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Original Article

Identifying the factors and root causes associated with the unintentional usage of an adrenaline auto-injector in Japanese children and their caregivers

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ABSTRACT

Background: The unintentional usage of adrenaline auto-injectors may cause injury to caregivers or patients. To prevent such incidents, we assessed the causative factors of these incidents.

Methods: The Anaphylaxis Working Group of the Japanese Society of Pediatric Allergy and Clinical Immunology requested that society members register cases in which adrenaline auto-injectors were unintentionally used. One hundred cases were reported from June 2015 to March 2016. We identified the root causes of 70 child and 25 adult cases, separately.

Results: The incidents occurred with repeated prescriptions as well as the first prescription. Three cases resulted in a failure to administer an adrenaline auto-injector to children with anaphylaxis. Four caregivers used it with improper application (epilepsy or enteritis). Among the child cases, the median age at the time of the incident was 5.5 years (range, 2–14 years). Five children injected the adrenaline auto-injector on their own body trunk. Twenty children were not the allergic patients themselves. Improper management protocol of the device and the child's development were concomitantly involved in most of the cases. A variety of human behaviors were identified as the root causes in the adult cases. At least 34 cases were associated with mix-ups between the actual and training device.

Conclusions: Health workers should provide sufficient education regarding safety use of adrenaline auto-injector for caregivers tailored to their experience levels at both first and repeated prescriptions. Such education must cover anticipatory behavior based on normal child development. Devices should also be further improved to prevent such incidents.

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Introduction

For the safety of patients with severe food allergies, an emergency action plan to provide against anaphylaxis should ensure the appropriate use of adrenaline auto-injectors (AAIs) for first-aid treatment.¹ However, despite the efforts of health workers to train patients and/or nonmedical caregivers about the safe handling of AAIs, there have been cases of patient safety incidents caused by AAIs.^{2–4} In Japan, the Epipen (Pfizer Japan, Tokyo, Japan)

is prescribed as the sole AAI device. The current device, which has a user-friendly ellipse body, has been available since 2012, helping to distinguish actual AAI devices and improving safety use given its orange needle-cover and blue safety cap. The design of the trainer label was modified to distinguish it from the actual AAI device after 2013. However, despite these improvements to enhance the safety, recent reports have also described patient safety incidents caused by such improved AAI devices in Japan.^{5,6}

Patient safety incidents are known to be closely related to a lack of attention to technical, organizational, and human causes, and efforts to address patient safety have focused on the role of human behavior as well as the design of safe medical devices.^{7,8} Several frameworks and taxonomies to identify human causes have been developed to minimize unsafe acts that endanger patient safety.^{8–10} Human causes involve certain types of human behavior, specifically

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knowledge-, rule-, and skill-based behavior.¹¹ Skill-based behavior requires less attention for adequate performance and it is typically associated with very familiar tasks. Rule- and knowledge-based behaviors are distinguished by the degree of familiarity with the task: the former is involved with more familiar tasks than the latter.

As unintentional injections using AAls might injure the user as well as the recipient, both manufacturers and health workers should act to ensure the safe and reliable usage of AAls by caregivers. The key to preventing patient safety incidents is the clarification of the link between root causes and the cases. There have been several reports of case series,^{2–4} but to our knowledge, no reports have so far evaluated the root causes of incidents involving AAls. In the present study, we examined the cases of the unintentional usage of AAls in order to identify the root causes in Japan.

Methods

Subjects

The Anaphylaxis Working Group of the Japanese Society of Pediatric Allergy and Clinical Immunology conducted the present study (Supplementary Table 1). This project was announced to the members of the society (n = 3880 in November 2014) through the society's official journal.

We had asked the society members to report relevant incidents using a physician-administered report form from June 2015 to March 2016. The respondents were the physicians who prescribed AAls and examined the patients. We considered the incidents that occurred before and within this period as the subjects in this study. The definition of unintentional usage in this study was presented on the report form as follows: A) unintentional usage of an AAI with a patient or others; B) intentional usage of an AAI with a patient based on misjudgment of the indication; C) accidental usage of an AAI without the administration of adrenaline into the human body.

In the report form, the purpose and design of the investigation, protection of personal information of patients, and approval of anonymous affiliation were clearly stipulated. This study was approved by the Institutional Review Board of corresponding author's institution (No. 201529).

Inquiry items

The inquiry items included the year and month of the incident, attribution of the patient owning the AAI and the incidental user of the AAI (age, sex, and relationship between the patient and user), presence of adults at events involving children, and symptoms and treatment for the unintentional usage of AAls. The items also included the date of the first prescription of an AAI. The details of the course of the incident were freely described by the respondents.

