptoms consistent with SJS, involving >30% BSA.

We stratified data by condition (EM, SJS, SJS/TEN, and TEN). For each condition, we analyzed reports by sex; age group (<4 years, 4–10 years, 11–18 years, 19–49 years, ≥50 years, and age not reported), roughly corresponding with the recommended schedules for vaccination [15]; seriousness of report (serious or non-serious); and time from vaccination to onset of symptoms. Reports were further analyzed for persons with exposure to a known trigger [8,10] proximal to onset of symptoms (viral or *Mycoplasma* infection, medications (anticonvulsants, sulfa drugs, penicillins, non-steroidal anti-inflammatory drugs (NSAIDs), macrolide antibiotics, and acetaminophen); history of predisposing conditions (past history of EM/SJS/TEN, atopic dermatitis, asthma/reactive airway disorder, allergies to medications, or malignancy) [16]; and whether vaccines were given alone or concomitantly with other vaccines.

2.3. Estimated reporting rates

Estimating reporting rates of AEs after vaccination using data from VAERS is challenging because data about doses of vaccine that were distributed or administered are difficult to obtain. However, we were able to estimate crude reporting rates of EM, SJS, SJS/ TEN, and TEN after varicella vaccine using reports received during 2006 through 2016 as the numerator, divided by doses distributed by the manufacturer [17] during the corresponding time period (Merck and Company, Inc., personal communication) as the denominator; rates were estimated as reports per 1 million doses distributed. For influenza vaccine (all types), annual crude reporting rates for EM, SJS, SJS/TEN, and TEN were estimated during 2010 through 2017 using reports received as the numerator, with population estimates and vaccine coverage for that year multiplied as the denominator [18,19]; rates for 2 age groups (1–17 years, ≥18 years) were estimated. From these annual crude reporting rates, median rates of reports per million doses administered were estimated for 2010–2017.

2.4. Data mining (disproportionate reporting)

We used Empirical Bayesian data mining to assess whether vaccine-AE combinations were reported more frequently than expected (when compared to all other vaccine-AE combinations in the VAERS database) using the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [20]. We analyzed U.S. reports received by VAERS during October 1, 1999 – December 31, 2017 (received as of April 27, 2018). We stratified by age group (<4, 4–10, 11–18, 19–49, ≥50 years, and unreported), and adjusted for sex, and year in which the report was received by VAERS. We analyzed disproportionate reporting for vaccine-EM/SJS/TEN combinations using: (1) the PTs “erythema multiforme,” “Stevens Johnson Syndrome,” and “toxic epidermal necrolysis”; and (2) PTs included in reports with the words “skin ulcer,” “blister,” “blister infected,” or “blister rupture” in the narrative, symptoms text, or comments fields, if the words “multiforme”, “Johnson”, and/or “necrolysis” were also present. We conducted our analyses for all reports, and serious reports only, in Oracle’s Empirica™ Signal System [20,21]. The main statistical scores computed were the Empirical Bayes Geometric Mean (EBGM) and its associated 90% confidence interval (EB05, EB95). We used the lower 5% bound of the 90% confidence

interval for an EBGM (EB05) of ≥2.0 as the threshold to define vaccine-AE combinations reported at least twice as often as expected, indicating combinations of potential significance [21].

3. Results

3.1. Descriptive analysis

Of 466,027 reports to VAERS during the analytic period [22], we identified 1086 (0.2%) reports of EM/SJS/TEN. Overall, over half (51%) of reported EM occurred among children aged <4 years (Table 1), with a median age of 3 years (range: <1 year to 89 years); among reports of SJS, overall median age was 15 years (range: <1 year to 84 years). Most (91%) reports of EM were non-serious, while most (52%) reports of SJS, and all reports of SJS/TEN and TEN, were serious. Most reports of EM/SJS/TEN described onset of symptoms within 14 days of vaccination; for cases of SJS with known time to onset, 71% described onset of symptoms within 3 days of vaccination.

