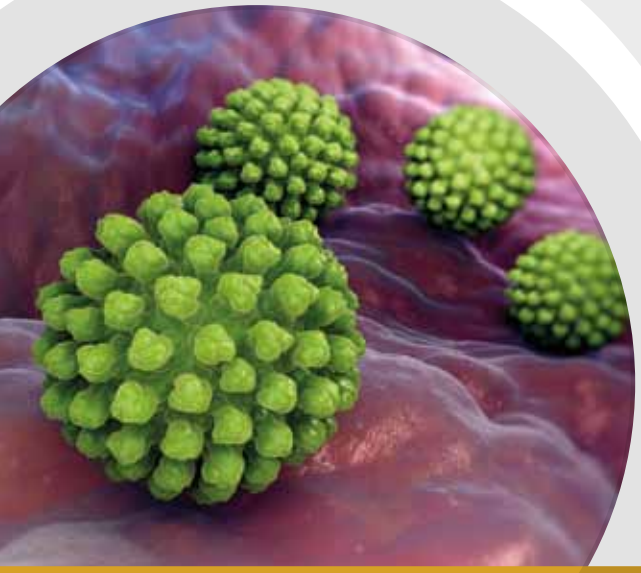

TECHNICAL DOCUMENT

Effectiveness of rotavirus vaccination – Generic study protocol for retrospective case control studies based on computerised databases

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Effectiveness of rotavirus vaccination

Generic study protocol for retrospective case control studies based on computerised databases

This technical document was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by ECDC project manager Kari Johansen and produced by Epiconcept, France.

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Suggested citation: European Centre for Disease Prevention and Control. Effectiveness of rotavirus vaccination - Generic study protocol for retrospective case control studies based on computerised databases. Stockholm: ECDC; 2013

Stockholm, April 2013

ISBN 978-92-9193-397-6

doi 10.2900/64929

Catalogue number TQ-32-12-488-EN-N

Contents

Abbreviations

AGE	Acute gastroenteritis
EU	European Union
OR	Odds ratio
RV	Rotavirus
SAGE	WHO Strategic advisory group of experts on immunization
US	United States
VE	Vaccine effectiveness
WHO	World Health Organization

Introduction

Rotavirus (RV) is the most common cause of gastroenteritis in children worldwide. It has been estimated that by the age of five years, nearly every child in the world has been infected with RV at least once. It is estimated that RV infections lead to about 700 000 outpatient visits resulting in >87 000 hospitalisations in Europe every year [1]. The infections, occurring mainly in young children less than three years of age are associated with direct costs for hospitalisation and indirect costs for family members taking care of their sick children and occasionally developing gastrointestinal symptoms of their own preventing them from their daily duties.

In 2006, two new live, oral, attenuated RV vaccines were licensed for infants < six months of life: the monovalent human RV vaccine (Rotarix, GSK) [2] and the pentavalent bovine-human, reassortant vaccine (RotaTeq, Sanofi Pasteur MSD) [3].

Rotavirus vaccination was first recommended to US children in February 2006. Subsequently, in April 2009 the WHO Strategic Advisory Group of Experts (SAGE) recommended RV vaccine for all children [4]. Worldwide, a number of countries have adopted this recommendation and implemented RV vaccines in their paediatric immunisation programmes, but only a limited number of the European countries have done so.

Clinical trials from the two licensed vaccines show high efficacy against the serotypes included in each of the vaccines [5, 6].

In addition to efficacy results, after licensing a new vaccine, it is crucial to conduct studies evaluating the direct effect of the vaccine when using it routinely in the population (vaccine effectiveness studies).

Rationale

In the European Union (EU), routine RV vaccination of infants at national level has been introduced with one or two vaccine brands in Finland, Austria, Luxembourg and Belgium within well-baby clinics, or administered by general practitioners and paediatricians. In other EU Member States , rotavirus vaccine is available but not included in the paediatric vaccination programme. Some Member States or regions have computerised electronic databases from which information on rotavirus cases and vaccination status can be extracted. When available, these databases represent an excellent setting to estimate rotavirus vaccine effectiveness.

