Chapter 8

General discussion and future perspectives

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The aims of this thesis were to investigate the reasons for the under-prescription of auto-injectors in food allergic patients at high risk for anaphylaxis, and the reasons for non-compliance and non-use of EAs by this group of patients. With regard to our first aim, we first determined the prevalence of food allergy and EAI ownership in high-risk food allergic adolescents in the Netherlands (chapter 2) and secondly we explored the practice in EAI prescriptions by general practitioners to food allergic patients in the Netherlands (chapter 3). Regarding our second aim, we explored the burden of treatment of an EAI and examined the relationship between this burden and compliance with carrying an EAI at all times (chapter 4). We also investigated the health-related quality of life in food allergic patients (chapter 5). Concerning our third aim, we determined the knowledge, attitudes and beliefs regarding food allergy and anaphylaxis among pharmacists in the Netherlands including how accurately they demonstrated how and when to use an EAI to food allergic patients (chapter 6). Finally, we determined the prevalence, severity and clinical characteristics of late reactions in food allergic children and adolescents after DBPCFCs, and ascertained factors that were associated with late reactions after DBPCFCs (chapter 7).

Part I. Prevalence of food allergy and under-prescription epinephrine auto-injectors

In this first part of this thesis, chapter 2 demonstrated that the prevalence of food allergy in high-risk food allergic adolescents, when compared to a previous study in 2009 by Flokstra-de Blok et al., has not increased in the last six years. In 2009 as well as in 2016 the calculated questionnaire-based prevalence of probable food allergy was 6.2%. This is not in keeping with other studies reporting that the prevalence of self-reported food allergy is increasing. These studies report a higher self-reported food allergy prevalence than our study varying from an increase of 1.7% to 4.2% in the community for a time interval of about six years. However, the prevalence of food allergy as diagnosed by the diagnostic gold standard DBPCFC is estimated to be about 3% for all foods together. Therefore, the prevalence reported in these self-reported food allergy prevalence studies may be an overestimation.

Chapter 2 also demonstrated that epinephrine auto-injector (EAI) ownership has improved marginally when compared to a previous study in 2009 by Flokstra-de Blok et al. Even though this improvement was not significant and may therefore not be generalizable, there is ultimately still a substantial under-prescription of EAs by this group of patients. It remains a fact that when a severe food allergic reaction occurs, prompt administration of epinephrine may be life-saving. Therefore, all food allergic patients at high risk of anaphylaxis should possess an EAI and carry this device at all times.
In our study the adolescents classified as probably food allergic were not referred for further testing for an objective diagnosis of food allergy. However, if all probably food allergic adolescents underwent the diagnostic gold standard DBPCFC, our experience is that approximately half of those adolescents would have a positive test outcome. Ultimately, adolescents reporting having experiences a (severe) allergic reaction would still require an EAI until challenge tests could be done, and overestimation of the need for EAls would be thus only be apparent after such tests had been completed. Our finding may thus eventually be an overestimation of the problem of under-prescription of EAls to high risk food allergic patients to some degree.

An overestimation of the prevalence of self-reported food allergy may also be due to an erroneous perception of symptoms of food allergy among the general public. The general public might use the term ‘food allergy’ to describe any adverse response to foods. Previous studies have shown that the food allergy knowledge among the general public seems to be limited.\textsuperscript{15-19} The general public had wide variation in knowledge about food allergy with many misconceptions of key concepts related to prevalence, definition, and triggers of food allergy. Food allergy knowledge among parents of food allergic children from the Netherlands was suboptimal when compared with their counterparts from the USA,\textsuperscript{19} although Dutch parents tend to be more optimistic toward food allergy than parents from the USA. This optimism may be explained by an underestimation of the severity and risks of having an accidental food allergic reaction.\textsuperscript{15,19}

The limited knowledge about food allergy and underestimation of the severity and risk of a food allergic reaction mentioned in the previous paragraph may contribute to the under-prescription of EAls in food allergic patients. Adolescents with problems with food may not visit their general practitioner, and may consequently be ignorant of the fact that they are at high risk for food-induced anaphylaxis. We also have to take into account the role of puberty in the developing adolescent brain. Adolescence is a period of developmental transition between childhood and adulthood, involving multiple physical, intellectual, personality, and social development changes.\textsuperscript{20-26} Therefore there may be a variety of (unknown) reasons why food allergic adolescents behave the way they do. Details about these reasons will be discussed further on in this general discussion (\textit{chapter 4}).

Most food allergic accidents and anaphylaxis fatalities in children and adolescents take place at schools.\textsuperscript{27-29} Previous studies showed that six to eighteen per cent of children with food allergy experience an allergic reaction at school\textsuperscript{30,31} and four to six fatal anaphylactic reactions in children occurred at school.\textsuperscript{32} It is therefore important that schools are prepared for the management of food allergic children. However, previous studies have also shown that in reality many schools are poorly prepared: preventive measures of food allergen exposure are absent, teachers have little knowledge of food
allergy, anaphylaxis, and EAI.\textsuperscript{27,33-36} To our knowledge, the preparedness of Dutch high schools have not yet been investigated,\textsuperscript{35} and it would thus be of interest to investigate how prepared they are. Le et al. investigated 37 primary schools in the Netherlands.\textsuperscript{35} Their study showed that there is a low preparedness for food allergy as perceived by school staff, as is the case for other primary schools across Europe.\textsuperscript{35} Not every school’s staff was aware of symptoms associated with food and not all schools identified children with food allergy.\textsuperscript{35} Few schools had written operating procedures that included how to deal with food allergy. This may also be the case for (Dutch) high schools. This lack of precautionary measures for food allergic children may give rise to food allergic accidents and (fatal) anaphylaxis.

