SUMMARY STUDY RESULTS

1.1. Summary

A non-interventional, open observational non-inferiority study was conducted in two cluster-assigned cohorts of children aged 14 months to investigate reactogenicity of NeisVac-C® vaccines manufactured at two different production sites, the "old" production site in Beltsville, MD, USA and the "new" production site in Orth/Donau, Austria (to be referred to as "old NeisVac-C®" vs "new NeisVac-C®") and given simultaneously with measles-mumps-rubella vaccine, by web-based intensive monitoring using questionnaires covering days 0-4, 5-14 and 15-28 post vaccination.
In the routine setting of the Netherlands Immunization Program, 2727 children were evaluable for the primary endpoint. Old NeisVac-C® was given to 1729 and new NeisVac-C® to 998 children. Enrollment was from May 2014 to April 2016.
Primary endpoint: we found similar incidences of rectally measured fever ≥38.0°C during days 0 to 4 after vaccination with new NeisVac-C® versus old NeisVac-C® (8.2% and 8.3% respectively), and similar relative risk (unadjusted 0.99, adjusted 0.96) with an upper margin of 95% CI below 1.50. Non-inferiority of the new vaccine to cause more fever than the old vaccine was demonstrated.
Secondary endpoints: NeisVac-C® related injection site reactions and systemic reactions were found in both groups at similar proportions of children from days 0 to 4, and days 5 to 28.
It was concluded from the study results that for both endpoints new NeisVac-C® is non-inferior to old NeisVac-C®. Both have similar reactogenicity as assessed by rectally measured fever ≥38.0°C, injection site reactions, and systemic reactions.

1.2. Structured abstract

1. Title

A non-interventional, open observational non-inferiority study in two cluster- assigned cohorts of children aged 14 months into the safety of NeisVac-C® vaccines manufactured at two different production sites and given simultaneously with measles-mumps-rubella vaccine, assessed by web-based intensive monitoring
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2. Keywords

NeisVac-C® - reactogenicity – toddlers - post authorization safety study – ENCePP study

3. Rationale and background

To compare the safety of the NeisVac-C® vaccine bulk material produced at Pfizer Inc (formerly Baxter Ltd) in Orth/Donau (new) with the material produced in Beltsville (old) in toddlers aged 14 months, administered simultaneously with measles-mumps-rubella (MMR) vaccine. The study was done at the request of the MHRA as primary reviewer of the dossier applying for approval of a new production site. MHRA required a post-authorization safety study (PASS) to obtain additional clinical safety data comparing vaccines from the old and the new production facility. It was specifically asked to monitor fever (rectally measured, 38 Celsius or above) during the first 4 days after vaccinations with old or new vaccine. Moreover it was proposed that the study would last at least one year to cover possible seasonal influence.

The Netherlands was selected for this study being a country where MenC vaccine is not given simultaneously with other non-replicating vaccines but only with live attenuated MMR vaccine. Therefore, fever during days 0-4 may be ascribed to only one product, i.e. MenC vaccine, while fever due to MMR vaccine is expected to occur later (between 5 to 12 days after vaccination).

4. Research question and objectives

The objective of this study was to show that the vaccines produced at the new production site in Orth/Donau, Austria would not be more reactogenic than the vaccines produced at the old production site in Beltsville, MD, USA. Fever defined as a rectally measured temperature ≥38.0°C during days 0 to 4 after vaccination was used as the most important marker for reactogenicity.
The primary endpoint is the proportions of subjects with fever reactions within 4 days after administration.
The secondary endpoints are proportions of subjects with
- solicited other systemic and local reactions within 4 days after administration
- non-solicited other systemic and local reactions within 4 days after administration
- non-solicited other systemic and local reactions from 5 to 28 days after administration

For these endpoints possible differences between old and new vaccines were assessed.

5. Study design

Non-interventional, open observational non-inferiority study with two cluster- assigned cohorts using three questionnaires to obtain data covering days 0-4, 5-14 and 15-28 after vaccination.

6. Setting

The study was conducted as an intensive web-based monitoring of children vaccinated according to the regular National Immunization Program. All children in The Netherlands receive childhood vaccinations at baby clinics. Study regions were defined where Child Health Care organizations agreed to facilitate the study. The baby clinics were supplied with either 'old' or 'new' NeisVac-C® vaccines according to a distribution plan that aimed at a 50-50% distribution of each. Thus, one clinic was supposed to vaccinate children with only 'old' or only 'new' vaccine. The study started in the province of Noord-Brabant (5 organizations, 135 clinics), and because of lower than expected enrollment, extended to two more provinces (Zeeland with one organization, and Limburg (with 3 organizations in the southern part). Baby clinic staff did not enroll children but facilitated that parents of the children had reliable data on the vaccinations to complete the web-based questionnaires if they decided on their own to enroll their child in the study.
Thus, two study groups of similar size were to be formed according to the MenC vaccination that was given at the baby clinics, i.e. NeisVac-C® from either the new production site in Orth/Donau or old production site in Beltsville. All children were given MMR vaccine (M-M-R-VaxPro®) simultaneously.

7. Subjects and study size

At least 2430 healthy toddlers aged 13-18 months old, eligible to receive MenC and MMR vaccinations according to the NIP, were required to study the primary endpoint parameter with sufficient power.
Inclusion criteria were age 13-18 months old (boundaries included) and eligibility to receive MenC and MMR vaccinations according to the NIP.
Exclusion criteria were children receiving either MenC or MMR vaccine and not both at the same time, and children with parents that are not able or willing to understand or complete the questionnaires.

