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Hospitalisations due to allergic reactions in Finnish and Swedish children during 1999-2011

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Abbreviations:

ATC	Anatomical Therapeutic Chemical
EAI	Epinephrine auto-injector
ED	Emergency Department
ICD-10	International Disease Classification, 10 th Revision
NHDR	National Hospital Discharge Register (Finland)
NPR	National Patient Register (Sweden)

Abstract

Background: Several authors have reported on allergic reactions that resulted in presentation to the emergency department. However, studies of the secular trend of hospitalisations for paediatric allergic reactions, including anaphylaxis, are scarce.

The aim of this study was to describe the secular trends of hospitalisations for allergic reactions, including anaphylaxis, among children aged 0-19 years old in Finland and Sweden, and to establish the trend of prescribed epinephrine auto-injectors (EAI) among paediatric populations.

Methods: Using national databases, we identified hospitalisations between 1999 and 2011 with the primary diagnosis of allergic reaction per International Classification of Diseases, 10th Revision.

Results: Hospitalisations for allergic reactions totaled 1987 in Finland and 5433 in Sweden.

Incidence rates increased in both countries. In Finland, the incidence of admission was 7.8 per 100,000 person-years at the start of the study period and 15.8 at the end of the study period. The corresponding numbers among Swedish children were 13.7 and 31.8 per 100,000 person-years. In Finland, 60% of children hospitalised were under 10 years old. In Sweden, this proportion was somewhat lower, at 48%. Most hospitalisations occurred between May-September. The prevalence of EAI prescriptions in Finland increased by 4-fold during the study period. In Sweden, such an increase was not identified.

Conclusions: The incidence of allergic reactions leading to hospitalisations between 1999 and 2001 increased in Finland and Sweden among children aged 0 to 19 years. In Finland, the incidence was lower throughout the study period compared to Sweden. Younger children constituted the majority of hospitalised children.

Introduction

Despite an enhanced understanding of factors associated with severe (1) and recurrent (2) allergic reactions, paediatric allergy poses a substantial (3-6) and financial burden to both society (7) and households (8). Allergic reactions may also lead to serious complications, hospitalisations, and even death. In food allergic children, multi-morbidity of asthma, eczema and respiratory allergies are all risk factors for allergic reactions, including anaphylaxis (9, 10).

Anaphylaxis is defined as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with, or ingestion of allergy-causing substances(11). In Europe and North America, foods, especially peanuts, tree nuts, milk, egg, fish and shellfish, are the most common triggers of anaphylaxis amongst children(10, 12). Epinephrine is only well-recognised treatment for anaphylaxis, and may be life-saving when administered properly

and without delay⁽⁹⁾ (13). To this end, children with severe allergies, or their caregivers, are advised to carry an adrenaline auto-injector (EAI) at all times (11).

Several authors have reported on allergic reactions that resulted in presentation to the emergency department (ED) (12, 14, 15). Previous studies suggest that hospitalisations resulting from allergic reactions, including anaphylaxis and angioedema, occur in approximately 13-15% of children presenting with allergic reactions (10, 16-18). However, these reports have been based on small samples, often from a single hospital. Large, multicentre and international studies of the secular trend for hospitalisations for paediatric allergic reactions, including anaphylaxis, are scarce (19, 20). The aim of this study was to describe the secular trend of allergic reactions, including anaphylaxis, leading to hospitalisation between 1999 and 2011, among Finnish and Swedish children. As we hypothesized that treatment may have some effect on hospitalisation trends for allergic reactions, we also aimed to explore the trend of prescribed EAI among paediatric populations.