Few reports of EM/SJS/TEN described a known trigger or stimulus for these conditions near when vaccine was administered (Table 2). No reports of SJS/TEN or TEN reported recent infection (such as with *Mycoplasma* or herpes simplex virus 1). Of persons with a history of EM/SJS/TEN, 4 had a similar reaction to past vaccination: (1) a female aged 15 months with EM after varicella vaccine, who later experienced EM after combined measles, mumps, and rubella (MMR) vaccine; (2) a female aged 2 years with EM after influenza vaccine, who later experienced EM after influenza vaccine; (3) a male aged 10 years with EM after combined diphtheria, tetanus, and acellular pertussis (DTaP), who later experienced EM after a combined diphtheria tetanus booster; and (4) a male aged 27 years with SJS after anthrax vaccine who later experienced SJS after another dose of anthrax vaccine. One patient had an active malignancy: a male aged 78 years who was undergoing radiation therapy for non-small cell lung cancer, who developed EM 4 days after receiving trivalent inactivated influenza vaccine; notably, this patient had been taking phenytoin for 2 months prior to developing EM.

The most commonly administered vaccines described in reports of EM/SJS/TEN were vaccines commonly administered in infancy and childhood: MMR (22%), DTaP (18%), varicella (18%), and 7-valent pneumococcal conjugate (13%) vaccines (Table 3). Among reports describing the administration of only one vaccine, the most common vaccines were smallpox (16%), trivalent inactivated influenza (15%), and varicella (7%) vaccines.

3.2. Reported deaths

We identified 6 reports of persons who developed EM/SJS/TEN after vaccination, and subsequently died (Table 4): 4 received medications known to trigger EM/SJS/TEN prior to or at the time of vaccination. Two patients received varicella vaccine, and 2 patients received inactivated trivalent influenza vaccine.

3.3. Estimated reporting rates

During 2006 through 2016, EM after varicella vaccine was reported to VAERS at an estimated rate of 1.0 per 1 million doses distributed; SJS after varicella vaccine was reported at an estimated rate of 0.1 per 1 million doses distributed. No reports of SJS/TEN or TEN after varicella vaccine were identified. Regardless of age group, estimated median reporting rates of EM, SJS, and TEN to VAERS during 2010 through 2017 after influenza vaccine (all types) were ≤0.1, <0.1, and <0.1 per 1 million doses administered, respectively; no reports of SJS/TEN after influenza vaccines were identified.

3.4. Data mining (disproportionate reporting)

We found elevated data mining statistics (EB05 ≥ 2.0) for “erythema multiforme” following smallpox vaccination among persons aged 19–49 years. When we restricted data mining analyses to serious reports only, or to reports identified through text field searches, we did not identify disproportional reporting for any vaccine-EM/SJS/TEN combination.

4. Discussion

Historically, EM/SJS/TEN have rarely been reported after vaccination [1]. Consistent with this history, an analysis of VAERS reports during 1990 to 1999 found few reports of SJS and/or TEN after vaccination [9]. Our analysis of VAERS data during 1999 through 2017 identified no new safety concerns, despite the introduction of several new vaccines since 1999. While these data are reassuring, new vaccines continue to be introduced to the market [23,24]. Continued surveillance for increased reporting of EM/SJS/ TEN (SJS and TEN in particular) is therefore warranted.

Data from a systematic review by Chahal et al. and case reports from other groups have described median ages of 7 years for EM (range of <1–49 years) and 13–15 years (range of 1–75 years) for both SJS and TEN after vaccination [25,26]. The younger reported median age for EM in our analysis might reflect the younger age at which persons receive most of their vaccinations [15]. Reported sex was generally consistent with previous analyses [8,27].

Reported times from exposure to the suspected trigger, to onset of the rash, vary for SJS and TEN, ranging from a median of 10 days to a median of 3 weeks or longer [28,29]. A median of 6 days from vaccination to onset of EM has been observed [25]. Similarly, we observed varying reported times to onset of symptoms after vaccination but found that most events occurred within 14 days and rarely after 30 days; most SJS with known time to onset began within 3 days of vaccination. Notably, AEs are frequently reported when occurring within a short time after a potentially attributable trigger, regardless if a true association exists [30].

