

## Research Article

# Successful Implementation of Double-blind Placebo-controlled Food Challenge for Suspected Cow's Milk Protein Allergy in Youth Health Care: Experiences from a Municipal Healthcare Service in the Netherlands

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## ABSTRACT

**Background:** The double-blind, placebo-controlled food challenge (DBPCFC) is the preferred diagnostic test for suspected cow's milk protein allergy (CMA). A national multidisciplinary guideline published in 2012 recommends performing low-risk challenges at a Well-Baby Clinic (WBC) or general practitioner's (GP) office, instead of in a hospital setting. This article describes our lessons learned during the implementation of low-risk DBPCFCs at WBCs in the 's-Hertogenbosch region of the Netherlands. We also describe the results of the first 50 DBPCFCs performed there.

**Methods and Findings:** Children < 1 year old with suspected CMA in the 's-Hertogenbosch region were included in the study. Low-risk children were eligible for DBPCFC at the WBC, high-risk children were referred to the Jeroen Bosch Hospital (JBZ).

Organizational aspects during implementation included: funding structure, communication and coordination between professionals, availability of personnel, facilities and resources at the WBC, education of staff members and knowledge transfer to GPs.

The first 50 DBPCFCs at the WBC were performed between March 21, 2016 and July 3, 2017. In the same time period, 33 DBPCFCs were performed at the JBZ. The diagnosis of CMA was confirmed in 34% (WBC) to 45% (JBZ) of the children. One child (2%) tested at the WBC experienced an allergic reaction for which medication was needed, compared to 21% of the children tested at the JBZ ( $p = 0.0058$ ).

The savings for health insurance companies add up to €43,510, compared to the old situation where all 83 DBPCFCs would have been performed in a hospital setting.

**Conclusion:** The current study shows that it is possible, safe and cheaper to perform low-risk DBPCFCs at WBCs instead of hospital settings. Wider implementation can lead to substantial savings in national health care costs. The lessons learned during our study can be used by other Youth Health Care organizations when implementing DBPCFCs.

**Keywords:** Primary health care; Infant; Allergy; Cow's milk; Double blind method

## How This Fits in with Quality in Primary Care

### What do we know?

Infants with cow's milk protein allergy (CMA) present themselves with a broad variety of symptoms. Suspected (self-reported) CMA is far more common than confirmed (diagnosed) CMA, a discrepancy that can lead to unnecessary, potentially harmful elimination diets. The Double-Blind, Placebo-Controlled Food Challenge (DBPCFC) is the preferred diagnostic test for suspected cow's milk protein allergy (CMA).

### What does this paper add?

The current study describes the successful and safe implementation of low-risk DBPCFCs at Well-Baby Clinics. The lessons learned during our study can be used by other Youth Health Care organizations when implementing DBPCFCs. Wider implementation can lead to substantial savings in national health care costs.

## Abbreviations :

CMA: Cow's Milk Protein Allergy

DBPCFC: Double-Blind, Placebo-Controlled Food Challenge

GGD HvB: GGD Hart voor Brabant

GP: General Practitioner

IRKA: Implementatie Richtlijn KoemelkAllergie (implementation guideline cow's milk protein allergy)

JBZ: Jeroen Bosch Hospital

WBC: Well-Baby Clinic

YHC: Youth Health Care

## Introduction

Infants with cow's milk protein allergy (CMA) present themselves with a broad variety of symptoms. No single symptom is specific for the diagnosis of CMA. Suspected (self-reported) CMA is far more common than confirmed (diagnosed) CMA, with a prevalence of 17.5 and 2.4% respectively. This discrepancy can lead to unnecessary, potentially harmful elimination diets.

In 2012, the multidisciplinary guideline *Diagnosis of Cow's Milk Allergy in Children in the Netherlands* was published [1]. This guideline was created in a collaboration between the Dutch Society for Pediatrics, the Dutch Youth Health Care Association and the Dutch Society for General Practitioners. The guideline states that the Double-Blind, Placebo-Controlled Food Challenge (DBPCFC) is the preferred diagnostic test in case of suspected CMA. Also, the guideline recommends performing low-risk cow's milk food challenges at a Well-Baby Clinic (WBC) or a general practitioner's (GP) office, provided that the conditions are met to safely carry out these provocations there. This was in contrast to the state of affairs at that moment, with DBPCFCs only taking place in general or university hospital settings, and with - less reliable - open oral food challenges taking place at home or in WBCs [2].