Le et al. proposed that their findings warrants the preparation of guidelines for a standardized approach to identifying children at risk and to preventing and managing the effects of food allergies.\textsuperscript{35} Guidelines have been developed and are intended to assist those working in school and early childhood. Guidelines of the European Academy of Allergy and Clinical Immunology (EAACI),\textsuperscript{27,33} the American Academy of Allergy, Asthma, and Immunology (AAAAI)\textsuperscript{37} and the Australasian Society of Clinical Immunology and Allergy (ASCIA)\textsuperscript{38-40} have outlined the roles and responsibilities of schools, namely (1) identification of children with food allergy; (2) avoidance strategies that create a safe environment for children with food allergy; and (3) treatment strategies to educate the staff. Unfortunately, these guidelines are not yet sufficiently implemented in Dutch schools.\textsuperscript{35} In addition, there are no laws in the Netherlands as there are in Canada,\textsuperscript{41} in the United States of America (USA)\textsuperscript{42} or Ireland\textsuperscript{43} that focus specifically on the preparedness of schools for medical emergencies, such as food-induced anaphylaxis.

In the Netherlands, safety, health-care and welfare for students at schools results from several laws: ‘Wet op het Primair Onderwijs’ (Primary Education Law), ‘Wet op het Voorgezet Onderwijs’ (Secondary Education Law) and ‘Wet Ondersteuning Onderwijs Zieke leerlingen’ (Assistance of Education for Diseased Students Law).\textsuperscript{44-46} Regarding the safety, health-care and welfare for students at schools, these laws demand from schools that they take preventive measures for creating a healthy and safe learning environment for their students. Schools should understand that certain chronic conditions are serious and can be potentially life threatening, particularly if not correctly managed or misunderstood. Schools should have a personal record about each student that has a (chronic) disease.

This record should state which measures should be taken for these individual students.\textsuperscript{44-47} Schools should have a clear communication plan for staff and parents to ensure the safety of these students. Parents have a duty to inform the school of their child’s condition and provide the necessary medical equipment to respond to emergencies. School staff should be provided with training to learn more about these (chronic) diseases and what to do in case of emergencies. Nevertheless, (severe) allergic reactions may occur
in previously undiagnosed children. Therefore, the availability of epinephrine in schools is important for emergency treatment. However, according to Dutch law, medication may only be prescribed to individuals. This means that children that have a (severe) allergic reaction at school may only be treated with their own personal EAI. This also means that schools in the Netherlands are not allowed to have undesignated EAs available. In the USA there is a law since 2013 that permits schools to have an undesignated EAI available for any student or staff member experiencing anaphylaxis. The undesignated EAI may be available in unlocked and easily accessible places in schools and may be used by trained personnel. Such a law might also be helpful in the Netherlands in order to protect food allergic children who experience anaphylaxis when their personal EAI is not easily accessible and those who experience anaphylaxis and do not have an EAI. Currently, in Ireland, regulations about to be changed “to provide for the supply and administration of specified prescription-only medicinal products without a prescription to a person by a pharmacist or by an individual appointed by a listed organisation for the purpose of saving life or reducing severe distress in emergency situations.” The EAI is one of these products. However, that pharmacist or individual must have completed an approved course of training regarding the administration of such products and the management of any adverse reaction.

In the Netherlands the safety of school staff is provided for in the ‘Arbeidsomstandighedenwet’ (Working Conditions Act) and regulated in collective employment agreements of schools. When school staff administer an EAI for emergency treatment in a food allergic child or adolescent they are legally protected by this law and related regulations. But they are only legally protected if their school did take all preventive measures necessary to ensure a healthy and safe environment and trained their school staff to handle these emergencies.

The cornerstones of food allergy and anaphylaxis management should include training of staff members to improve understanding of food allergy and anaphylaxis and establishing management and emergency plans to minimize risks, and to provide a safe educational environment. However, the board of management of schools and school staff face problems with the implementation of laws to create a safe and supportive learning environment for students. It is often unclear which preventive measures should be taken and school staff experience problems caring for students with special health requirements. This may explain that school staff are unprepared and do not want to take responsibility for these emergency treatments. This suggests that there is room for improvement of existing practices. A combination of initiatives undertaken in Canada, Australia and Ireland may be suitable for schools in the Netherlands. For example, in Canada, Sabrina’s Law signed into effect on January 1, 2006, requires that every school board establish and maintain an anaphylaxis policy to help students with serious allergies.
It also requires that schools create individual plans for each student at risk of anaphylaxis.\textsuperscript{41} In Australia, there are guidelines to assist staff in school and childcare settings to plan and implement appropriate risk minimisation strategies, taking into consideration the needs of the allergic child, the likely effectiveness of measures and the practicality of implementation.\textsuperscript{40,53} And in Ireland there is a resource pack ‘Managing Chronic Health Conditions at School’ to help teachers and parents to work together and provide a safe and enjoyable school environment for students with (food) allergies.\textsuperscript{43}

Another problem where food allergic children and adolescents stumble upon is bullying, teasing, and harassment because of their food allergy.\textsuperscript{54,55} Low preparedness of schools for food allergic children and adolescents may contribute to this as well. All this may also have a potential negative impact on a child’s quality of life. Schools must therefore be assisted through government in the implementation of laws to care for food allergic children in case of emergency. National regulations may therefore be required in order to improve food allergy and anaphylaxis knowledge of school staff, to improve anaphylaxis preparedness and to improve health-related quality of life (HRQL) of food allergic children, adolescents and their families.