We defined child cases as those caused by incidental users under 20 years of age and subdivided those cases into prescribed patient and other children cases, based on the attribution of user. We divided the adult cases into two categories, nonmedical caregivers and other adults. The nonmedical caregivers included parents, grandparents, and schoolteachers of patient.

Root cause of unintentional usages of AAls

Three physicians (KS, SS, and TN) who specialized in allergy and/or public health classified the root causes. First, we formulated a causal tree for each report and repeatedly asked why the problem occurred until the answers were identified as actionable root

causes. Second, the identified root causes were classified using the Eindhoven Classification Model, a corresponding taxonomy with the conceptual framework for the WHO World Alliance for Patient Safety's International Classification for Patient Safety.¹² We adjusted the definitions of some root causes in the original classification developed for nosocomial incidents to assess the incidents that occurred during home medical care (Table 1).

Statistical analyses

Nominal scale data were analyzed using Fisher's exact test or the Kruskal–Wallis test. When a significant difference was observed in these tests, comparisons of proportions were tested using Ryan's test.¹³ These analyses were done with using the statistical program R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).¹⁴ A *P* value < 0.05 was considered to be statistically significant.

Results

A total of 100 cases were reported from 60 clinics, including 4 anonymous institutions, in 28 prefectures. Ninety-two cases involved a device prescribed for children, and the remaining 8 cases involved a device prescribed for adults (4 cases) or unknown (4 cases). The incidental users were classified as 72 children, 25 adults, and 3 unknown cases. Five cases were excluded from the root cause analysis because of insufficient information.

Table 1
Definition of the root cause of unintentional usage of the adrenaline auto-injector.

Category	Root cause	Definition
Technical	External	Technical failures beyond the control of the investigating home or facility
	Design	Failure due to poor design of the device or label.
	Construction	Correct design that was not constructed properly.
	Materials	Material defects not classified under design or construction.
Home/Facility	External	Failure at the home or facility beyond the control of the investigating home or facility
	Transfer of knowledge	Failure resulting from inadequate transfer of knowledge to inexperienced person.
	Protocol	Failure relating to the quality of the protocols within the home or facility.
	Management priority	Internal management decisions in which safety is relegated to an inferior position.
Human	External	Human error beyond the control of the investigating home or facility
	Knowledge-based behavior	The inability of an individual to apply their knowledge to a novel situation.
	Rule-based behavior	Qualification
	Coordination	An incorrect fit between an individual's training and a particular task.
Skill-based behavior	Verification	A lack of task coordination among the caregivers.
	Intervention	An incorrect assessment of the situation of the patient and device before usage.
	Monitoring	Failure due to faulty task-planning and execution.
	Slip	Failure due to poor monitoring of the process or subjects.
Other Factors	Tripping	Failure in the performance of developed skills.
	Patient related factor	Failure in whole body movements.
	Unclassifiable	Failure related to individual characteristics.
		Failure that cannot be classified into any other category.

Background characteristics of child cases

The median age at the time of the incident was 5.5 years (range, 2–14 years; interquartile range, 4–7 years). In more than half of all cases (46 [63.9%]), the incidents occurred in either their own home or a relative's home. Eleven cases happened in educational or childcare facilities, and two happened in hospitals. Adults were nearby at the time of the usage in 31 (43.1%) cases, whereas there were no adults nearby in 29 (40.3%) cases. Consequently, adrenaline was confirmed to have been injected in 52 child cases (72.2%). The main injection sites were the lower limbs and hands (Table 2). Most of the cases presented with only mild localized symptoms, such as paleness at the injection site (data not shown). Some cases showed transient general symptoms, such as palpitation ($n = 5$) and headache ($n = 2$). No cases experienced any aftereffects of injuries caused by the AAI injection. Only one case with palpitation after suffering a hand injury received intravenous fluid for observation at a clinic. Five children injected the AAI into their own body trunk, and they fortunately presented only with symptoms of minor bleeding and pain at the injection site (Table 2, 3; case 1–5).

Twenty children (27.8%) other than the patient used the AAI in all of cases (Table 2); specifically, a sibling of the patient used it in 15 cases, 10 of which were younger siblings. A friend of the patient used the AAI in 4 cases by gaining access to an AAI kept in the patient's bag in their classrooms. One child injured himself using an AAI prescribed to his mother. There was no statistically significant difference in the distributions of sex of user, prescription, and hit spot between the prescribed patient and other children cases.