Methods

This study is based on register data from Finland and from Sweden. First, we used information from hospital patient registers: the National Hospital Discharge Register (NHDR) in Finland and the National Patient Register (NPR) in Sweden. Both registers contain inpatient data from all hospitals including age, time of hospitalisation, length of hospital stay, and diagnosis. Data are collected and maintained annually by the National Research and Development Center for Welfare and Health in Finland and by the National Board of Health and Welfare in Sweden. All children aged 0 to 19 years who were

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hospitalised with a primary diagnosis of allergic reaction between 1999 and 2011 were identified by computer searches using the International Classification of Diseases, 10th Revision (ICD-10) codes. During this period, hospital discharge data were available in both Finland and Sweden. Our main outcome variable was the number of children hospitalised with a primary diagnosis and corresponding ICD-10 codes: Anaphylaxis codes were T78.0 (Anaphylactic shock due to adverse food reaction) and T78.2 (Anaphylactic shock unspecified) and other allergic reactions were T78.1 (Other adverse food reactions not elsewhere classified), T78.3 (Angioneurotic edema) and T78.4 (Allergy unspecified). Consideration was given to sex and age groups (0-4, 5-9, 10-14 and 15-19 years) as we hypothesised that incidence might vary by gender or age.

Second, we used the prescription drug registry-based databases, The Finnish Prescription Registry and The Swedish Prescribed Drug Register to report numbers of prescribed EAI among children 0 to 19 years (21). These registries include codes for pharmaceutical agents according to Anatomical Therapeutic Chemical (ATC) Classification System (22). We collected data on ATC-codes for agents aimed to treat anaphylaxis (C01CA24). In The Finnish Prescription Registry, data were available across the entire study period, whereas the Swedish Prescribed Drug Registry only includes data from 2006 onward (21). Both registers provide valuable data on exposures to prescribed drugs and are useful to study patterns (21, 23).

In order to compute the incidence of allergic reactions leading to hospitalisation, the annual age-specific mid-populations were obtained from the Official Statistics of Finland (24) and Statistics Sweden (25), which are computer-based national population registers. In

Finland, there were 1,278,313 children 0-19 years in 1999 and 1,218,255 in 2011. The corresponding figures for Sweden were 2,148,435 and 2,180,105 respectively. The incidence of hospitalisation due to allergy (per 100,000 persons) was based on the results of the entire population of children in Finland and Sweden rather than cohort or sample based estimates. As such, 95% confidence intervals and p-values were not calculated. Statistical analysis was performed using SPSS 21.0 for Windows software (SPSS Inc, Chicago, Illinois).

The Finnish and Swedish Ethics Committees approved the study (Finnish Reference Number THL 89/5.0500/2012 and Swedish Reference Karolinska Institutet Dnr. 33010/2014).

Results

Between 1999 and 2011, hospitalisations for allergic reactions totaled 1,987 in Finland and 5,433 in Sweden. The incidence of hospitalisation per 100,000 person-years among Finnish children in 1999 and 2011 were 7.8 and 15.3, respectively.

The corresponding incidence per 100,000 person-years among Swedish children was 13.7 in 1999 and 31.8 in 2011. The increasing trend was seen across all age groups in both countries.

Compared to Finland, the incidence of hospitalisations for allergic reactions in Sweden was 1.8-fold higher in 1999 and 2.1-fold higher in 2011. The incidence increased for both boys and girls in both countries during the study period (Figure 1).

The median length of hospital stay throughout the study period for both countries was one day (range, 1- 13 days in Finland; 1- 52 days in Sweden). In Finland, 92 % of children with allergic reactions were hospitalised for one day, and 3% were hospitalised for three or more days. In Sweden, 94 % of the children were hospitalised for one day and 1% for three or more days.

Most children (83% in Finland; 89% in Sweden) were hospitalised for allergic reaction only once during the study period. However, 17% (n=344) of children in Finland and 11% (n=613) in Sweden had two or more admissions. In Finland, 2 % (n=35) of children had four or more admissions. In Sweden, the corresponding figure was 1% (n=71).

The median age at the time of hospitalisation was lower in Finland than in Sweden. Finnish boys had a median age of six years and nine years in girls, respectively. In Sweden, the median ages were eight years in boys and 12 years in girls.

In Finland, the incidence of hospitalisations for anaphylaxis increased by 3.1-fold during the study period, from 2.7 per 100,000 person-years in 1999 to 8.3 per 100,000 person-years in 2011. In Sweden, the trend was similar: the incidence of hospitalisations for anaphylaxis increased by 3.6-fold during the study period, from 4.3 per 100,000 person-years in 1999 to 15.3 per 100,000 person-years in 2011 (Figure 2).