General practitioners (GPs) play an important role in diagnosing and treating food allergic patients. In the Netherlands, the GP is the gatekeeper of the Dutch health-care system controlling access to specialized medical care. Chapter 3 described and evaluated the practice in EAI prescriptions by GPs to food allergic patients in the Netherlands. Although the knowledge of GPs regarding food allergy and anaphylaxis has previously been studied using questionnaires and hypothetical cases,\textsuperscript{56-59} this study is the first to examine actual EAI prescription practices and the first to make use of data collected by GPs themselves. Our study showed with data recorded by GPs themselves that those food allergic patients at high risk for anaphylaxis that do visit their GPs are often not prescribed an EAI, even to those with a previous severe anaphylactic reaction. This shows that previously identified low rates of EAI ownership may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so.

The management of food allergy and anaphylaxis should be familiar to GPs. However, previous studies showed that there is a lack of food allergy knowledge in primary care, especially the recognition and treatment of anaphylaxis were problematic and that (inter) national guidelines were often not followed.\textsuperscript{29,60-64} Knowledge and/or practice behavior gaps in GPs may be explained by the fact that anaphylaxis is relatively uncommon and that therefore they do not see and treat them that often. However, there are guidelines and algorithms for the diagnosis and management of food allergy and anaphylaxis in case food allergic patients do visit the GP. Primary care guidelines in the Netherlands, the \textit{food allergy guidelines of the Dutch College of General Practitioners} (NHG) guidelines differ from the internationally accepted guidelines for the diagnosis and management of food
allergy and anaphylaxis. Surprisingly, the NHG guidelines recommend that an EAI should only be prescribed after a previous case of anaphylaxis. Significantly, risk factors for a life-threatening food-induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction. Although in our study it may therefore be argued that GPs are simply following their own guidelines to whom prescribing an EAI, this, however, does not seem to explain the lack of EAI prescription in high risk patients who had experienced prior anaphylaxis as well as in patients presenting with anaphylaxis to their GP. The latter situation is in agreement with previous studies of anaphylaxis management in emergency rooms, where patients presenting with anaphylaxis are not always prescribed an EAI or referred to appropriate specialist care.

In our study, a limitation is the number of patients excluded from analysis due to inaccessible or incomplete patient’s medical records. The incomplete data might be due to under-reporting of patients (or their parents), under-documentation of clinical information by GPs or lack of knowledge and/or practice behavior gaps experienced by GPs. In this regard, it may be expected there would be more food allergic patients at high risk for anaphylaxis not being prescribed an EAI. We did not find patients who had been prescribed an EAI who were not high risk patients. Ultimately, some of these patients would probably show no reactions when challenged with the food in question. However, such patients would still require an EAI until challenge tests could be done, and overestimation of the need for EAI would thus only be apparent after such tests had been completed. Our findings may thus eventually be an overestimation of the problem of inadequate EAI prescription to high-risk food allergic patients to some degree. More urgent, however, is the obvious extent to which high risk food allergic patients are not prescribed an EAI by their GPs.

It is important that GPs in the Netherlands become prepared for high risk food allergic patients. Our study highlights that there is a need for improvement of the quality of care for these patients in primary care and that the NHG guidelines should be revised.
Part II. Non-compliance, burden of treatment and HRQL

Food allergic patients at high risk for (fatal) anaphylaxis should carry an EAI at all times. Compliance with EAI carriage is a major clinical problem and important contributor to anaphylactic deaths. Carriage of an EAI may be perceived as burdensome and this may affect compliance. In the second part of this thesis, we examined in chapter 4 the relationship between self-reported compliance with carrying the EAI and the burden of treatment as perceived by food allergic adolescents and their parents. We found that the majority of food allergic adolescents and their parents were positive about the EAI which means that the burden of treatment was low. Parents were even more positive about the EAI than the adolescents themselves. This is in keeping with a previous study that showed that a prescription of an EAI did not increase the parental burden of food allergic children. In contrast to the low burden of treatment we found in food allergic patients, it was previously shown that patients with vespid allergy carrying an EAI reported a high burden of treatment. This may be due to the fact that an EAI is much more likely to be perceived as burdensome in vespid allergy, where it is a temporary measure until curative treatment makes the EAI superfluous. In food allergy it is the only meaningful measure offering protection when accidental food allergic reactions occur. Also, vespid exposure is usually limited to certain seasons while food allergen exposure may occur every day.

However, for food allergic adolescents, a higher burden of treatment was associated with self-reported non-compliance with carrying an EAI at all times. There may be a variety of reasons for non-compliance with carrying an EAI at all times by food allergic adolescents. As mentioned before we have to take into account the role of puberty in the developing adolescent brain. Adolescents are the age-group with the highest risk for food allergy fatalities. Food allergic adolescents take risks pertaining to their food allergy, including not carrying their EAI at all times. One reason for this may be caused by problems occurring at the time of the transfer of responsibility for managing their food allergy from their parents to themselves. They have to make decisions for themselves, which might be difficult and they may find risks difficult to judge, particularly with regard to eating outside home, buying food and reading and interpreting food labels (e.g. ‘may contain’). In our study, as in previous studies, we found that compliance is often selective, where food allergic adolescents report having the EAI with them in restaurants and during holidays more often than at other times. Reasons given by adolescents for eating ‘may contain’ food include low perceived risk of reaction and having previously eaten such foods before without developing allergic symptoms. A reason for not carrying an EAI at all times may be due to the design of the EAI itself. However in our study the inconvenience, shape and size of the EAI were not associated with self-reported non-compliance with carrying the device. Food allergic adolescents should be advised how best to ensure EAIs are accessible at all times, and should not vary such compliance according to their convenience.
important to develop interventions for food allergic adolescents to engage effective self-management of food allergy and anaphylaxis.