In 2013, research was conducted [a] into how the guideline could be responsibly implemented in the catchment area of the Jeroen Bosch Hospital (JBZ), a large general teaching hospital in the city of 's-Hertogenbosch in the South of the Netherlands. The existing practice for diagnosing CMA in infants was assessed, and discrepancies with the desired method as described in the guideline were described. Also, a process diagram for the implementation of the guideline method was developed. The conclusion was that it would be feasible to perform the majority of the DBPCFCs at the WBC, provided the following conditions would be met:

- 1 An adequate funding structure (until January 2015, a DBPCFC in a WBC was not reimbursed by health insurance companies – in contrast to DBPCFCs performed in a hospital setting);
- 2 Adequate communication and coordination between care professionals; in this case the youth health care (YHC) physician, GP and pediatrician, enabling adequate "back-up" outside WBC office hours by a GP or a pediatrician;

- 3 Adequate availability of personnel, facilities and resources (test kit and emergency medication) at the WBC;
- 4 Education of staff members at the WBC;
- 5 Education of GPs regarding CMA in general, supporting them in working according to the guideline.

In January 2015, the National Health Care Institute [b] of the Netherlands published a report on the use of the DBPCFC in primary health care stating that the DBPCFC for suspected CMA should be included in the standard national health insurance coverage also when performed in primary health care [3]. They expected that would not only lead to better health care for children with suspected CMA, but also to a reduction of health care costs of approximately 1.6 to 2.5 million euros in five years.

In the light of this national development, the project *Implementatie Richtlijn KoemelkAllergie* (IRKA; 'implementation guideline CMA') was started. The IRKA-project is a collaboration between the JBZ and the GGD Hart voor Brabant (GGD HvB), a Municipal Healthcare Service responsible for the public youth health care in the 's-Hertogenbosch region, which has a birth rate of approximately 3000 per year. The primary objective (Part A) of the IRKA project was the implementation of the CMA guideline in the catchment area of the JBZ, more specifically, the implementation of low-risk DBPCFCs at the WBC of the GGD HvB (taking into account points 1 to 5 above). The secondary objective (Part B) of the IRKA project is to record the results of DBPCFCs carried out in both WBCs and the JBZ in encoded form, and to study, analyze and publish these data at a later date. This part of the project concerns a long-term observational study of unlimited duration. This article aims to describe our lessons learned in the process of implementing the low-risk DBPCFCs at the WBCs (Part A of the IRKA project). We will also describe the results of the first 50 DBPCFCs performed there (first results of Part B).

## Methods

### Patients

The inclusion criteria of the IRKA project are: all children (<18 years old) in the catchment area of the JBZ to whom the guideline *Diagnosis of Cow's Milk Allergy in Children in the Netherlands* applies; there are no exclusion criteria except lack of informed consent from the parents and, if applicable, the child ( $\geq 12$  years old). Children >1 year of age at initial diagnosis are considered as having a higher risk for serious adverse events and are not tested at the WBC. Therefore, only children aged <1 year of age are described here. Mead Johnson supplied the Nutramigen® DBPCFC test kits for the WBCs for the first fifty patients of the implementation project. Therefore, only children tested at the WBC with this provocation test kit are reported here. The study was approved by the medical ethical committee METC Brabant (NW-2016-11 IRKA).

<sup>a</sup> Executed by a master student in Supply Chain Management of Tilburg University, supervised in the clinic by author EdV.

<sup>b</sup> Every person in the Netherlands is entitled to health care offered in the basic care package. They all contribute to this through their health insurance. The National Health Care Institute ('Zorginstituut Nederland') advises the government on which types of health care should be included in the basic care package.

**Execution of DBPCFC**

DBPCFCs were performed according to the guideline *Diagnosis of Cow's Milk Allergy in Children in the Netherlands*. The ready-to-use Nutramigen® provocation kits provided by Mead Johnson consisted of bags of powder for placebo and for verum, which only need to be diluted with water. The test material is standardized and validated. The verum contains 4 grams of intact cow's milk protein per 300 ml of test feed.

