TECHNICAL DOCUMENT

Impact of rotavirus vaccination – Generic study protocol

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Impact of rotavirus vaccination

Generic study protocol

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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Abbreviations

AGE	Acute gastroenteritis
CDC	United States Centers for Disease Control and Prevention
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
GCP	Good clinical practice
GEP	Good epidemiological practice
ICD-10	International statistical classification of diseases and related health problems (10th revision), here also used to refer to the hospital discharge diagnosis dataset
HAI	Hospital-acquired infection
LAB	Laboratory, here used to refer to the hospital laboratory dataset
RT-PCR	Reverse transcriptase polymerase chain reaction
RV AGE	RV acute gastroenteritis
RV	Rotavirus
RV+/RV-	Rotavirus positive/rotavirus negative
SAGE	Strategic advisory group of experts (World Health Organization)
VE	Vaccine effectiveness

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 approximately 700 000 outpatient visits resulting in more than 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 less than six months old: the two-dose monovalent human RV vaccine (Rotarix, GSK) and the three-dose 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 World Health Organization 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.

Initial data from the US suggest that the vaccine introduction leads to a reduced number of hospitalisations (70-90% in different small studies) and a delayed onset of the season 2007/2008 [3, 4]. Similar data from Europe are still scarce [5–8].

When introducing a new vaccine, it is crucial to conduct studies evaluating the vaccination‘s impact and effectiveness in order to decide on recommendations for its future use, and to allow more precise estimates of the impact of current vaccination strategies on the burden of disease.

Rationale

In Europe, routine RV vaccination of infants at the 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. This represents an opportunity for assessing the public health impact of this immunisation policy through a surveillance study.

In other EU Member States, rotavirus vaccine is available but not included in the paediatric vaccination programme.

The number of RV cases in EU Member States is expected to decrease due to the vaccination programme, as was the case in the United States [3, 4].

A generic protocol is presented for developing studies to assess the impact of RV vaccination in EU Member States. The proposal is to compare the number/incidence/proportion of rotavirus cases in the period before the introduction of the vaccine to the number/incidence/proportion of rotavirus cases in the period following the introduction of the vaccine. The impact of the vaccination can be quantified in children in the age group targeted for the vaccine (overall effect) or in children in the other age groups (indirect effect).

This generic protocol will need to be adapted to each country/regions 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, reimbursement
- estimated vaccination coverage
- sources to identify RV related outcomes:
  - hospital registers to identify RV hospitalisation related outcome (i.e. hospitalisations for RV AGE, RV laboratory tests)
  - computerised primary care databases
  - specific rotavirus surveillance systems (i.e. laboratory surveillance, hospital surveillance, primary care surveillance)
  - laboratory registers
- availability of study population denominator
- number of years of data availability
- data sources, their nature and their stability along the years
- access to data
- available variables
- ethical/consent requirements
- other

Each country/region to describe the specific background for the country/region: introduction of vaccine, calendar, previous studies, surveillance data, etc.

Objectives

Primary objective

To estimate the impact of RV vaccination through comparison of rotavirus related outcome in children less than XX years (e.g. five years used in several studies), before RV vaccine introduction to the same rotavirus related outcome in the post-vaccination period in the country or region site.

Each country/region to define which rotavirus related outcomes will be used

- number/incidence of hospitalised acute gastroenteritis
- number/incidence of hospitalisations for rotavirus;
- number/incidence of laboratory tests positive to rotavirus;
- proportion of tests positive to rotavirus;
- number/incidence of rotavirus diarrhoeas reported by primary care practitioners

Each country/region to specify the age groups in which the impact will be measured and define if overall or/and indirect effect of the vaccine will be estimated.

Specific objectives

To describe the temporal trends of RV related outcome before and after the introduction of RV vaccination in order to compare the two periods using the following indicators:

Hospital related outcomes:

- Number of AGE hospitalisations < X years old
- Number of RV AGE hospitalisations < X years old
- Rate of AGE hospitalisation in children < X years old
- Rate of hospitalisations due to RV (RV AGE) in children < X years old
- Number of RV laboratory tests performed in children < X years old
- Proportion of RV positive tests in hospitalised children < X years old

Primary care related outcomes

- Number of diarrhoea consultations in < X years old
- Number of RV diarrhoea in < X years old
- Rate of diarrhoea consultations in children < X years old
- Rate of RV diarrhoea in children < X years old
- Number of RV laboratory tests performed in children < X years old
- Proportion of RV positive tests in hospitalised children < X years old

Surveillance systems (laboratory, hospitals, primary care)

- Number of rotavirus cases (according to case definition used) reported by the reporting units in < X years old
- Rate of rotavirus cases (according to case definition used) reported by the reporting units in < X years old

Rotavirus seasons

- Duration of RV season and week of peak
- Mean, minimum, maximum weekly number of reported cases in children < X years old
- RV vaccination coverage by year, number of doses (completeness of vaccination course) and age groups

Age distribution of the study outcomes

Each country/region to define specific objectives depending on the context. Note that the age of children included in each specific study should be defined according to the context.