We observed no concerning patterns of reporting of EM/SJS/TEN after any particular vaccine. Reported vaccines seemed to reflect age groups for which vaccines are recommended: EM/SJS/TEN were mostly reported after childhood vaccines among persons receiving multiple vaccines simultaneously, but mostly reported after smallpox and inactivated influenza vaccines among persons receiving single vaccines (Table 3) [15,31]. Likewise, our data mining analyses identified no notable vaccine-AE combinations for EM/SJS/TEN following vaccination overall. Data mining did identify disproportionate

reporting of EM following smallpox vaccination among persons aged 19–49 years. This age distribution is consistent with the age ranges of military personnel and selected civilian populations vaccinated due to concerns of potential bioterrorism and orthopoxvirus outbreaks per U.S. vaccination policy [32–34]. EM is a well-documented complication of smallpox vaccination, and the package insert for ACAM2000™ (live vaccinia virus smallpox vaccine) includes a "boxed warning" alerting about the risk of "EM major" (i.e., SJS), following either primary vaccination or revaccination with live vaccinia virus smallpox vaccine. Overall, our observations are consistent with previous descriptions of EM/SJS/TEN after vaccination [35–37].

While prior episodes of EM/SJS/TEN in a patient might indicate a predisposition to subsequent episodes, the likelihood of such an occurrence is unclear. Of the 4 persons we describe who previously experienced EM or SJS after vaccination, two experienced another episode of EM or SJS after the same vaccine (positive rechallenge). In a case series of nine children with a history of SJS precipitated by *Mycoplasma* infection, one developed a subsequent episode of SJS after a repeat infection with *Mycoplasma* [38,39]. Likewise, persons with a history of EM after infection with herpes simplex virus (HSV) can develop subsequent episodes of EM with recurrence of HSV [40]. However, our analysis (Table 2) and reports by other investigators [41] describe few persons with exposure to known precipitants of EM/SJS/TEN, or a history of allergies or other hyper-sensitivities. Notably, a patient who experienced SJS after infection with wild-type influenza B virus received multiple seasonal influenza vaccinations with no subsequent episodes of SJS [42]. Together, these observations suggest further exploration into predisposing factors for EM/SJS/TEN, including vaccines, is warranted.

SJS and TEN can be dire conditions, with case fatalities as high as 35% observed for TEN [43]. Consistent with this observation, 5 of the 6 deaths among reports of EM/SJS/TEN after vaccination had either TEN or SJS/TEN (Table 4). However, any association with vaccination is dubious, given that 4 reports described receipt of a medication known to cause SJS or TEN. Additionally, 1 report involved treatment for anti-N-methyl-D-aspartate (NDMA) receptor encephalitis and subsequent TEN; while treatment was unspecified, cyclophosphamide has been used to treat anti-NDMA receptor encephalitis and is known to cause SJS and TEN [44,45]. The 1 report of death after EM described a woman who experienced considerable vomiting, subsequent dehydration, and shock; the degree to which EM contributed to her death is uncertain.

Previous investigators have estimated rates of EM/SJS/TEN after drug exposure as high as 200 per 1 million persons exposed (phenobarbital) [8]. Our estimated reporting rates of EM/SJS/TEN after varicella and influenza vaccines were well below this figure (i.e., the highest estimate was 1.0 report of EM per million doses of varicella vaccine distributed), a notable observation considering that varicella vaccine was one of the most commonly reported vaccines after which EM/SJS/TEN occurred. Despite potentially underestimating rates, our data suggest that EM/SJS/TEN is reported no more frequently after vaccination than after known causes of these conditions. Importantly, while EM/SJS/TEN can occur after vaccination, previous post-marketing analyses and case-control studies demonstrate that vaccination itself does not increase the likelihood of these conditions [46,47].

These data have limitations. As a passive reporting system, VAERS is subject to reporting biases, under-reporting, inconsistent data quality and completeness, and changes in reporting over time; reports to VAERS also lack an unvaccinated comparison group. These limitations generally do not allow VAERS data to determine if a vaccine caused a particular adverse event, including EM/SJS/TEN [11]. Because data on doses distributed or administered are not available for many of the vaccines in this analysis, our ability to estimate reporting rates for EM/SJS/TEN was limited to varicella and influenza vaccines and are likely underestimates. Despite these limitations, results from data mining reflect known associations (i.e., smallpox vaccine and EM) [48,49].

While EM (and to a lesser degree, SJS) is typically benign and self-limiting [1,50], SJS/TEN and TEN can be life-threatening. [43] Surveillance for unexpected, increased reporting of these conditions after vaccination should therefore continue. Fortunately, our observations and the observations of other investigators [1,9] suggest that EM/SJS/TEN rarely occur after vaccination.