**Organizational aspects**

*Funding structure*

In 2015, negotiations started between the GGD HvB and health insurance companies and in December 2015 the first contract with a health insurance company was signed. In September 2016, 'GGD GHOR Nederland' [c] started a project concerning the reimbursement of DBPCFCs performed by YHC-organizations leading to agreements between the participating YHC-organizations and three large health insurance companies with a combined market share of 64.5% in 2017.

<sup>c</sup> GGD GHOR Nederland is an association for public health and safety in the Netherlands. It is the umbrella organization of the 25 GGD (Municipal Health Service) and GHOR (Medical Aid Organization in the Region) offices. The main task as a national association is to collectively represent the interests of its members - the public health directors and the regional GGD and GHOR agencies - towards politics, (local) governments, cooperation partners, media and the public.

This meant that the participating YHC-organizations would only receive reimbursement for patients with a health insurance policy taken out with one of these insurance companies. We decided however not to exclude patients based on their health insurance company; all patients were eligible for a DBPCFC at the WBC without a personal financial contribution.

**Communication and coordination between professionals**

At the start of the IRKA project, agreements were made between the JBZ and GGD HvB regarding referral, aftercare and reporting (Tables 1 and 2). Information flyers, website-texts and a referral form were developed. In January 2016, all YHC-physicians, GPs and dieticians in the 's-Hertogenbosch area were invited to a lecture concerning the diagnosis of CMA in primary health care. In this lecture information was given on CMA, the diagnosis according to the guideline and the process of a DBPCFC. Also, attendees were informed about the arrangements concerning the referral of children with suspected CMA. The arrangements were further exemplified in staff meetings in both the JBZ and the GGD HvB.

**Availability of personnel, facilities and resources at the WBC**

Three YHC-physicians and two YHC-nurses were recruited at two WBC-locations selected as suitable locations for DBPCFC's. The YHC-nurse had the following tasks: an intake with standardized questions, preparation of the test feedings,

**Table 1: Agreements between the Jeroen Bosch hospital and GGD Hart voor Brabant**

Children with a higher risk of serious adverse events during the DBPCFC (see Table 3) are referred to the JBZ as before. Children without these risk factors (i.e. low risk children) are tested at specifically appointed WBC-locations. Other care professionals in the region (YHC-physicians of other WBC-locations, GPs and pediatricians of the JBZ) can refer children to these locations for a DBPCFC. The locations which perform the DBPCFC have one shared email address for referrals and consultation. During office hours (between 8 am and 5 pm) the nurse of the WBC is the first contact person for parents. Parents receive a direct telephone number of the nurse. The YHC-physician is available for consultation when needed. Outside office hours (between 5 pm and 8 am the next morning) parents can contact the emergency department of the JBZ, where the pediatrician will assess the child if necessary. As a reference for the pediatrician parents receive a form on which the findings thus far have been noted. The result of the DBPCFC is communicated to the GP, YHC-physician and, if concerned, the pediatrician. **Abbreviations:** DBPCFC, double-blind placebo-controlled food challenge; JBZ, Jeroen Bosch hospital; WBC, well-baby clinic; YHC, youth health care; GP, general practitioner.

**Table 2: Children with a higher risk of serious adverse events during DBPCFC**

Serious and life-threatening reactions after ingestion of or contact with cow's milk such as:

- Anaphylactic reaction of Müller stage 3 or 4
- Respiratory symptoms such as asthmatic symptoms, inspiratory stridor, throat swelling, etc.
- Collapse or shock
- Severe gastrointestinal complaints during or shortly after ingestion

Symptoms other than described in the guideline

Angioedema

Asthma(-like) symptoms for which maintenance medication is used or regular use of bronchodilators is necessary

Severe therapy-resistant constitutional eczema (TIS-score ≥6)

Children older than one year at initial diagnosis

Infants receiving an amino acid-based formula\*

**Abbreviations:** DBPCFC, double-blind placebo-controlled food challenge; TIS-score, three-item severity score [6].

\* Amino acid-based formula is only prescribed in the hospital, according to the multidisciplinary guideline 'Diagnosis of Cow's Milk Allergy in Children in the Netherlands' (Sprikkelman, et al. 2012). Therefore, these children remain under the care of a pediatrician but are not necessarily at higher risk of serious adverse events during DBPCFC.