In *chapter 4* we also analyzed which factors contribute to the burden of treatment of the EAI as perceived by food allergic adolescents and their parents. Remarkably, the burden of treatment scores of both adolescents and their parents were not associated with health-related quality of life, trait anxiety, illness perception or perceived disease severity. However, our study showed that individuals not using available epinephrine perceived their disease as being less severe than those who did. Reasons given for non-use of the EAI were “other medication used”, “unsure if it was necessary”, “didn’t seem severe enough”, “unsure they ingested the food” and one patient did not dare to use the EAI. These explanations for the non-use of the EAI are similar to those found in a previous study. This suggests that perceived disease severity is a motivating factor for use of the EAI during an allergic reaction to foods.

The burden of treatment measure seems to measure a distinct concept related to compliance behavior and relatively subtle differences in burden of treatment have an impact on compliance. Further studies on factors influencing the burden of treatment of food allergic adolescents may be helpful in order to improve compliance.

Health-related quality of life is increasingly being recognized as an important outcome measurement for both research and clinical practice. Even though we demonstrated in *chapter 4* that the majority of food allergic adolescents and their parents perceived a low burden of treatment with carrying an EAI at all times, the burden of treatment was not associated with HRQL. In *chapter 5* we demonstrated that experiencing anaphylaxis or being prescribed an EAI did not seem to be related to HRQL of neither food allergic adults (≥ 18 years) nor children (8-12 years). We were surprised to find the limited impact of being prescribed an EAI on HRQL in food allergic children. A previous study by Pinczower et al., who used parent-proxy-reports to determine HRQL of food allergic children, found more impaired HRQL in children being prescribed an EAI compared to those who were not prescribed an EAI. However, they did not adjust the inverse relationship between EAI prescription and HRQL for self-perceived disease severity (FAIM). Their proposed relationship between EAI prescription and HRQL may thus be confounded by this self-perceived disease severity.

*Chapter 5* also demonstrated that important predictors other than self-perceived disease severity for HRQL of food allergic adults in Europe were type of allergenic food, type of symptoms, and gender. For children important predictors were type of allergenic food and country of origin. However, the explained variance in adults was high, suggesting that the factors discovered here are important predictors of HRQL in food allergic adults. Further study will be necessary to improve prediction in children. Moreover, an important issue is whether clinicians can use the factors identified in our study to manage their
food allergic patients. In principle, knowledge of factors contributing to poor HRQL could assist clinicians to identify at risk patients and might inform preventive and/or therapeutic interventions. Therefore, further research is required in this area.
**Part III. Non-use**

Successful treatment of anaphylaxis in the community relies on early and correct use of EAIs. In the Netherlands pharmacists supply EAIs to patients and have a crucial role in instructing patients in how and when to use EAI. In the last part of this thesis, *chapter 6* demonstrated that there are knowledge gaps about food allergy and its management among pharmacists in the Netherlands, and that they often give incorrect and incomplete demonstration of EAI use. Anaphylaxis usually occurs in the community, and thus all food allergic patients and their families should be provided with educational resources and training about when and how to administer an EAI. However, in *chapter 3* we showed that GPs in the Netherlands feel that giving instructions about how to use an EAI is the responsibility of the pharmacist, even though the NHG guidelines recommends giving clear instructions about the use of an EAI. The reason for not giving instructions about how to use an EAI may be due to the limited time available to the GP to see a patient. Another reason might be that the knowledge and/or practice behavior gaps of GPs in the management of food allergy. Therefore, it is important and necessary that pharmacists in the Netherlands know about food allergy and can demonstrate how and when to use an EAI to food allergic patients. Studies in this area are limited to evaluation of EAI demonstration rates and open assessment of EAI demonstration steps. There is, to our knowledge, no study assessing real-world EAI instructions and demonstrations by pharmacists in Europe. One study by Salter et al. assessed real-world community pharmacist demonstrations of EAIs in Australia. They showed that it was disappointing that only 18% of the pharmacist in Australia accurately demonstrated all four steps for auto-injector administration listed on the ASCIA action plan for anaphylaxis. This is a better result than our study, as our study showed that of the pharmacists in the Netherlands who agreed to demonstrate how to use an EAI, none of them demonstrated the device correctly according to a ten step scoring system. This is worrisome given the importance of timely and correct administration of epinephrine in case of a (severe) food allergic reaction.

The errors in demonstration in our study were similar to those observed in other studies. The most frequent errors in demonstration in our study were ‘massage injection site after use’ (100%) and ‘call the emergency number to ask for an ambulance and say ‘anaphylaxis” (100%). Other common errors were failure to state to press the tip of EAI firmly into mid-anterolateral thigh until a ‘click’ is heard confirming the injection has started, and incorrect positioning of the thumb over the needle of the EAI. The instructions given by the pharmacist in our study may lead to a patient not receiving epinephrine or unintentional injection of epinephrine. Although the true rate of occurrence of unintentional injection of epinephrine from auto-injectors is unknown, it is said to be increasing. Although dealing with the errors in device technique is very important, it may be difficult to achieve because aspects critical for correct epinephrine injection are
not intuitive. New approaches should be developed for EAI training. One may speculate that opportunities to improve EAI demonstrations by pharmacists to food allergic patients may be of international concern.