A generic protocol is presented for developing case control studies to assess the effectiveness of the RV vaccination in EU Member States. In this protocol, we describe methods to estimate rotavirus vaccine effectiveness using data already available in existing databases (retrospective studies). A second generic protocol will propose prospective cohort study designs to estimate rotavirus vaccine effectiveness.

This generic protocol will need to be adapted to each country/region's specific situation.

In order to conceive each study, the following information for the specific study setting should be reviewed:

- date of introduction of the vaccine(s);
- vaccination calendar;
- target groups for vaccination;
- estimated vaccination coverage;
- sources to identify RV related outcomes;
  - hospital registers to identify RV hospitalisation related outcome (i.e. hospitalisations for RV acute gastroenteritis, RV laboratory tests)
  - computerised primary care databases
  - specific rotavirus surveillance systems (i.e. laboratory surveillance, hospital surveillance, primary care surveillance)
  - laboratory registers
- sources to document vaccination status;
- sources to document potential confounding factors;
- ethical/consent requirements;
- Each country/region to describe the specific background for the country/region: introduction of vaccine, calendar, previous studies, surveillance data, etc.

Objectives

General objective

To estimate rotavirus vaccine effectiveness against a laboratory confirmed rotavirus related outcome in the population eligible for the vaccine in the country/ region site.

- Each country/region to define the outcomes to be measured (i.e. diarrhoea consultation with laboratory confirmed rotavirus, hospitalisation for acute gastroenteritis with laboratory confirmed rotavirus).

Secondary objectives

To estimate the effectiveness of the rotavirus vaccine:

- By age group among the population eligible for the vaccine
- For different number of doses received
- For different serotypes
- For different vaccines (if different vaccines are used).
- Each country/region to define the secondary objectives

Methods

Study design

Case-control study.

Study population

The study population is composed of children belonging to the birth cohorts eligible for vaccination and living in the catchment area of the laboratory/practitioners/hospitals participating in the study, for whom information is included in the database (practitioners/paediatricians, hospital, health insurance, well-baby clinics).

- Each country/region to define the study population

Study setting

- Each country/region to define the study setting according to the source available for recruiting cases and controls
- Description of the sources or institutions used to recruit cases: hospitals, laboratories practitioners/paediatricians networks
- Number of participating institutions, proportion out of the total number of existing institutions (e.g. participating paediatric hospitals/total number of paediatric hospitals)
- Representativeness of the institutions/units recruiting cases and controls

Study period

The study period will depend on the date that the vaccine started to be available for the eligible population in the country/region. The study period will start on the date on which eligible children would have had the possibility to have received at least one dose of the vaccine.

- Each country/region to describe the study period: start and end

Outcome

The outcome of interest is laboratory confirmed rotavirus. The outcome can be consultation for diarrhoea with laboratory confirmed rotavirus infection, hospitalisation for acute gastroenteritis confirmed as rotavirus infection or a positive rotavirus stool sample as reported by a laboratory. If sample size allows and results are available, specific rotavirus serotype could be used as outcome.

- Each country/region to precisely define the outcome

The test for rotavirus laboratory confirmation should be described with its sensitivity and specificity.

Case finding

Case identification

Several sources for case identification can be used:

- Hospital registers
- Practitioners registers
- Laboratory registers
- Cases reported through existing surveillance system
  - each country/region to define the source of case identification and procedures.
  - each country/region to define criteria for collecting and testing stool samples (i.e. testing all children hospitalised for acute gastroenteritis, testing a systematic sample of cases consulting the paediatrician for gastroenteritis, the paediatrician defines children to be tested based on clinical criteria, etc.).