administration of the test feedings according to the guideline, identifying possible allergic reactions and instruction of parents for registration of possible allergic reactions at home. The nurse remained in the direct vicinity of the child during the entire test and observation period. The YHC-physician had the following tasks: performing physical examination prior to the test and after the observation period, assessing whether food challenge can take place for the child in question, assessing any possible allergic reactions, treatment of allergic reactions when necessary, and deciding to stop or continue the challenge when reactions occur. The YHC-physician was immediately available for consultation or action throughout the test. In order to treat allergic reactions when necessary, adrenalin auto-injectors (0,15 mg/dose) and desloratadine syrup (0,5 mg/ml) were present at the WBC-locations.

#### **Education of staff members at the WBC**

The YHC-physicians and YHC-nurses performing the DBPCFCs attended the lecture mentioned above. They were further instructed by the staff of the JBZ and observed food challenges performed there. The physician assistant of the JBZ (HD) was present during the first DBPCFCs performed at the WBC. During the following DBPCFCs the staff of the JBZ was available for consultation by phone. Also, a number of evaluation meetings between the staff of the WBC and JBZ were held.

#### **Knowledge transfer to GPs**

All GPs in the catchment area of the JBZ were invited to the lecture on CMA mentioned above, but only two attended. Additionally, all GPs in the area received information on the DBPCFCs performed at the WBCs through the regular GP-newsletter of the JBZ in April 2016.

#### **Collection and storage of data**

Patient data were recorded in Kidos, the electronic patient file of the GGD HvB. The privacy and storage period of this data was regulated at that time by the *Wet bescherming persoonsgegevens (Wbp)*, a national law for the protection of personal information, now replaced by the European General Data Protection Regulation) and the *Wet op de geneeskundige behandelingsovereenkomst (WGBO)*, a national law defining the rights and obligations of patients).

Data collected for part B of the study concerned age, gender, presenting symptoms, type of cow's milk free diet, the course of the provocation (including end-result and any adverse events) and follow-up one month after the DBPCFC. For comparison, similar data were collected on the DBPCFCs performed in the JBZ in the same time period. The data were extracted from the patient files and stored in an electronic Case Record Form (Research Manager®, Cloud9 software). The data were encrypted and patients were indicated with a study number. Only the principal investigator Prof. de Vries and the treating physician (assistant) were authorized to trace the code to the individual patient.

#### **Statistical analysis**

The data were initially analyzed using descriptive statistical methods, followed by univariate non-parametric techniques (Fisher's exact and Chi-squared test).

## **Results**

### **Patients**

The first 50 DBPCFCs in low-risk children aged <1 year were performed at the WBC between March 21, 2016 and July 3, 2017. 65 children fulfilled the inclusion criteria during this period, 9 children were excluded from the study because of lack of informed consent, an additional 6 children were excluded from the analysis because they were tested with a provocation test kit other than Nutramigen®. In 3 children the DBPCFC was initially not completed, due to an intercurrent infection obscuring the result of the test; 2 of these children completed the DBPCFC at a later stage. In the same time period, 33 DBPCFCs in children aged <1 year were performed at the JBZ. The results of the total 83 DBPCFCs performed are shown in Table 3.

The 50 children tested at the WBC were referred by YHC-physicians (90%) and pediatricians (10%). There were no referrals from GPs to the WBCs. In line with the methods of the study, all DBPCFCs performed at the WBCs were low-risk. However, of the DBPCFCs performed at the JBZ, 76% were also low-risk. These were either children residing in municipalities outside the catchment area of the GGD HvB region 's-Hertogenbosch, or children that were tested with a test kit that was not available at the WBCs at that time.

The diagnosis of CMA was confirmed in 34% of the children tested at the WBC and in 45% of the children tested at the JBZ. The rate of successful reintroduction one month after a negative DBPCFC ranged between 56% (JBZ) and 61% (WBC). Both differences were not statistically significant. Only one child (2%) tested at the WBC experienced an allergic reaction for which medication (desloratadine) was needed, compared to 21% of the children tested at the JBZ ( $p = 0.0058$ ).