The gold standard in the diagnosis of food allergies is the DBPCFC. A DBPCFC can result in immediate onset of symptoms, but late onset of symptoms has also been reported. The time during which children are observed following a DBPCFC varies in clinical practice. Recommendations vary from between 2 to 24 hours. There is little data on late reactions (LRs) following DBPCFCs. Therefore, to compare our data about LRs following DBPCFCs (chapter 7) to other studies was difficult. A previous study by Wensing et al., in 26 adults having a peanut allergy, showed that no late or delayed reactions (≥2 hours) occurred after DBPCFC, apart from the reaction in one patient, who started vomiting 2.5 hours after the last ingestion of peanut. In chapter 7 we demonstrated that LRs in food allergic children and adolescents after DBPCFC do occur, even when taking the frequency of such “reactions” on placebo challenge days into account. However, isolated LRs occurred with comparable frequency after active and placebo challenges, suggesting that reported LRs in the absence of immediate reactions on the same day are likely to be chance occurrences rather than true allergic reactions.

In chapter 7 we also demonstrated that LRs are poorly predictable. The prediction model for the active challenge day accounted for only 8.0% of the variance in LRs. Variables that had a significant and independent contribution to this variance were: age, having rhino-conjunctivitis, having a hazelnut allergy, and the severity of the immediate reaction. Previous studies showed that patients who developed severe immediate reactions may experience severe late or recurrent reactions. This suggests that severe late reactions are associated with severe immediate reactions. Therefore, it is probably not necessary to observe food allergic children for more than 2 hours after DBPCFC except following exceptionally severe immediate reactions.

In chapter 7 we also demonstrated that the prediction model for the placebo challenge day accounted for only 12.1% of the variance in LRs. Variables that had a significant and independent contribution to this variance were: age, level of food-specific IgE, having rhino-conjunctivitis, and undergoing a DBPCFC with cashew or milk. In our study, we found a high rate of placebo events 110/400 (27.5%). For most of these events objective symptoms were reported. This is in keeping with the findings of a previous study describing symptoms during challenges with placebo. A variety of symptoms were reported after challenges with placebo in the present study, such as skin symptoms, gastro-intestinal symptoms, lower- and upper airway symptoms. No anaphylaxis was observed. Clinicians conducting DBPCFC tests should thus be aware that various types of symptoms, including objective symptoms, may occur after a placebo challenge day.

In conclusion, LRs in food allergic children after DBPCFC are poorly predictable, and
are generally not severe. Isolated LRs occur with comparable frequency after active and placebo challenges and are thus unlikely to be true allergic reactions. All LRs, including those on the placebo day, are more frequently reported in younger children. Children who do not experience severe immediate reactions may thus be safely discharged home 2 hours after a DBPCFC.
Recommendations for future research, policy and clinical practice

1. Food allergy and anaphylaxis today: the extent of the problem?

Although it is suggested that the prevalence of food allergy has increased, we have to keep in mind that reliable population-based data are limited.\textsuperscript{2,5,7,102} In the Netherlands, food allergies are thought to be responsible for several hundred hospital admissions every year.\textsuperscript{103} Although anaphylaxis to food is not uncommon, fatal food-induced anaphylaxis is very rare.\textsuperscript{104} Overall, the case fatality rate is low, below 0.0001%.\textsuperscript{104} However, the social impact of a fatality is enormous. Estimates of the actual prevalence of anaphylaxis are uncertain. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials in anaphylaxis. Therefore, to get a better insight in the physician visits for food allergies and anaphylaxis, hospital admissions and fatalities caused by anaphylaxis in the Netherlands, the first recommendation would therefore be to register them in a national database or to collaborate with an established international database. In 2006 an anaphylaxis registry was established in German-speaking countries and since 2011 several other European countries started to participate as well.\textsuperscript{105-107} The data can only be entered by an allergist from participating countries.\textsuperscript{106} The data cover demographical data, data on the elicitors, concomitant diseases, circumstances of the allergic reactions, and information about the treatment of affected patients.\textsuperscript{106} This registry is an important clinical epidemiological tool which allows the generation of research but also disease management-related questions.\textsuperscript{105} It may be of interest for health-care professionals and researchers in the Netherlands to participate in this anaphylaxis registry to know more about food allergies and anaphylaxis in the Netherlands, and to be able to make cross cultural comparisons. It would be recommended to allow also other health-care professionals than allergist to enter data in this anaphylaxis registry because not only allergist see food allergic patients. This will provide data about to whom patients turn to in case of allergic reactions (e.g. general practitioners, emergency departments, pediatricians, etcetera), and it will also possibly provide interesting data about EAI prescription practices by different health-care professionals and referral patterns.\textsuperscript{105}
2. Improvement of the diagnosis and management of food allergy and anaphylaxis in clinical practice

The management of food allergy and anaphylaxis is suboptimal by patients and their families, GPs, pharmacists, and schools. In addition, the general public has also significant variations in their knowledge about food allergy with many misconceptions.\textsuperscript{108} Therefore, until a cure is found for food allergies or better treatments developed, improving knowledge of symptoms, acute and long-term treatment, and prevention is the best strategy to protect food allergic patients from potentially fatal food allergic reactions. Interventions aimed specifically at knowledge gaps may help improve the quality of life of food allergic patients and their families.