In Finland, anaphylaxis was the cause of hospitalisation in 49% of all allergic reactions. In Sweden, the corresponding figure was 40%. Unspecified allergic reactions accounted for 46% of cases in Finland and 39 % in Sweden. Angioneurotic edema accounted for 3% of hospitalisations for allergic reactions in Finland and 12 % in Sweden (Table 1).

In Finland, 60% of children hospitalized were under 10 years old (Table 1). In Sweden, this proportion was lower (48%). Children aged 15-19 years constituted the smallest proportion (17%) of hospitalisations in Finland. In contrast, this age group accounted for the larger proportion (30%) of hospitalisations in Sweden (Table 1).

In both countries, rates of hospitalisations were highest in the summer months between May and September, reaching a peak in Finland in July (12%) and in Sweden in August (12%) (Figure 3).

The prevalence of children prescribed an EAI in Finland increased by 4-fold during the study period. In Sweden, data were only available from 2006 to 2011. An increase in prescriptions for EAI was not identified during this time (Figure 4).

Discussion

From 1999 to 2011, the overall incidence of allergic reactions leading to hospital admission increased among Finnish and Swedish children age 0 to 19 years. The incidence increased for both boys and girls in the two countries. The incidence was lower in Finland than Sweden throughout the study period. Most hospitalisations occurred during May-September in both countries. The prevalence of EAI prescriptions among Finnish children increased by 4-fold during 1999-2011. In Sweden, an increase in prescriptions was not identified.

The present study has some limitations. First, as data were based on ICD-codes and hospitalisation statistics, we were unable to consider ED treatments, or post-discharge outcomes. Some admissions may have not captured in our study due to chosen diagnosis.

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For example, the diagnosis R57.9 (shock unspecified) was not included. We were also unable to determine the offending allergen resulting in allergic reactions, including anaphylaxis. Moreover, we cannot be certain if there were differences in diagnosing allergic reactions in Finland and Sweden.

Nonetheless, our findings are novel, as they describe the national trends of hospitalisations due to allergic reactions over a period of 13 years among children in two well-defined populations. The major strength of this study is that the hospitalisation data were obtained at the national level using validated and well-established registers (23, 26). To our knowledge, similar national level secular trends over time have not been previously described. Most previous studies cover shorter periods of time and were conducted within one hospital catchment area or within one state (17, 27). ED visits for allergic reactions and anaphylaxis in childhood have been reported (10, 28), but rates of hospital admissions are rarely published (17, 27). National healthcare databases in the Scandinavian countries provide a novel opportunity to study national trends and perform international comparisons, such as those performed in this study. Moreover, the use of standardised ICD-10 diagnostic coding permitted estimations of incidence rates and an international comparison.

Few previous studies have examined the secular trends of allergic reactions or anaphylaxis leading to hospital admissions (18). From the limited evidence available, it is believed that allergic reactions and anaphylaxis are more prevalent than previously suspected. Moreover, the incidence of allergic reactions, including anaphylaxis, resulting in hospitalisation may be increasing (11, 17, 29, 30) and may vary between middle- and high-

income countries (12). In a nationwide study from Turkey, the authors reported incidence of 1.95 per 100,000 person-years for hospital admissions due to anaphylaxis in 2010-2011 (17). This estimate is much lower than the incidence we identified in Finland or Sweden. This may be attributable to lower prevalence in allergic diseases, and/or under-recording of anaphylaxis in those admitted to hospital(17).

Consistent with our findings, there has been a 4-fold increase in anaphylaxis hospitalisations amongst children of the same age in the present study in one American state between 1990-2006 (27). However, in Finland and Sweden, the incidences of hospitalisations for anaphylaxis are somewhat higher than in the American report (27). In a study from Southern Israel, the incidence of anaphylactic reactions requiring hospitalisation among children between 2005-2010 was 7.0 per 100,000 person-years (31). However, this study did not capture the secular trend of the incidence of hospitalisations.