Background characteristics of adult cases

Adrenaline was confirmed to have been injected in 16 adult cases (64.0%). The most frequent injection site was the lower limbs (Table 2). Most of the cases presented with only mild localized symptoms (data not shown). Some cases showed transient general symptoms, such as palpitation ($n = 2$), nausea ($n = 2$), and anxiety ($n = 1$). No cases experienced any aftereffects of injuries caused by the AAI injection. The nonmedical caregivers, including 3 schoolteachers, were involved in 16 (64.0%) cases. In the cases caused by other adults, there was one case involved a nursing student and another case involved a garbage collector. The proportions of first vs. repeat prescription were comparable.

Usage of AAI for patients with symptoms

There were three cases that resulted in failure to use an AAI in children with anaphylaxis (Table 3; case 6–8). Although all three patients were successfully treated afterwards at a hospital, a boy sustained a laceration resulting from the device on his leg because of insufficient immobilization of his leg. Four caregivers administered adrenaline to children without allergic symptoms (Table 3; case 9–12). Two patients suffered from unconsciousness caused by their first epilepsy seizure, while the other two patients vomited due to enteritis. Three other children also used the AAI by themselves due to misidentifying the symptoms (Table 3; case 13–15). In case 14, the child did not know proper handling of the AAI, which fortunately reached atraumatic result. His mishandling of the device can be summarized as follows: he pulled off the safety cap, and inserted the projection of the safety cap into the hole of the needle cover. Then, when the child pushed the AAI on the thigh of the mother, the needle was thus prevented from injecting normally.

Root causes of unintentional usage of the AAI

We identified 177 root causes in 70 child cases. The root causes are shown in Table 4. Home/facility root causes and patient-related factors, e.g. curious usage of the AAI without the caregivers' permission, were concomitantly associated with almost all of the child cases. The most frequently occurring home/facility root cause was the "protocol", due to the improper safekeeping of the device, thus enabling children to gain access to the device. Seven of these cases occurred at educational or childcare facilities without effective protocols to prevent the misuse of the device. The distributions of home/facility root cause subcategories differed between user types. The problems with "management priority", e.g. placing the device near children for a moment, were associated only with the prescribed patient cases. By contrast, the other children cases highly related to "protocol" as compared to the prescribed patient cases.

Rule-based behavior accounted for all of the human root causes, which was highly associated with the prescribed patient cases. The "qualification" was associated with the usage of the AAI by three children for symptoms other than anaphylaxis. Two rule-based behaviors of caregivers—"intervention", e.g. leaving children alone in a room with an AAI, and "monitoring", e.g. poor monitoring of children's behavior—led to the inappropriate usage of the AAI by children.

Table 2
Characteristics of cases.

	User of adrenaline auto-injector					
	Child			Adult [†]		
	Total ($n = 72$)	Prescribed patient ($n = 52$)	Other children ($n = 20$)	Total ($n = 25$)	Nonmedical caregiver ($n = 16$)	Other adults ($n = 9$)
Sex of User						
Male [n (%)]	46 (63.9)	37 (71.2)	10 (50.0)	8 (32.0)	1 (6.3)	7 (77.8)
Prescription						
First prescription [n (%)]	30 (41.7)	25 (48.1)	5 (25.0)	8 (32.0)	6 (37.5)	2 (22.2)
Repeated prescriptions [n (%)]	29 (40.3)	20 (38.5)	9 (45.0)	5 (20.0)	4 (25.0)	1 (11.1)
Unknown [n (%)]	13 (18.1)	7 (13.5)	6 (30.0)	12 (48.0)	6 (37.5)	6 (66.7)
Hit spot						
Lower limbs [n (%)]	24 (33.3)	19 (36.5)	5 (25.0)	11 (44.0)	7 (43.8)	4 (44.4)
Hands (palm or digit) [n (%)]	23 (31.9)	13 (25.0)	10 (50.0)	5 (20.0)	4 (25.0)	1 (11.1)
Body trunk [n (%)]	5 (6.9)	4 (7.7)	1 (5.0)	0 (0)	0 (0)	0 (0)
Outside of the body [n (%)]	11 (15.3)	9 (17.3)	2 (10.0)	2 (8.0)	1 (6.3)	1 (11.1)
Unknown [n (%)]	9 (12.5)	7 (13.5)	2 (10.0)	7 (28.0)	4 (25.0)	3 (33.3)

The child cases were defined as those caused by incidental users under 20 years of age. The nonmedical caregivers were defined as parents, grandparents, or schoolteachers of patient.