Abbreviations:

AE	adverse event
BSA	body surface area
CDC	Centers for Disease Control and Prevention
DTaP	combined diphtheria, tetanus, and acellular pertussis vaccine
EM	erythema multiforme
FDA	Food and Drug Administration
IIV	trivalent inactivated influenza vaccine
MGPS	Multi-Item Gamma Poisson Shrinker
MedDRA	Medical Dictionary for Regulatory Activities
MMR	combined measles, mumps and rubella vaccine
NDMA	N-methyl-D-aspartate
NSAID	non-steroidal anti-inflammatory drug
PNC7	7-valent conjugated pneumococcal vaccine
PT	Preferred Term
SJS	Stevens Johnson Syndrome
TEN	toxic epidermal necrolysis
VAERS	Vaccine Adverse Event Reporting System

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Table 1

Description of U.S. reports of Erythema Multiforme (EM), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and SJS/TEN to VAERS, 1999–2017.

	EM, n = 984	SJS, n = 89	SJS/TEN, n = 6	TEN, n = 7	Total, N = 1086
Sex, no. (%)					
Male	550 (56)	37 (42)	1 (17)	5 (71)	593 (55)
Female	413 (42)	49 (55)	5 (83)	2 (29)	469 (43)
Not reported	21 (2)	3 (3)	0 (0)	0 (0)	24 (2)
Seriousness, no. (%)					
Death	1 (<1)	0 (0)	1 (17)	4 (57)	6 (1)
Serious, non-death	88 (9)	46 (52)	5 (83)	3 (43)	142 (13)
Non-serious	895 (91)	43 (48)	0 (0)	0 (0)	938 (86)
Age, no. (%)					
<4 years	502 (51)	17 (19)	1 (17)	2 (29)	522 (48)
4–10 years	111 (11)	9 (10)	3 (50)	1 (14)	124 (11)
11–18 years	60 (6)	18 (20)	0 (0)	0 (0)	78 (7)
19–49 years	162 (16)	18 (20)	2 (33)	2 (29)	184 (17)
50+ years	126 (13)	20 (22)	0 (0)	2 (29)	148 (14)
Not reported	23 (2)	7 (8)	0 (0)	0 (0)	30 (3)
Time from vaccination to onset of symptoms, no. (%)					
<1 day	113 (11)	20 (22)	0 (0)	0 (0)	133 (12)
1–3 days	326 (33)	31 (35)	1 (17)	3 (43)	361 (33)
4–6 days	134 (14)	5 (6)	2 (33)	2 (29)	143 (13)
7–14 days	262 (26)	12 (13)	0 (0)	1 (14)	275 (25)
15–30 days	52 (5)	3 (3)	0 (0)	0 (0)	55 (5)
>30 days	16 (2)	1 (1)	0 (0)	0 (0)	17 (2)
Not reported	81 (8)	17 (19)	3 (50)	1 (14)	102 (9)

Table 2

History of hypersensitivity and exposure to known triggers among U.S. reports of Erythema Multiforme (EM), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or SJS/TEN to VAERS, 1999–2017.

	EM (%), (n = 984)	SJS (%), (n = 89)	SJS/TEN (%), (n = 6)	TEN (%), (n = 7)	Total, N = 1086
Infection, no. (%)					
Yes	4 (<1)	2 (2)	0 (0)	0 (0)	6 (1)
No	980 (>99)	87 (98)	6 (100)	7 (100)	1080 (99)
Medication,[a] no. (%)					
Anticonvulsant	1 (<1)	5 (6)	0 (0)	2 (29)	8 (1)
Antibiotics					
Sulfa drugs	4 (<1)	3 (3)	0 (0)	1 (14)	8 (1)
Penicillin	52 (5)	3 (3)	1 (17)	0 (0)	56 (5)
Macrolides	6 (1)	3 (3)	0 (0)	0 (0)	4 (<1)
NSAIDs[b]	11 (1)	6 (7)	0 (0)	0 (0)	8 (1)
Acetaminophen	5 (1)	5 (6)	0 (0)	0 (0)	10 (1)
Existing/history of hypersensitivity,[a] no., (%)					
EM-SJS-TEN	6 (1)	5 (6)	0 (0)	0 (0)	11 (1)
Atopic dermatitis	25 (3)	2 (2)	1 (17)	1 (14)	29 (3)
Respiratory allergies[c]	47 (5)	4 (4)	0 (0)	1 (14)	52 (5)
Drug allergy					
Anticonvulsant	0 (0)	1 (1)	0 (0)	0 (0)	1 (<1)
Antibiotics					
Sulfa drugs	8 (1)	2 (2)	0 (0)	0 (0)	10 (1)
Penicillin	27 (3)	6 (7)	1 (17)	0 (0)	34 (3)
Macrolide	7 (1)	0 (0)	1 (17)	0 (0)	8 (1)
NSAIDs	4 (<1)	3 (3)	0 (0)	0 (0)	7 (1)
Acetaminophen	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Not mutually exclusive.