According to our knowledge, the prevalence of allergic diseases is not different between Finland and Sweden (32). In hospitalisations due to pediatric asthma higher incidences in Sweden has not been reported compared to Finland (33). The reason for the higher in incidences of hospitalisations due to allergic reactions in Sweden in the present study is unclear. Thresholds for admission from the emergency department to the hospital ward may vary in countries since there are no unanimous criteria for hospitalisation due to allergic reaction. It is also possible that the duration of observation in outpatient clinics differs. This may explain some of the variation between countries. Additional studies are also warranted to understand the differences in incidences between these two Nordic countries.

Epinephrine is the only drug proven to be effective in treating severe allergic reactions(11). Nonetheless, EAI are underprescribed for high-risk food allergic children(34, 35). EAI are expensive in Nordic countries (approximately 45-53 € each) and the majority of these costs are absorbed by families(36, 37). Anaphylaxis treatment guidelines recommend that at-risk patients are provided with EAI (38). We suspected that higher prescriptions of EAI may have some effect on the incidence of hospital admissions due to anaphylaxis. For example, the incidence of hospitalisations may be lower among children with anaphylaxis treated promptly with an EAI. In the present study, we found an increasing prevalence of EAI prescriptions along with increasing incidence of hospitalisations for anaphylaxis in Finland. Such patterns could not be identified in Sweden. One possible reason for this may be that data on EAI have only been available since 2006, an insufficiently long period to identify changes.

Most hospitalisations occurred between May-September, a period which includes the main pollen season in both countries. Previous literature has shown that seasonal changes has had impacts on the incidence of anaphylaxis (12) and the sensitivity of exercise testing (39, 40). Insect stings could be one explanation for increased hospitalisations during summer months. High pollen levels, which are found during summertime, may exacerbate asthma. In turn, allergic children may be at greater risk of anaphylaxis following exposure to allergens at a lower level than would be trigger a reaction at other times of the year. This is further exacerbated by typically summertime behaviours, such as spending more time outdoors, being more active, travelling more, and eating more fresh fruits, vegetables and snacks (12).

The rising trend of hospitalisations due to allergic reactions and anaphylaxis was observed in both countries. Reasons for the differences between countries are not completely understood. Our study showed that hospitalized children are younger in Finland and that incidence in hospital admissions is higher in Sweden. Regional differences and different periods of ED presentation may partly explain some of the differences. After treatment of anaphylaxis, an observation period is recommended given the risk of a biphasic reaction as the effect of epinephrine diminishes (11). In Finland, the proportion of readmissions was higher, possibly due to discharging children too early as biphasic reactions may occur (41). Consideration to differences in patient outcomes between countries is warranted in future studies. Notably, rates of hospitalisations for paediatric asthma, another allergic disease and a risk factor for more severe allergic reactions, between these countries have been previously reported, but the total hospitalisations between country did not appear to differ dramatically (33).

Future research is also needed to reduce burden of allergic diseases (3, 5, 6) and to curtail the rising trend of hospitalisations due to allergic reactions and anaphylaxis, such as those reported in the present study.

In conclusion, between 1999-2001, the overall incidence of allergic reactions leading to hospital admission increased among children in Finland and Sweden. Most hospitalisations occurred between May and September. Younger children constituted the majority of hospitalisations, but children aged 15-19 years accounted a higher proportion of hospitalisations in Sweden compared to Finland. Moreover, the incidence was lower in Finland throughout the study period. The reasons for these differences between the countries are unknown, but may reflect differences in management of these patients in the two countries.

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Contributors' Statement Page

Juho E. Kivistö conceptualized and designed the study, designed the data collection instruments, carried out the analyses and drafted the initial manuscript, and approved the final manuscript as submitted.