[†] These cases include seven cases in which the caregivers administered the adrenaline auto-injector to children with anaphylaxis or symptoms caused by other diseases (see Table 3 for short summary of these cases).

Table 3
Short summary of notable cases.

No.	User	Age and sex of patient	Description of incident
Unintentional injection of adrenaline auto-injector into user's own body trunk			
1	Prescribed patient	2 y/o, male	When the mother of a boy asked him to fetch the device by himself, he picked it up and injected it into his own epigastric region with no adult around.
2	Prescribed patient	3 y/o, female	A girl took the device from her mother's bag and injected it into her own epigastric region while her mother was talking with a visitor.
3	Prescribed patient	4 y/o, female	A girl injected the device into her own abdomen when her grandmother left it near her for a moment.
4	Prescribed patient	10 y/o, male	Father staying at home with his mentally retarded son was unaware that the boy had injected the device into the boy's own abdomen.
5	Other children	7 y/o, female	An older sister of a patient injected the device, which was kept in her mother's bag, into her own abdomen while her family was out.
Error in administration of adrenaline auto-injector to patient with anaphylaxis			
6	Nonmedical caregiver	4 y/o, male	A boy developed anaphylaxis after the accidental ingestion of wheat. His mother failed to administer a device because of insufficient immobilization of his leg. This boy sustained a 5-cm laceration on his leg, which required no surgical operation.
7	Nonmedical caregiver	5 y/o, male	The mother of a boy attempted to use the device, but instead accidentally injected her own finger, due to holding the device upside down.
8	Nonmedical caregiver	6 y/o, male	A boy developed anaphylaxis after the accidental ingestion of wheat. His mother failed to administer a device because of insufficient immobilization of his leg.
Usage of adrenaline auto-injector to someone without allergic symptoms			
9	Nonmedical caregiver	2 y/o, male	The father of a boy mistakenly used the device for the vomiting and pale face due to enteritis.
10	Nonmedical caregiver	12 y/o, male	When a boy suffered from unconsciousness caused by their first epilepsy seizure, his mother mistakenly used the device.
11	Nonmedical caregiver	13 y/o, male	When a boy suffered from unconsciousness caused by their first epilepsy seizure, his mother mistakenly used the device.
12	Other adults	8 y/o, male	An emergency life-saving technician mistakenly injected the device into a mentally retarded boy, who had communication difficulty, for the vomiting and pale face due to enteritis.
13	Prescribed patient	5 y/o, male	A boy with carsickness injected the device into his left thigh while no caregivers were nearby.
14	Prescribed patient	5 y/o, male	A boy who found his mother sleeping tried to wake his mother using the device which he had found in his mother's bag. This boy did not know how to properly use the device and the mother was not injured by the device.
15	Prescribed patient	7 y/o, female	A girl injected the device due to contact dermatitis on her hand caused by <i>Ipomoea batatas</i> while no caregivers were nearby.

The nonmedical caregivers were defined as parents, grandparents, or schoolteachers of patient.

We identified 43 root causes in 25 adult cases. Human root causes were the most common types and they were characterized by a variety of behavior types (Table 4). "Knowledge-based behavior" was associated with cases in which the caregivers mistakenly used the AAI for the symptoms in four patients without anaphylaxis. "Qualification" caused the failure to use the device in three children with anaphylaxis. "Slip", a skill-based behavior, caused two operational errors involving an AAI. There was no statistically significant difference in the distribution of root causes between the nonmedical caregiver and other adults case.

The "design" of AAI was associated with at least 22 child and 12 adult cases, resulting in mix-ups between using the actual device and trainer. All of these child cases were concomitantly associated with the "protocol" or "management priority", and 10 cases resulted from the rule-based behavior of their caregivers. All adult cases were concomitantly associated with the skill-based behaviors of "qualification" or "slip". Since the manufacturers recently improved the packaging of the current AAI, we subdivided the cases and the root causes according to the prescription year of the current device with an ellipse body (Table 5). We found no statistically significant difference over time in the types of root causes in child and adult cases.

Discussion

We collected data on patient safety incidents in which AAI were unintentionally used. As the usage of AAI is indispensable for the first-aid treatment of anaphylaxis, the inaccurate usage of such a device might result in the dose of adrenaline being insufficient to save the life of a patient.² We found three cases that resulted in a failure to administer adrenaline to children with anaphylaxis. Fortunately, all patients were later successfully treated at a hospital,

but one boy sustained a laceration on his leg. Recent reports have also promoted awareness that insufficient immobilization of the leg and a lengthy time of needle injection (recommended as a few seconds by the manufacturer) can provoke lacerations during use in children.¹⁵ These cases suggested the need for instruction not only in the handling of AAIs, but also in how caregivers should hold the patient during the administration of an AAI.