Food allergic patients and their families

Food allergy is the trigger of anaphylaxis in the community. Therefore, it is of utmost importance to provide food allergic patients and their families with comprehensive information on food allergen avoidance, and prompt recognition and management of allergic reactions. Provision of an EAI and education on how and when to use it are also very important. Better knowledge is likely to diminish undiagnosed and untreated food allergy as well as inappropriate self-diagnosed food allergy. Moreover, food allergic patients and their families at high risk for anaphylaxis may become aware of the risk factors, allergic symptoms and potential severity of reactions. Educating food allergic patients to recognize severe allergic symptoms and when use an EAI and to seek medical help may lead to a better compliance and HRQL. Furthermore, when EAs are prescribed, patients should be educated properly about the need to carry an EAI at all times, and about how and when to use this device. Patient education should also identify and correct patients’ fears regarding EAI use to increase compliance. Using self-administration of an EAI (when needed) as a didactic tool (training program) may be more effective in alleviating fear and uncertainty incurred by the prospect of using the device. This may, in turn, lead to improved HRQL. Further research is needed and interesting to ascertain whether EAI self-administration does indeed have these effects. Patient education should also include instructions about how to read food ingredient labels. Patients can be referred to a dietician for education about this. It has been shown that correct food ingredient label identification was associated with prior instruction by a dietician.\textsuperscript{17} In addition, there is an increased use of defensive precautionary food labelling, such as ‘may contain’ or ‘may contain traces of’. Food allergic patients are advised to avoid these products, which limits them in their food choices and may also impair their HRQL.\textsuperscript{109} It has been previously reported that patients ignore warnings on the labels of pre-packed foods.\textsuperscript{110} This may be due to over-use of precautionary food labelling.\textsuperscript{111} Therefore, over-use of precautionary labelling should be avoided whenever possible, since every additional ‘may contain’ or
'may contain traces of' warning diminishes the impact, and thereby increasing the risk of unnecessary risk taking by food allergic patients and hence exposure.\textsuperscript{112} The food industry plays an important role in the safety of patients with food allergies. There are differences between countries regarding food labeling regulations, with a different level of mandatory allergen information and different allergens that require labeling.\textsuperscript{112} It would be advisable to harmonize food labeling regulations in the food industry worldwide in order to avoid unnecessary avoidance of food products and possibly increase the HRQL of food allergic patients.\textsuperscript{113} The food industry suffers from a lack of knowledge on the level of allergen required to elicit a significant allergic reaction, and also there are no analytical systems to detect small amounts of allergenic food.\textsuperscript{112} This may explain their defensive precautionary food labelling.\textsuperscript{111,112,114,115} To guarantee an absolute safety of food allergic patients seems impossible, however, evidence-based references are urgently needed to determine threshold levels for all allergenic food.\textsuperscript{112} With these evidence-based references food allergy management systems can be improved.\textsuperscript{116} If food allergen management by the food industry improves this may ultimately lead to decrease risk taking behavior in patients and may help improve their HRQL.

**General practitioners**

Not only food allergic patients and their families but also general practitioners (GPs) and other health-care professionals should know about food allergen avoidance, and prompt recognition and management of (severe) allergic reactions. The management of anaphylaxis requires special attention of GPs and they should be familiar with it. To GPs there is limited time to record the patient’s symptoms during a consultation and to think of a management plan. An allergy service is currently being developed to assist GPs to diagnose and treat food allergic patients.\textsuperscript{112} This allergy service may be useful to GPs in the management of food allergic patients.

Primary care guidelines in the Netherlands, the *food allergy guidelines of the Dutch College of General Practitioners* (NHG) guidelines differ from the internationally accepted guidelines for the diagnosis and management of food allergy and anaphylaxis.\textsuperscript{117} The NHG guidelines recommend that an EAI should only be prescribed after a previous case of anaphylaxis. The main difference that needs urgent attention is that risk factors for a life-threatening food-induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction. This implies that food allergic patients at high risk for anaphylaxis are not being prescribed an EAI, and put them at serious risk for a fatal allergic reaction. It would therefore be recommended to revise the NHG guidelines and put risk factors for a life-threatening food-induced anaphylactic reaction forward as a reason to prescribe an EAI. Furthermore, educational programs for general practitioners are needed to get acquainted with these
(inter)national guidelines. The educational programs should consist of at least the following items: (1) diagnosis of food allergy and anaphylaxis; (2) acute management of food allergy and anaphylaxis; and (3) long-term management of food allergy and anaphylaxis. The latter should preferably consist of prescription of EAI, including education on when and how to use it. This in turn may improve EAI use in the community and save lives. Also, it would be beneficial to implement clear referral criteria to assist GPs to refer patients to a specialist with specific expertise on allergology when this is needed.