Jennifer L P Protudjer and Anna Bergström conceptualized the study, designed the data collection instruments, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Jussi Karjalainen conceptualized the study, reviewed and revised the manuscript, and approved the final manuscript as submitted

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Ville M Mattila conceptualized and designed the study, carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Table 1. Distribution of diagnoses of hospitalisations for allergic reactions among Finnish (a) and Swedish (b) children aged 0-19 years between 1999 and 2011. Absolute number of hospital admissions given in parentheses.

a. Finnish children

ICD-10 code	Diagnosis	0-4 years	5-9 years	10-14 years	15-19 years	Total
Anaphylaxis						
T78.0	Anaphylactic shock due to adverse food reaction	20.2% (147)	19.5% (92)	15.9% (72)	4.8% (16)	16.5% (327)
T78.2	Anaphylactic shock (unspecified)	27.5% (200)	35.2% (166)	36.1% (163)	36.3% (122)	32.8% (651)
Other allergic reactions						
T78.1	Other adverse food reactions (not elsewhere classified)	2.1% (15)	1.9% (9)	1.5% (7)	1.2% (4)	1.8% (35)
T78.3	Angioneurotic oedema	2.3% (17)	1.7% (8)	2.0% (9)	8.0% (27)	3.1% (61)
T78.4	Allergy, unspecified	47.9% (348)	41.7% (197)	44.5% (201)	49.7% (167)	45.9% (913)
		36.6% (727)	23.8% (472)	22.7% (452)	16.9% (336)	100.0% (1987)

b. Swedish children

ICD-10 code	Diagnosis	0-4 years	5-9 years	10-14 years	15-19 years	Total
Anaphylaxis						
T78.0	Anaphylactic shock due to adverse food reaction	15.8 % (263)	15.2% (147)	16.8% (194)	17.0% (280)	16.3% (884)
T78.1	Other adverse food reactions (not elsewhere classified)	11.9% (198)	10.2% (98)	7.1% (82)	5.9% (97)	8.7% (475)
Other allergic reactions						
T78.2	Anaphylactic shock (unspecified)	19.1% (318)	24.7% (238)	27.5% (319)	24.3% (399)	23.4% (1274)
T78.3	Angioneurotic oedema	13% (216)	12.7% (122)	11.5% (133)	12.0% (198)	12.3% (669)
T78.4	Allergy, unspecified	40.2% (671)	37.2% (359)	37.1% (430)	40.8% (671)	39.2% (2131)
		30.1% (1666)	17.7% (472)	21.3% (1158)	30.3% (1645)	100.0% (5433)

ICD-10: International Disease Classification, 10th Revision

Figure 1. Incidence of hospitalisations for allergic reactions per 100,000 person-years among Finnish and Swedish children (aged 0 to 19 years) between 1999 and 2011.

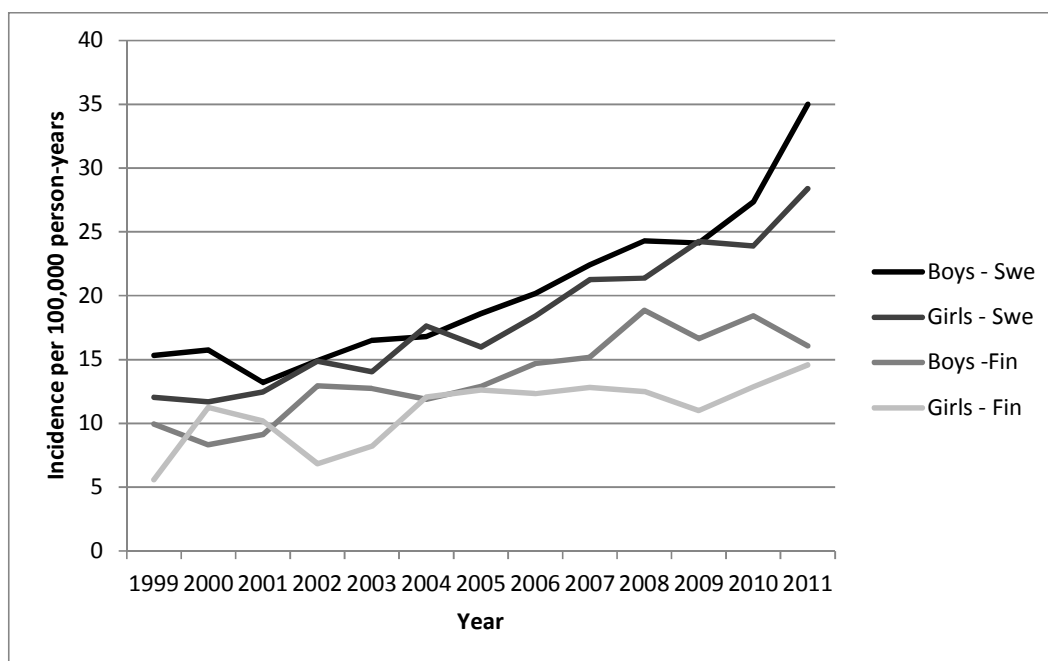


Figure 2. Incidence of hospitalisations for anaphylaxis per 100,000 person-years among Finnish and Swedish children (aged 0 to 19 years) between 1999 and 2011.