In this study, some cases showed the usage of AAIs for patients with symptoms other than allergic symptoms. Three nonmedical caregivers and an emergency life-saving technician used AAIs in children with epilepsy seizures or enteritis, as it is difficult for them to differentiate those pathological conditions from anaphylaxis. Three children used the AAI by themselves after misjudging the indications: their ages (less than 8 years old) seemed to be too young for the self-management of an AAI.

This study is the first application of a root cause analysis to identify the reasons why the unintentional usage of an AAI occurred. Human root causes were the most common in the adult cases, which included different types of causal human behavior, i.e. knowledge-, rule-, and skill-based behavior. These human behavior types were distinguished by the degree of familiarity with the task.¹¹ Therefore, the incidents caused by adult users were closely linked with their familiarity with using the device. The present study showed that the "patient-related factors", such as exploratory behavior and mimicking the behavior of adults, and home/facility root causes were comorbid facilitating factors for the child cases. There were a number of incidents caused by children other than patients, particularly younger siblings. This finding was supported by an earlier report that identified children with older siblings as a facilitating factor for unintentional injury.¹⁶ In this study, the cases caused by younger siblings highly associated with "protocol", e.g. the improper safekeeping of the device, which enable them to

Table 4

Type of root cause of unintentional usage of the adrenaline auto-injector.

Root cause type	User of adrenaline auto-injector					
	Child			Adult		
	Total (n = 70)	Prescribed patient (n = 50)	Other children (n = 20)	Total (n = 25)	Nonmedical caregiver (n = 16)	Other adults (n = 9)
Technical [n (%)]	22 (31.4)	15 (30.2)	7 (35.0)	12 (48.0)	8 (50.0)	4 (44.4)
Design [n (%)]	22 (31.4)	15 (30.0)	7 (35.0)	12 (48.0)	8 (50.0)	4 (44.4)
Home/Facility [n (%)]	68 (97.1)	48 (96.0)	20 (100)	6 (24.0)	3 (18.8)	2 (22.2)
Transfer of knowledge [n (%)]	0 (0)	0 (0)	0 (0)	1 (4.0)	1 (6.3)	0 (0)
Protocol [†] [n (%)]	55 (78.6)	35 (70.0) [‡]	20 (100) [‡]	4 (16.0)	2 (12.5)	1 (11.1)
Management priority [†] [n (%)]	13 (18.6)	13 (26.0) [‡]	0 (0) [‡]	1 (4.0)	0 (0)	1 (11.1)
Human [n (%)]	17 (24.3)	16 (32.0) [‡]	1 (5.0) [‡]	23 (92.0)	15 (93.8)	8 (88.9)
Knowledge-based behavior [n (%)]	0 (0)	0 (0)	0 (0)	4 (16.0)	3 (18.8)	1 (11.1)
Rule-based behavior [n (%)]	17 (24.3)	16 (32.0) [‡]	1 (5.0) [‡]	10 (40.0)	8 (50.0)	2 (22.2)
Qualification [n (%)]	3 (4.3)	3 (6.0)	0 (0)	9 (36.0)	8 (50.0)	1 (11.1)
Intervention [†] [n (%)]	7 (10.0)	7 (14.0)	0 (0)	0 (0)	0 (0)	0 (0)
Monitoring [†] [n (%)]	7 (10.0)	6 (12.0)	1 (5.0)	1 (4.0)	0 (0)	1 (11.1)
Skill-based behavior [n (%)]	0 (0)	0 (0)	0 (0)	9 (36.0)	4 (25.0)	5 (55.6)
Slip [n (%)]	0 (0)	0 (0)	0 (0)	8 (32.0)	4 (25.0)	4 (44.4)
Tripping [n (%)]	0 (0)	0 (0)	0 (0)	1 (4.0)	0 (0)	1 (11.1)
Other factors [n (%)]	70 (100)	50 (100)	20 (100)	2 (8.0)	0 (0)	2 (22.2)
Patient related factors [n (%)]	70 (100)	50 (100)	20 (100)	2 (8.0)	0 (0)	2 (22.2)

Data are shown as the number of cases (%). The child cases were defined as those caused by incidental users under 20 years of age. The nonmedical caregivers were defined as parents, grandparents, or schoolteachers of patient. The definitions of the root causes are shown in Table 1. The total number of identified root causes were as follows: child cases, 177; adult cases, 43. Two child cases caused by prescribed patient were excluded from the root cause analysis because of insufficient information.