**Pharmacists**

The EAACI food allergy and anaphylaxis guidelines, in the section on managing patients with food allergy in the community, intend to provide guidance to reduce the risk of accidental allergic reactions to foods in the community. Although these recommendations target numerous health-care professionals relevant to food allergy, pharmacists are surprisingly not included. Pharmacists play an important role in the management of food allergic patients, at least in the Netherlands. Here pharmacists and pharmacy staff dispense EAs to food allergic patients, and are required to provide all the appropriate medication-related information and instruction. However, Van Dijk et al. showed that when dispensing first (or repeat) prescription medications, pharmacy staff do provide medication-related information, but this information is incomplete according to the professional guidelines of the pharmacist organization. In addition, GPs in the Netherlands feel that giving instructions about how to use an EAI is the responsibility of the pharmacist. Therefore, it is necessary that pharmacists in the Netherlands know about food allergy and its management in order to give patients proper instructions on when and how to use an EAI. Therefore, the same recommendation is relevant as for GPs and other health-care professionals, educational programs are needed for pharmacists and pharmacy staff.

Pharmaceutical care in European countries are quite diverse because of differences in legal and political aspects of health-care systems and because practices have developed in different ways and at different paces. It may therefore be that the roles and responsibilities of pharmacists and pharmacy staff differ between European countries. According to ‘Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)’ (The Royal Dutch Pharmacists Association), the roles and responsibility of pharmacist do differ between European countries, mainly because of the different health-care systems. The roles and responsibilities have been evolving from product-oriented to patient-oriented service provision in the last two decades. Extended and new roles for pharmacists, as professionals of health care services and as scientists, are increasingly being recognized and valued. It would be of interest to investigate to what extent the roles and responsibilities differ between the different countries differ. According to KNMP,
pharmacists within Europe should be able to provide essential medicines expertise, and in case of an EAI they should be able to explain to a food allergic patients how to use an EAI. However, to our knowledge there are no studies investigating the knowledge, attitudes, and beliefs and management regarding food allergy and anaphylaxis among pharmacists elsewhere in Europe. It would be of interest to further investigate the cross-cultural differences in these areas, so that the management of food allergic patients by pharmacists may eventually be optimized and that guidelines for pharmacies can be developed and implemented.

**Schools and other public places**

Schools in the Netherlands all should have a system to identify food allergic children and should know how to manage food allergies and anaphylaxis. Pro-active management is important. School staff responsible for student supervision should be properly instructed to recognize the onset of an allergic reaction, including anaphylaxis, should know how and when to use an EAI and when to seek medical help. Schools should be allowed to have undesignated EAI available for use in students not being prescribed an EAI who experience a (severe) allergic reaction. In order to implement this, national legislation is needed. There should be a law for schools (and possibly also for all other public places) to ensure that all school boards have policies or procedures in place to address anaphylaxis in schools, which includes providing instruction to staff and guidance on the administration of medication. School, families, health-care professionals and the government should work together to create a safe educational environment. It would be of interest to investigate further the preparedness of schools for food allergy and anaphylaxis after implementing such a law. After this implementation it would be of interest to investigate whether or not this law caused a decrease in food allergy accidents in schools and whether or not the HRQL of food allergic children and their families improved.

There should also be a law that permits schools and other public places to have an undesignated EAI available for individuals experiencing anaphylaxis. The undesignated EAI should be available in unlocked an easily accessible places in schools and other public places and may be used by trained individuals. Preferably, it should be next to the Automatic External Defibrillators (AED) available in public places. In addition, companies who provide first-aid training courses for the general public should also cover food allergies, anaphylaxis and its management including how and when to use an EAI. This may lead to a better understanding of the seriousness of food allergies and anaphylaxis among the general public and better treatment of food allergic patients in case of emergency.
**General public**

Improved food allergy and anaphylaxis knowledge among the general public is desirable as the general public plays a significant role in the well-being of food allergic patients. Many people believe that they are allergic to foods or food ingredients. Estimates range from five to twenty per cent. This means that between one and three million Dutch people believe, rightly or wrongly, that they are allergic to specific foods. Besides this, food allergic patients are often misunderstood, ignored, bullied or not taken seriously, which may considerably affect their physical and psychological well-being. Therefore, raising public awareness about food allergy and anaphylaxis is needed. In recent years, the Dutch government has made an effort to increase the public awareness of several health-related topics by using campaigns. Surprisingly, food allergy and anaphylaxis has never been a topic until now. Food allergy and anaphylaxis may be particularly suitable for a governmental campaign as they seem to increase knowledge and change attitudes and behaviors.

**Epinephrine auto-injectors**

Worryingly, food allergic patients, food allergic adolescents in particular, are often poorly compliant and do not always carry and use their EAI. There are a number of possible reasons why poor compliance and non-use is so prevalent with EAsls amongst food allergic adolescents. An area of interest is the device itself to determine the ideal features of an EAI from a food allergic patient’s perspective. Interestingly, the ideal features from a patient’s perspective have not been investigated. Even though, in our study (chapter 4), the inconvenience, shape and size of the EAI were not associated with self-reported non-compliance with carrying the device, other studies showed that the size and shape discourages adolescents from carrying the EAI at all times. Therefore, research is needed to investigate the ideal features from a food allergic patient’s perspective, and researcher and pharmaceutical companies should together with food allergic patients to focus on a new design for an EAI. Further research is also needed regarding the impact of EAI prescription on HRQL. It may be interesting to investigate this prospectively and longitudinally. It would also be interesting to investigate the effects of the newly designed EAsls on compliance, non-use and HRQL of food allergic patients.