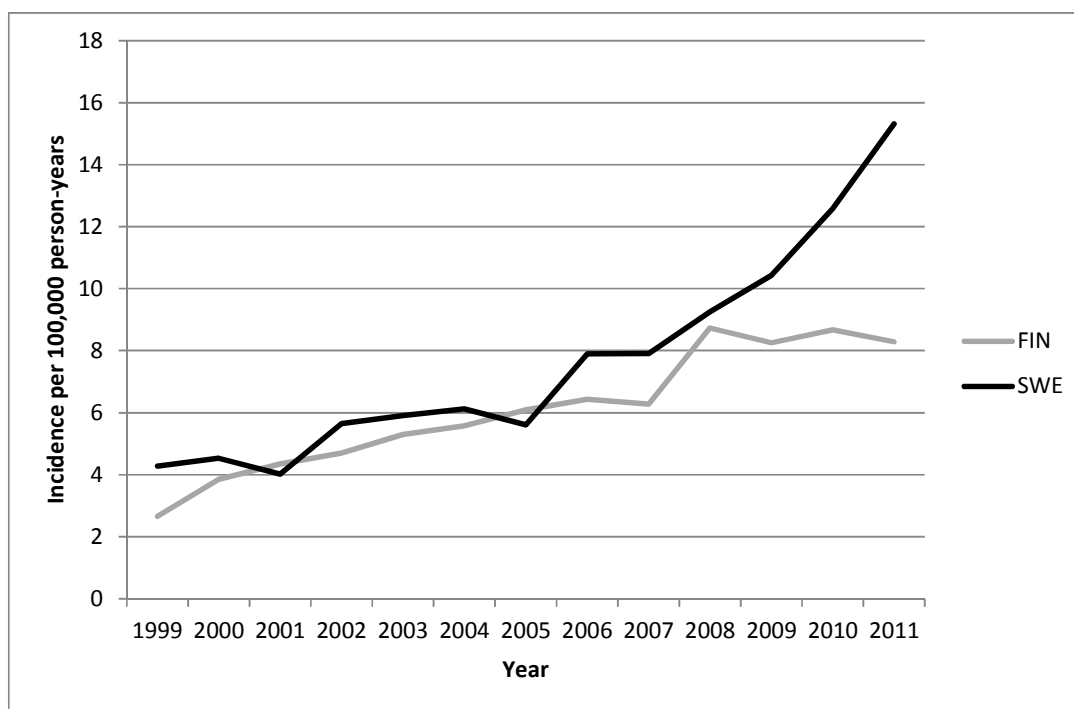


Figure 3. Seasonal distribution of hospitalisations for allergic reactions among Finnish and Swedish children (aged 0 to 19 years) between 1999 and 2011.

