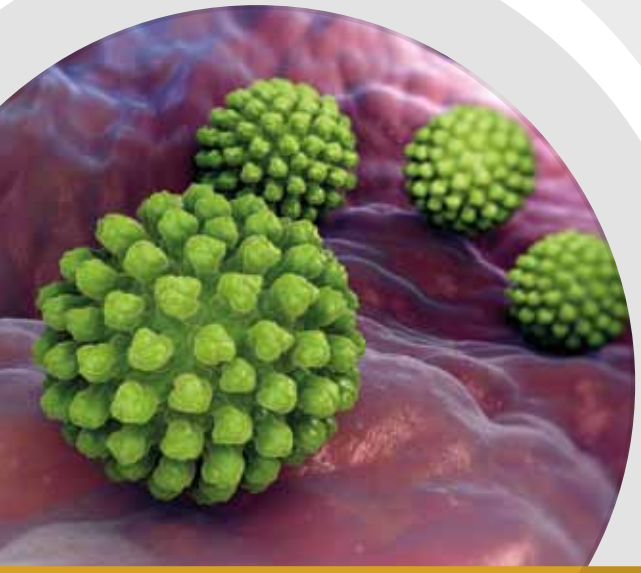

TECHNICAL DOCUMENT

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

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ECDC TECHNICAL DOCUMENT

Effectiveness of rotavirus vaccination

Generic study protocol for retrospective cohort 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

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Contents

Abbreviations

AGE	Acute gastroenteritis
EU	European Union
RR	Rate ratio, or relative risk
RV	Rotavirus
SAGE	Strategic advisory group of experts
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. Studies suggest 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) and the pentavalent bovine-human, reassortant vaccine (RotaTeq, Sanofi Pasteur MSD).

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 [2]. 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 [3, 4].

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

This generic protocol for cohort study will need to be adapted to each country's/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 preferably through electronic immunization registries
- 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
- availability of study population denominator
- 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.

Aim and objectives

Aim

To measure rotavirus vaccine effectiveness (VE) among the population eligible for the vaccine in the country/region site.

General objective

To estimate the relative risk of defined outcome(s) in vaccinated versus unvaccinated individuals in the study population

- Each country/region to define the outcomes to be measured

Secondary objectives

To estimate 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 were used)

Methods

Study design

Retrospective cohort study design.

Study population and source to identify the study population

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

To recruit the cohorts, several data sources can be used, depending on the available databases

- Computerised practitioner/paediatrician databases: vaccinated and unvaccinated cohorts may be identified through extraction from the computerised databases
- Health insurance databases: vaccinated and unvaccinated cohorts may be identified through extraction from their computerised databases
- Population registries: the vaccinated cohort is selected using a vaccination registry. The unvaccinated cohort is selected from the population registry
- Others

Each country/region to define the study population and source(s) to identify relevant population.

Study setting

Each country/region to describe, according to the source used to identify the study population

- Total number of practitioners/hospitals/ baby-clinics included in the database(s)
- Representativeness of database(s)
- Completeness of database(s);
- Structure of database(s)

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

Exposure

An individual is defined as vaccinated against rotavirus according to the following categories:

- **Fully vaccinated:** children who 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 who have received only one dose of RotaTeq or Rotarix at least 14 days before onset of symptoms;
- **Vaccinated two doses** (for RotaTeq only): children who 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.

Ascertainment: Vaccination status is extracted from the study databases (vaccination register, practitioner databases). Individuals with no information on vaccination status are considered unvaccinated. The vaccination history includes date of administration of each dose and brand names.

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

Outcome(s)

The preferred outcome for the vaccine effectiveness study would be laboratory confirmed rotavirus acute gastroenteritis (AGE). If the sample size allows for it, serotype specific VE could be estimated. Other potential outcomes could be diarrhoea, acute gastroenteritis hospitalisation, rotavirus acute gastroenteritis hospitalisation.

For laboratory confirmed outcomes, the criteria for a child to have a stool sample collected should be defined (e.g. clinical criteria, systematic swabbing of children with diarrhoea).

- Each country/region to define the outcome and its source of identification.

Confounding factors and effect modifiers

To control for differences in health, social status and health seeking behaviour in vaccinated compared to non-vaccinated children, 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 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 like 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 to be 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 sample size of their study population
- an alpha error of 0.05
- the expected vaccination coverage
- the expected rate of the selected outcomes
- the minimum sample size for stratified analysis

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 tests performed, their sensitivity and specificity

Analysis

Descriptive analysis

- total number of eligible cases
- total number included: fully vaccinated, partially vaccinated and unvaccinated
- distribution of vaccinated and unvaccinated cases by time (week, month).

Study population baseline characteristics by rotavirus vaccination status (see table 2):

- age group
- gender
- socio-economic status indicators
- co-morbidities
- other vaccines

Baseline characteristics of vaccinated and unvaccinated participants should be described using proportions and mean/median (depending on variable type). Missing data for each characteristic should be described, and an account should be given on how missing data were handled in the analysis.

In order to test for differences between vaccinated and unvaccinated characteristics, 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) will be used.

Table 2. Study population baseline characteristics by rotavirus vaccination status

Group of variables	Fully vaccinated (n =)	Unvaccinated (n =)
Demographic characteristics • gender • age groups • socio-economic status		
Symptoms		
Comorbidities		
Other vaccinations		

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

Crude vaccine effectiveness estimates

VE will be computed as (1 – RR) * 100, the exact 95% CI will be calculated around the estimate for each outcome. This is a person-time analysis and vaccination status should be used as a time-varying variable.

Stratified analysis

Analysis will be stratified according to:

- age group
- number of doses
- vaccine brand

Effect modifiers are assessed one by one, comparing the relative risk (RR) across the strata of baseline characteristics.

Confounding factors are assessed by comparing crude and adjusted RR for each baseline characteristic.

- Each country/regions to specify the stratified analysis planned

Multivariable analysis

A multivariable analysis is conducted to control for negative and positive confounding.

Adjusted VE estimates are calculated for each of the outcomes included.

- A priori confounders and level of significance for inclusion of other covariates in adjusted analysis should be outlined and clinical relevance noted if necessary;
- Presence of effect modification/interaction terms should be explored.
  - Each country/region to describe the type of multivariable analysis (Poisson, Cox) 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 the bias might affect the estimates.

Outcome

VE depends on the specificity of the selected outcome. With less specific outcomes, VE is underestimated. A laboratory confirmed outcome should be prioritised.

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

Selection bias

- Each country/ region to describe any selection bias that may come from a differential definition of outcome status depending on the child's vaccination status (e.g. vaccinated children less likely to have a stool sample for laboratory confirmation).

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 data extraction
- payment for laboratory tests
- payment for application to ethical committe
- others

Each country/region to describe the budget lines.

References

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2. World Health Organization, PATH, GAVI Alliance: WHO Recommends Global Use of Rotavirus Vaccines. Geneva and Seattle; 2009 [updated 2009; cited]; Available from: http://www.rotavirusvaccine.org/files/WHO_GAVI_PATH_Press-Release-on-SAGE_FINAL_4June09_000.pdf.

3. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006 Jan 5;354(1):11–22.

4. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006 Jan 5;354(1):23–33.