Controls

Various control groups can be selected depending on the available resources. All the controls should be selected among the birth cohorts eligible for vaccination. Examples:

- Children (i.e. consulting for gastroenteritis, admitted for acute gastroenteritis) with a rotavirus negative stool sample (test-negative design). This control group can be used in settings that have information about cases testing negative for rotavirus.
- For studies recruiting acute gastroenteritis cases at hospital level
  - Hospital controls: children hospitalised for non-acute gastroenteritis (preferably matched by hospital, age, e.g. born +/- 30 days of matched case, and date/week of hospital admission).
- For studies recruiting cases at practitioner level
  - Children consulting the practitioner for reasons other than gastroenteritis (preferably matched by practitioner, age, e.g. born +/- 30 days of matched case, and date/week of consultation).
- Community controls:
  - Children living in the catchment area of the hospital or practitioner or laboratory that recruited the case (preferably matched by age, e.g. born +/- 30 days of matched case)
  - Rotavirus vaccination coverage in the catchment area of the hospital or practitioner or laboratory that recruited the case (for screening method)
- Each country/region to define procedures for control selection
- Each country/region to define the matching criteria, if any
- Each country/region to specify criteria for inclusion/ exclusion of cases and controls.

Exposure (vaccination)

Definition of vaccination status

- **Fully vaccinated:** children that have received three doses of RotaTeq or two doses of Rotarix, of which the last dose was at least 14 days before onset of symptoms;
- **Vaccinated one dose:** children that have received only one dose of RotaTeq or Rotarix at least 14 days before onset of symptoms;
- **Vaccinated two doses** (for RotaTeq only): children that have received a second dose of RotaTeq at least 14 days before onset of symptoms;
- **Unvaccinated:** absence of written records for RotaTeq or Rotarix vaccination in the vaccination registry or medical record, or if the first vaccination dose was given less than 14 days prior to onset of symptoms;
- **Uncertain vaccination history:** children with incomplete vaccination information (vaccine brand name not mentioned, number of doses received unknown, date of administration unknown) or vaccinated during a clinical trial.

Vaccination status ascertainment

The exposure of interest in this study will be history of vaccination with rotavirus vaccine. The vaccination history includes date of administration of each dose and brand names.

Vaccination status is extracted from the study databases (vaccination registry, practitioners' database and hospital medical records). Individuals with no information on vaccination status are considered unvaccinated.

For studies using the screening method, the vaccine coverage can be estimated using various sources: surveys, administrative data, well-baby clinics.

- Each country/region to describe the data quality of the database used for vaccination status ascertainment and whether they plan to validate the database using other sources or studies.

Confounding factors and effect modifiers

To control for differences in health, social status or health seeking behaviour in cases and controls, information on potential confounding factors can be collected. Those confounding factors may include chronic diseases, indicators of socio-economic status, number of children in the family, other vaccines.

- Each country/region to define the variables used to identify potential confounding factors and source of identification.

Data collection

Data for cases and controls will be extracted from existing databases. In countries or regions with a unique identifier for each child, investigators can link various databases. For each variable, the database source and its characteristics should be defined. A table such as the one below can be adapted and completed to summarise the sources for each of the variables to be extracted and included in the analysis.

- Each country/region to specify the list of variables to be extracted and the database source.

Table 1. Data sources for each collected variable

Group of variables	Variables	Data source	Characteristic
Demographic characteristics	Date of birth		
	Gender		
	Place of residence		
Exposure (for each dose of the vaccine)	Date of vaccination		
	Type of vaccine		
Outcome (for each outcome included in the study)	Date of onset		
	Date of hospitalisation		
	Date of laboratory testing		
	List of symptoms		
	Laboratory results		
Confounding factors / effect modifiers	List of chronic diseases		
	Indicators socio-economic status (e.g. rural / urban, parents level of education)		
	Other vaccinations		

Note: Table is to be completed/modified according to collected variables.