Prescription practices of EAsls differ considerably. There is data about absolute indications for a prescription of an EAI, however, there is no high quality data to help decide how many EAsls should be available to individual patients. A decision to prescribe one, two or more devices will be influenced by a number of factors (e.g. previous severity, access to medical care). The EAACI task force on anaphylaxis suggested indications for prescription of a second EAI. However, as mentioned above, food allergic adolescents are poorly compliant and do not always carry and use their EAI. It would
therefore be of interest to see whether or not prescribing more than one EAI has an effect on compliance, non-use and HRQL. Food-allergic patients are instructed to use their EAI if they have signs of an allergic reaction. However, there are different recommendations given by health-care professionals and manufacturers of EAI as to when an EAI should be administered. Administering an EAI after a patient has ingested the culprit food but is not yet experiencing allergic symptoms is unlikely to be necessary. However, to wait and see whether an allergic reaction progresses from mild to severe is not advisable. The reasons for the different recommendations are due to lack of studies evaluating acute interventions in anaphylaxis and making it therefore difficult to generate evidence based recommendations. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials in anaphylaxis. Therefore, even though fatal anaphylaxis is rare, early administration of an EAI may therefore be justified until experience proves otherwise.
3. Health related quality of life for patients with food allergy and minimal clinical important difference

Living with a food allergy may influence daily life in a negative way and may affect HRQL. The *Food Allergy Quality of Life Questionnaires* (FAQLQs) are disease-specific health-related quality of life questionnaires to may be used to measure the impact of food allergy on a patient’s HRQL. These reliable and validated questionnaires are important tools to measure a statistically significant differences or changes in HRQL. However, this does not necessarily mean that the observed change in quality of life is worthwhile or important to the patient. In order to understand, determine and interpret the magnitude of change, one requires an understanding of the minimal clinical important difference (MCID). A MCID is introduced as a threshold value for the smallest change in HRQL score that is actually perceived by the patient as being clinically meaningful. The MCID is defined as ‘the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive costs, a change in the patient’s management.’ The specific MCID of the FAQLQs has not been determined in earlier studies. The MCID of the disease-specific health-related quality-of-life questionnaires with a 7-point scale was commonly close to 0.5. We therefore recommend to determine the MCID of the FAQLQs, because it may give clinicians and researchers a better insight into whether a change in the FAQLQ score, for example before and after an intervention, is also a clinically important change.
4. Late reactions following DBPCFCs

An important point in the management of food allergic patients is the observation period after an allergic reaction. Besides immediate reactions, late reactions (LRs) have also been reported and may present with a variety of symptoms, of which anaphylactic symptoms are the most severe. Other variants of the usual monophasic anaphylaxis include biphasic anaphylaxis and protracted anaphylaxis. Position papers on anaphylaxis recommend that the observation should be individualized on the basis of the severity of the reaction.129 These recommendations for the observation period are for allergic reactions that occur in the community. A DBPCFC can also result in late onset of symptoms. The time during which children are observed following a DBPCFC varies also in clinical practice. Previous studies showed that patients who developed severe immediate reactions may experience severe late or recurrent reactions, even though such reactions may be uncommon. In our study no severe LRs were reported. Therefore, it is probably not necessary to observe food allergic children for more than two hours after DBPCFC except following exceptionally severe immediate reactions.

The prediction model for the active and placebo challenge day in our study accounted for only 8.0% and 12.1% respectively of the variance in LRs. Even though the LRs in food allergic children after DBPCFC in our study were not severe, they were poorly predicable. It would therefore be of interest to further investigate predictors of LRs after DBPCFC to be able to predict which food allergic patients are more at risk for LRs.
Concluding remarks

This thesis showed that the prevalence of food allergy in Dutch high-risk food allergic adolescents has not increased appreciably in the last six years. The calculated questionnaire-based prevalence of probable food allergy was 6.2%. It also showed that even though EAI ownership has improved marginally, there is still a substantial under-prescription of EAs in high-risk food allergic adolescents in the Netherlands. The under-prescription of EAs may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so. In this thesis we showed that food allergic patients at high risk for anaphylaxis who visit their GP are often not prescribed an EAI, even those with a previous allergic reaction. To those food allergic patients who are prescribed an EAI, this treatment may be perceived as burdensome and this may affect compliance. In this thesis we showed that the majority of food allergic adolescents and their parents were positive about the EAI. The perceived burden was thus low. However, for food allergic adolescents, a higher burden of treatment was associated with self-reported non-compliance with carrying an EAI at all times. The burden of treatment measure seems to measure a distinct concept related to compliance behavior and relatively subtle differences in burden of treatment have an impact on compliance.

In this thesis we showed that experiencing anaphylaxis or being prescribed an EAI did not seem to be related to HRQL of either food allergic adults (≥ 18 years) or children (8-12 years). We also showed that important predictors other than self-perceived disease severity for HRQL of food allergic adults in Europe were type of allergenic food, type of symptoms, and gender. For children important predictors were type of allergenic food and country of origin.

Food allergic patient being prescribed an EAI should receive training that covers avoidance strategies, recognition of symptoms, and most importantly when and how to administer an EAI. This thesis showed that there are knowledge gaps about food allergy and its management among pharmacists in the Netherlands. It also showed that food allergic patients at high risk for anaphylaxis who receive their EAI from a pharmacy in the Netherlands are often not or incorrectly instructed on how to use an EAI.

The time during which children are observed following a DBPCFC varies in clinical practice. Recommendations vary from between 2 to 24 hours. This thesis showed that late reactions in food allergic children and adolescents after DBPCFC do occur, are poorly predictable and are generally not severe. In our study no severe late reactions were reported. Therefore, it is probably not necessary to observe food allergic children for more than two hours after DBPCFC except following exceptionally severe immediate reactions.
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General discussion and future perspectives


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