[†] The root causes for these child cases were attributable to their caregivers.

[‡] Significant difference between prescribed patient and other children (Ryan's test, $P < 0.05$).

reach the device. Specifically, younger children rapidly develop their physical and cognitive abilities, which can increase the risk of unintentional injury.^{17–19} Taken together, these findings suggest that child cases could occur when caregivers lack the anticipation of behavior and rapid development in their children. As a result, caregivers should increase their awareness to anticipate problems and thereby prevent unnecessary injuries.

The “design” of the AAI, specifically the similarity of the labeling between the actual device and the trainer device, was a common root cause in both adult and child cases. Human behavior and its associated errors are heavily influenced by certain performance obstacles.¹¹ Although the manufacturers have revised the device design to reduce the misuse of the device, the packaging design of the actual device and training device thus require further improvements to minimize the cognitive load for users.²⁰ Importantly, young children cannot understand the instructions written on the device. We have reminded caregivers to keep the trainer device well away from the actual device, and this strategy has helped to prevent such incidents.⁶

Table 5

Prescription year of the adrenaline auto-injector and root cause type.

Root cause type	Prescription year			
	2012	2013	2014	2015
Child cases				
Reported cases [n]	3	8	23	23
Technical [n (%)]	1 (33.3)	3 (37.5)	10 (43.5)	5 (21.7)
Home/Facility [n (%)]	3 (100)	8 (100)	23 (100)	22 (95.7)
Human [n (%)]	0 (0)	2 (25.0)	7 (30.4)	5 (21.7)
Other factors [n (%)]	3 (100)	8 (100)	23 (100)	23 (100)
Adult cases				
Reported cases [n]	1	1	8	2
Technical [n (%)]	1 (100)	1 (100)	4 (50.0)	2 (100)
Home/Facility [n (%)]	0 (0)	0 (0)	2 (25.0)	0 (0)
Human [n (%)]	1 (100)	1 (100)	7 (87.5)	2 (100)
Other factors [n (%)]	0 (0)	0 (0)	0 (0)	0 (0)

Data are shown as the number of cases (%). The child cases were defined as those caused by incidental users under 20 years of age. The definitions of the root causes are shown in Table 1. This table did not include the 22 cases lacking information on the prescription year. Significant differences were not observed in variation per year for root cause type in child and adult cases (Kruskal–Wallis test, $P < 0.05$).

Unexpectedly, the number of cases that occurred with repeatedly prescribed patients were comparable to those among patients with their first prescription in this study. To minimize the unintentional usage of AAI, medical staff should periodically assess the safety knowledge and behavior of caregivers and provide suitable instructions at every prescription.

The present study is associated with several limitations. First, this study is based on a physician-reporting method for collecting data on the incidents. This might adversely affect the obtaining of an accurate course of each case. Second, the physicians who voluntarily sent in the reports were mainly pediatric allergy specialists. We could not exclude the possibility that more serious incidents may have occurred involving patients not instructed in the proper handling of an AAI. Third, our data lack some additional information, such as the academic achievement and socioeconomic background of the caregivers, which might be facilitators or barriers for such incidents. Despite these limitations, the strength of this study is that it is the first attempt to assess the root cause of the unintentional usage of AAI from the largest sampling of data available at this time. Patient safety practices are based on lessons derived from previous incidents. Therefore, the present study will help to inform not only caregivers, but also health workers on how to prevent such incidents in the future.

In conclusion, we advocate the following key approaches to avoid the unintentional usage of AAI: 1) health workers should educate nonmedical caregivers regarding the safety use of AAI tailored to their familiarity levels at both the first and repeat prescriptions; 2) such education should be based on previous incidents while stressing the need to anticipate potential problems; and 3) manufacturers must further improve these devices, such as by adding a child-resistant safety cap, to reduce the problems associated with human-related factors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.alit.2018.02.005>.

Conflict of interest

ME received honorarium from DBV Technologies. The rest of the authors have no conflict of interest.

Authors' contributions

KI planned the study design and was responsible for finalizing the manuscript. KS equally planned the study design and contributed to drafting the manuscript. TN and SS contributed to the data collection, reviewing reports, and the statistical analysis. ME supervised the study as the chief of the working group.

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