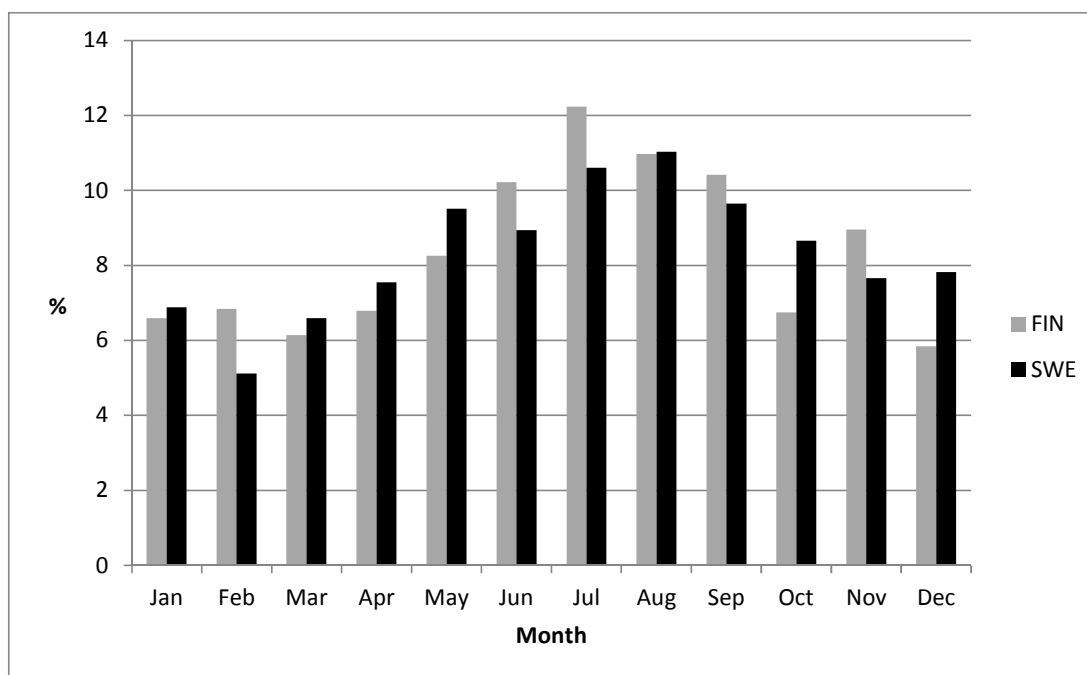
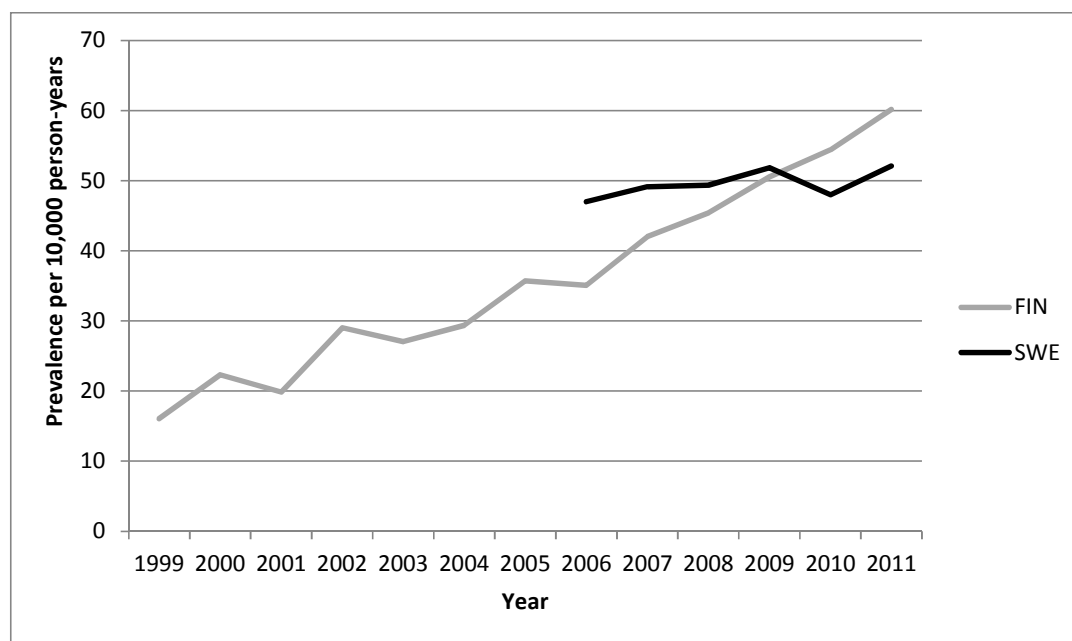


Figure 4. Prevalence of children aged 0-19 years prescribed epinephrine auto-injectors in Finland (FIN) during 1999-2011 and in Sweden (SWE) 2006-2011* per 10,000 person-years.



* In Sweden, data for prescribed drugs are available from 2006 onward.