Procedures for database management

- Each country/region to describe all procedures for each of the databases used:
  - who enters data?
  - who validates data?
  - how, by whom and when are data stored?
  - who links databases?
  - how are data extracted?
  - who extracts data?
  - who analyses data?
  - software used?
- If possible, validation of the information (especially for key variables such as outcomes, exposure and main confounding factors) using other data sources should be performed. To do this, it is recommended to develop a specific protocol for data validation.

Sample size

- Each country/region to estimate the power of the study taking into account:
  - the estimated number of cases that occurred during the study period;
  - the expected vaccination coverage among controls;
  - the stratified analysis planned.

Laboratory methods

Specimen collection

- Each country/region should describe how specimens are collected

Transport

- Each country/region to describe transport methods (how, when)
- Each country/region to describe where the samples are analysed

Test used

- Each country/region to describe the types of test performed, their sensitivity and specificity

Analysis

Descriptive analysis

Study participants will be described by baseline characteristics. Baseline characteristics of cases and controls in unmatched studies will be compared using the chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size). In matched case-control studies, characteristics of cases and controls will be compared using McNemar's chi-square test, paired t-test, conditional logistic regression, or the Wilcoxon signed-rank test (depending on the nature of the variable and the number of controls).

The association between vaccination status and baseline characteristics will be measured for both case and control groups.

Measure of effect:

Vaccine effectiveness will be computed as 1 – the odds ratio (OR). An exact 95% confidence interval will be computed around the point estimate. For studies using the screening method, vaccine effectiveness will be computed as

$$VE = \frac{PPV - PCV}{PPV\,(1 - PCV)}$$

in which PPV is the proportion of the reference group that is vaccinated (vaccine coverage in the reference group), and PCV the proportion of vaccinated rotavirus cases.

Stratified analysis

Analysis will be stratified according to age group, number of doses received and any other variable relevant for the study setting (e.g. hospitalised vs. non-hospitalised; children with chronic diseases vs. non-chronic diseases, etc.).

Effect modifiers should be assessed one by one, comparing the OR across the strata of baseline characteristics.

Confounding factors will be investigated by comparing crude and adjusted OR for each baseline characteristic.

- Each country/region to specify the stratified analysis planned

Multivariable analysis

A multivariable (conditional if matched) logistic regression analysis will be conducted to control for confounding. Odds ratios and standard errors will be obtained. Variables will be tested for multicollinearity. Interactions will be tested using the likelihood ratio test or Wald's test, and will be included in the model if significant at the 5% level. Factors other than statistical significance will also be used as criteria for inclusion of an interaction term.

- Each country/region to describe the type of multivariable analysis planned.

Limitations

Study population

- Each country/region to describe the limitations relating to the representativeness of the study population and thus the generalisability of the results.

Database(s) quality, validity

- Each country/region to describe the quality of the database. If the database has not been validated, the possibility of validating the information using other data sources should be addressed.

Exposure, vaccination status

- Each country/region to describe any potential bias related to ascertainment of vaccination status, ways to minimise the bias and how bias can affect the estimates.

Outcome

- Each country/region to describe any potential bias related to the outcome used and the way the outcome is ascertained.

Control group

- Each country/region to describe the limitations of the selected control group (i.e. do controls represent the vaccination coverage of the population giving rise to the laboratory confirmed cases?).

Selection bias

- Each country/region to describe any selection bias that may occur in the selection of children for which a stool sample is collected.

Confounding

- Each country/region to describe how they will minimise the effect of potential confounding factors and how residual confounding may affect the VE estimates.

Dissemination of results

- Each country/region to describe the plans to disseminate the results: preliminary reports, final report, publications.

Ethical approval

- Each country/region to describe the procedures to obtain the approval of the national/ethics committee.

Human resources

The roles and responsibilities of the members of the investigation team should be described: principal investigator, assistant, data manager, etc.

- Each country/region to describe the team members' roles and responsibilities

Budget

The main budget lines should be specified:

- payment of study team members
- payment for ethical committee application
- payment for data extraction
- others.

- Each country/region to describe the budget lines

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