The parents of one child tested at the WBC contacted the pediatrician outside office hours (2%). The symptoms of this child were interpreted by the pediatrician as due to an intercurrent infection unrelated to the DBPCFC. The parents of 2 children (6%) tested at the JBZ contacted the pediatrician outside office hours (no significant difference).

### **Organizational aspects**

#### **Funding structure**

In 32 of the 50 (64%) performed DBPCFCs at the WBCs the child had a health policy taken out with a contracted health insurance company and thus costs could be claimed by the GGD HvB. In 2017, the GGD HvB received a maximum of €726.15 for each chargeable DBPCFC, the rate set by The Dutch Healthcare Authority [4]. In comparison: the maximum rate for a DBPCFC performed at the JBZ in 2017 was €1,596.35 [5].

If all 83 DBPCFCs in this study would have been performed at the JBZ, the costs for health insurance companies would have been €132,497.05 [ $83 \times €1,596.35$ ]. In the current situation, with 33 DBPCFCs performed at the JBZ and 50 DBPCFC performed at the WBC, the costs would have been €88,987.05 ( $50 \times €726.15$ ) + ( $33 \times €1,569.35$ ), if all 50 DBPCFCs performed at the WBCs could have been charged. This adds up to a saving of €43,510 for health insurance companies.

**Table 3: Children with a higher risk of serious adverse events during DBPCFC**

| Location of DBPCFC  | WBC<br>N = 50 | JBZ<br>N = 33 | Statistical<br>significance |
|---|---------------|---------------|-----------------------------|
| <b>Referring physician: n (%)</b>   |               |               |                             |
| - Youth Health Care Physician   | 45 (90%)      | 3 (9%)        | $p < 0.00001$ (FE)          |
| - General Practitioner  | 0 (0%)        | 1 (3%)        | $p = 0.3976$ (FE)           |
| - Pediatrician  | 5 (10%)       | 29 (88%)      | $p < 0.00001$ (FE)          |
| <b>Risk group: n (%)</b>  |               |               |                             |
| - Low risk  | 50 (100%)     | 25 (76%)      | $p = 0.0004$ (FE)           |
| - High risk   | 0             | 8 (24%)       |                             |
| <b>Provocation test kit used: n (%)</b>   |               |               |                             |
| - Nutramigen®   | 50 (100%)     | 9 (27%)       | $p < 0.00001$ (FE) *        |
| - Pepti®  | 0             | 8 (24%)       |                             |
| - Neocate®  | 0             | 16 (49%)      |                             |
| <b>Result of DBPCFC: n (%)**</b>  |               |               |                             |
| - Positive  | 17 (36%)      | 15 (45%)      | $p = 0.613341$ ( $\chi^2$ ) |
| - Negative  | 28 (60%)      | 16 (48%)      |                             |
| - Inconclusive  | 2 (4%)        | 2 (6%)        |                             |
| <b>Medication given during DBPCFC: n (%)</b>  |               |               |                             |
| - Adrenalin   | 0             | 1 (3%)        | $p = 0.0058$ (FE)           |
| - Desloratadin  | 1 (2%)        | 6 (18%)       |                             |
| - Total   | 1 (2%)        | 7 (21%)       |                             |
| <b>Consultation of pediatrician outside office hours: n (%)</b>                           | 1 (2%)        | 2 (6%)        | $p = 0.56$ (FE)             |
| <b>Successful reintroduction of cow's milk &lt;1 month after a negative DBPCFC: n (%)</b> | 17 (61%)      | 9 (56%)       | $p = 1$ (FE)                |

\* Nutramigen® versus other test feeds.

\*\* Three DBPCFCs performed at the WBC were not completed due to an intercurrent infection obscuring the test results. Therefore, the results here do not add up to n=50.

**Abbreviations:** DBPCFC: Double-Blind Placebo-Controlled Food Challenge; FE: Fisher's Exact test; WBC: well-baby clinic; JBZ : Jeroen Bosch hospital;  $\chi^2$  : Chi-squared test.