[b] NSAID = non-steroidal anti-inflammatory drug.

[c] Includes asthma/reactive airway disease, allergic sinusitis, and allergic bronchitis.

Table 3

Most frequently reported vaccines included in U.S. reports of Erythema Multiforme (EM), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or SJS/TEN submitted to VAERS, 1999–2017.

All vaccines		Vaccines administered alone	
Vaccine[a]	No. (%)	Vaccine[a]	No. (%)
MMR	237 (22)	Smallpox	80 (16)
DTaP	199 (18)	Inactivated influenza, trivalent	74 (15)
Varicella	196 (18)	Varicella	34 (7)
7-valent pneumococcal conjugate	146 (13)	Pneumococcal polysaccharide	29 (6)
Inactivated influenza, trivalent	128 (12)	Hepatitis A	25 (5)
Haemophilus influenzae b	119 (11)	MMR	25 (5)
Inactivated polio	119 (11)	Hepatitis B	22 (5)
Smallpox	109 (10)	Herpes zoster	22 (5)
Hepatitis A	108 (10)	DTaP	17 (3)
Hepatitis B	67 (6)	4-valent human papillomavirus	17 (3)
13-valent pneumococcal conjugate	50 (5)	7-valent pneumococcal conjugate	16 (3)
Pneumococcal polysaccharide	43 (4)	Live attenuated influenza, trivalent	13 (3)

[a]DTaP = combined diphtheria, tetanus, and acellular pertussis vaccine; MMR = combined measles, mumps, and rubella vaccine; unless administered alone, listed vaccines are not mutually exclusive.

Table 4

U.S. reports to VAERS of Erythema Multiforme (EM), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or SJS/TEN with subsequent death of the patient, 1999–2017.

Patient	Age, years	Sex	Past medical history	Vaccine (s) received[a]	Diagnosis	Onset, days	Clinical course	Cause of death
1	1	Male	Bronchitis, atopic dermatitis	Hepatitis B, varicella	TEN	2	Receiving amoxicillin/clavulanate and phenobarbital at time of vaccination; developed TEN with desquamation on 50% of BSA.	Sepsis with *E. coli* and *S. aureus* and disseminated intravascular coagulopathy
2	1	Female	Allergies (unspecified), atopic dermatitis	MMR, PNC7, varicella	EM	9	Developed fever of 101° F, vomiting, dehydration, and rash consistent with EM; later presented to emergency room with marked dehydration, suffered from hypovolemic shock, and died.	Unknown (autopsy declined)
3	25	Female	None	Anthrax, typhoid	TEN	13	Few details available; treated for anti-N-methyl-D-aspartate receptor encephalitis, subsequently developed TEN and cardiopulmonary arrest	Cardiopulmonary arrest
4	43	Female	Post-herpetic neuralgia	IIV	SJS/TEN	3	Receiving amoxicillin at time of vaccination; presented with SJS, was diagnosed with SJS/TEN	Respiratory failure
5	71	Male	Multiple myeloma, rheumatic heart disease, gout	IIV	TEN	1	Began allopurinol for gout 8 weeks prior to vaccination; developed TEN with desquamation of 80–90% of BSA.	Not specified
6	82	Male	Chronic kidney disease, type I diabetes	Not reported	TEN	Not reported	Trimethoprim-sulfamethoxazole administered at time of vaccination, subsequently developed TEN	Not specified

[a]BSA = body surface area; F = Fahrenheit; IIV = trivalent inactivated influenza vaccine; MMR = combined measles, mumps, and rubella vaccine; PNC7 = 7-valent conjugated pneumococcal vaccine.