Enrollment for the study started May 2014, and ended per April 2016. In April 2015 the recruitment area was enlarged because enrollment rates were lower than expected. There were 42,704 parents addressed to participate, and 3002 reported for enrollment. Of these, 2727 fulfilled criteria for in- and exclusion, and had valid data for questionnaire 1. Old NeisVac-C® was given to 1729 children, and new NeisVac-C® to 998 children. Despite these unequal proportions of children that received old or new NeisVac-C® (63 vs 37%), a revised power calculation indicated that sufficient numbers of children were enrolled to evaluate the primary endpoint, after which enrollment was stopped.

8. Variables and data sources

Primary: reactogenicity defined as % of children with rectal temperature 38.0°C and above during the first 4 days after vaccination.
Secondary: other solicited and unsolicited complaints and symptoms at the injection site as well as systemic reactogenicity.
These parameters were collected using three questionnaires, to be completed by the parents. Questionnaire 1 covered days 0-4 after vaccinations, questionnaire 2 covered days 5-14, and questionnaire 3 covered days 15-28. Parents had up to 4 days after each period to complete the questionnaire in order to obtain best remembered and most accurate data.
The primary endpoint of the study, fever cases observed within 4 days after vaccination was analyzed using logistic regression with vaccination groups ("old" / "new" NeisVac-C®) and potential confounders as explanatory factors, applying a log link in order to obtain relative risk estimates at the end. Relative risk and its 95% CI of occurrence of fever cases with the "new" and "old" NeisVac-C® was calculated from the regression model assessing a potential increase of fever reactions with the "new" NeisVac-C®. If the upper limit of the 95% CI was below 1.5 then the "new" NeisVac-C® was considered to be non-inferior to the old NeisVac-C® as far as fever reaction is concerned.
The secondary endpoints were analyzed similarly and descriptively without the non-inferiority considerations.

9. Results

Both groups were comparable for age, weight and height, house hold size, daycare attendance and medical history. The study ran for over one year to account for seasonal variations.

The main result was that the incidence of fever (38.0°C or above) during pooled days 0-4 was similar for both groups: 8.2% for children that received new NeisVac-C®, and 8.3% for children that received old NeisVac-C®. Also for the other endpoints no differences were found. Incidence of reactions at the injection sites of NeisVac-C® occurred in 3.4% in old NeisVac-C® and 3.3% in new NeisVac-C® recipients, and systemic reactions in 32.2% and 35.2% respectively. For the primary endpoint of fever the relative risk for the new vaccine to cause a higher incidence of fever than the old NeisVac-C® was 0.99 in the unadjusted analysis, and 0.96 for the adjusted analysis, with upper limits of the 95% CI of 1.28 and 1.24 respectively, remaining below the predefined non-inferiority margin of 1.50.

Also for the secondary endpoints similar incidences were found: reactions at NeisVac-C® injection sites during days 5 to 28 in 0.3% and 0.2% for old and new NeisVac-C®, and systemic reactions in 47.6% and 48.1%, respectively. In 13 children convulsions were reported, 11 of them had febrile convulsions. All occurred within 14 days after vaccinations, with similar numbers in the old and new vaccine groups.

During the study, 11 subjects experienced a Serious Adverse Event. The events did not indicate a higher risk associated with the new NeisVac-C® compared to the old NeisVac-C®. The nature of these events was within the expected pattern of earlier reported symptoms or disease, including coincidental infections as a plausible cause..

10. Discussion

The study was conducted to assess non-inferiority of new NeisVac-C® compared to old NeisVac-C® with regard to fever (rectally measured 38.0°C or above) occurring from 0 to 4 days after vaccination as a primary endpoint. The study demonstrated that new NeisVac-C® had a similar profile of reactogenicity as old NeisVac-C®, with similar rates of fever during the observation period: 8.2 vs 8.3% respectively, and similar relative risk values (0.99 and 0.96 for unadjusted and adjusted RR analysis) to cause fever.

During 5 to 28 days the pooled incidence of fever was higher than during days 0 to 4. These differences may be associated with the longer period of observation, but also because the MMR vaccine given simultaneously with NeisVac-C® is known to cause fever in 10-20% of recipients during this period.

The observed incidence of fever during days 0 to 4 of 8.2-8.3% is somewhat higher than the incidence found before in a similar study in Netherlands children (approximately 6%). A reason for this difference cannot be concluded.

The study was conducted in children that were given the vaccines as a part of the routine schedule in the National Immunization Program, in approximately 7% of the eligible population. The study population is considered representative for the general eligible population.

It was concluded that the NeisVac-C produced at the new production facility in Orth/Donau, Austria is non-inferior to the NeisVac-C produced at the old production facility in Beltsville, MD, USA.

11. Marketing authorization holder

NeisVac-C® vaccine: Netherlands Marketing Authorization Number RVG 26343, ATC code J07AH07, a product of Pfizer Inc. Marketing authorization holder of NeisVac-C® vaccine is Pfizer Netherlands: Rivium Westlaan 142, 2909 LD Capelle aan den IJssel, The Netherlands.

12. Names and affiliations of principal investigators

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