### Logistics

Our team of three YHC-physicians and two YHC-nurses proved to be too small to guarantee sufficient testing capacity at all times.

Therefore, the team was expanded to four YHC-physicians and three YHC-nurses performing the DBPCFCs at three locations. Also, parents shared useful feedback regarding the locations: they suggested to avoid combining consultation hours with the DBPCFCs and a separate room for the children to sleep in to prevent undue agitation in the test children, as well as availability of Wi-Fi to ease the waiting during the test hours for themselves. Referral to the WBC by GPs did not occur, we therefore sent a reminder to them via a regular newsletter from the GGD in December 2017. Also, GPs can now refer children using a shortened form on the GGD website.

### Training

The YHC-staff reported a learning process during the execution of the DBPCFCs. Although the protocol seems clear, in day-to-day practice there is often a 'gray area'. Examples are the assessment whether or not to start the DBPCFC when there are mild complaints such as a runny nose, teething or some moodiness of the child. Also, the interpretation of subjective symptoms during and after the provocation test can be difficult.

Over time experience was gained in discussing the test result with parents, dealing with parents who doubt the test results and with symptoms that occur during the reintroduction period of cow's milk after a negative DBPCFC. There was a low threshold for the YHC-staff to consult the JBZ-staff for this. Also, periodic evaluation meetings between the WBC and JBZ added to the knowledge and experience of the YHC-staff.

### Discussion

The current study shows that it is possible to safely implement low-risk DBPCFCs at a WBC. Albeit the patient groups were relatively small, at this point there are no indications for a different outcome of DBPCFCs performed at the WBCs compared to the JBZ regarding the test results nor regarding the rate of successful reintroduction of cow's milk after a negative DBPCFC. Also, there was a low rate of serious adverse events in DBPCFCs performed at the WBCs, indicating that adequate selection of low-risk children is feasible. Based on the good experiences in this project, the GGD HvB decided to continue performing DBPCFCs and to further implement the procedure in other regions.

Our lessons learned can be used by other YHC-organizations in implementing DBPCFCs. A good collaboration with the hospital is necessary, both concerning referrals and back-up

outside office hours as well as concerning the education of the WBC-staff. The project taught us that it is necessary to ensure the availability of sufficient educated staff at the WBC to substitute in case of sudden absence of a colleague. Also, when choosing WBC-locations to perform the DBPCFCs, one should keep in mind the comments from parents: preferably a location where parents and children can retreat to a quiet room where children can sleep. Besides, attention is needed regarding the involvement of GPs.

Further implementation of DBPCFCs in WBCs may lead to savings in national health care costs, considering a DBPCFC performed at a WBC is cheaper than a DBPCFC performed in a hospital setting. A further reduction of costs can be expected as more low-risk children will be referred to the WBC instead of the hospital. This conclusion is not only based on the findings in our study, but is supported by calculations made by the National Health Care Institute in their report on the use of the DBPCFC in primary health care [3]. They calculated that in five years the costs of implementation of DBPCFCs in primary health care are compensated by the reduction of costs for unnecessary elimination diets. However, to keep the current practice feasible in the future the number of contracted health insurance companies should be expanded.

We are currently conducting follow-up research regarding the effects of the implementation of DBPCFCs in the WBCs, to assess whether this is leading to better health care for children with suspected CMA as expected by the National Health Care Institute: are the less reliable open oral food challenges being replaced by the use of the DBPCFC, and is there a decrease in unnecessary elimination diets? If this is indeed the case, it would further strengthen the new policy.

## Conclusion

The current study shows that it is possible, safe and cheaper to perform low-risk DBPCFCs at WBCs instead of hospital settings. Wider implementation can lead to substantial savings in national health care costs. The lessons learned during our study can be used by other YHC-organizations when implementing DBPCFCs. Further research on the effects of the implementation of DBPCFCs at WBCs on patient care is useful

and is currently being conducted.

## Ethical approval

The study was approved by the medical ethical committee METC Brabant (NW-2016-11 IRKA).

## Source of funding

Mead Johnson supplied the Nutramigen® DBPCFC test kits for the WBCs for the first fifty patients of the implementation project.

## Conflicting interests

There are no conflicting interests.

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