Methods

The study methods will depend on the setting where each study will be performed. Issues to be considered for designing the study are for example data sources and availability (e.g. national datasets, electronic databases, what information can be collected, how), vaccination coverage, prevalence of outcomes of interest, feasible study designs, and possible achievable sample size, etc.

Study design

The study will be a 'pre and post' study that assumes that rotavirus related outcomes would not change over time in the absence of vaccination and that rotavirus trends can be accounted for in the analysis. The period before the vaccination (pre-vaccination) is considered the reference period.

The indicator(s) that will be compared to estimate the impact should be computed for the pre and post-vaccination periods.

- For absolute numbers and incidence
  - Numerator = children < X years with RV related outcome
  - Denominator (if incidence computed) = children < X years in the study catchment area (i.e. hospitals, laboratories, practitioners, catchment area)
- For proportion of laboratory results positive to rotavirus
  - Numerator = children < X years with a positive laboratory test for RV
  - Denominator = total number of laboratory tests performed in children < X years

Study population

The study population will consist of children < X years living in the catchment area of the data source used to identify cases (i.e. hospitals, laboratory, practitioners, catchment area).

Each country/region to define the age group(s) included.

Study period

Rotavirus season

A RV season should be defined based on the normal rotavirus seasons in the country/region. In many EU Member States it may be defined to last from September in one year to September the following year. Alternatively, thresholds can be defined using incidence, absolute numbers or proportions. For example RV season could be defined based on the number of cases or the proportion of positive RV tests of all tests performed.

Definitions of periods before and after the introduction of the vaccine:

Pre-vaccination period: XX seasons before introduction of the RV vaccine in the country/region or start of the rotavirus universal vaccination programme (the number of seasons will depend on the data available).

Post-vaccination period: seasons starting from introduction of the RV vaccine or from start of the universal vaccination programme in the country/region.

Transitional period

In countries/regions where the vaccine was introduced progressively, the first season(s) in which the vaccine was available but low vaccination coverage was achieved may be considered as transitional periods between periods with no vaccine available and periods with high vaccine coverage (i.e. seasons with vaccine available prior to universal introduction).

Each country/region to define post-vaccination and pre-vaccination periods and a RV season definition. The highest number of years included in the pre-vaccination period, the better the seasonal rotavirus fluctuations and/or secular trends could be taken into account in the interpretation of the results.

Study setting

Studies may be conducted in hospitals, primary care practitioners, paediatricians and/or laboratories:

- reporting RV related outcomes.
- with databases from which RV related outcomes can be extracted

Each country to describe the study setting (number of hospitals/laboratories/practitioners included, catchment population, number of beds, distribution, representativeness, stability of their reporting during the study periods, potential changes, etc.)

Case definitions

Below are some proposals of case definitions to be used depending on the outcome selected to measure impact. The same case definition should be used in all study periods.

Rotavirus consultation

A consultation coded as rotavirus by the practitioner/paediatrician.

Acute gastroenteritis hospitalisations (all causes)

Children discharged with first or second diagnosis of acute gastroenteritis: ICD-10 available at http://www.who.int/classifications/icd/en/index.html (specific codes' inclusion to be discussed, see appendix 1). The objective is to identify hospital admissions for AGE; i.e. hospital stays that are attributable to AGE.

Acute RV gastroenteritis hospitalisations

Children discharged with ICD code A08.0 (RV enteritis) on first or any diagnosis position (to be discussed) will be considered as RV AGE cases.

Confirmed RV case

A confirmed case of AGE due to RV corresponds to a child with a positive RV laboratory test.

Laboratory tests performed among AGE cases for RV identification may include:

- ELISA
- PCR
- Rapid diagnostic test

Each country/region to describe the case definitions and laboratory methods (for the confirmed cases) used. For laboratory-confirmed RV cases, the criteria for doing a rotavirus test should be defined (systematic sampling of all diarrhoea cases, medical criteria to do a rotavirus test), and sampling method and specimen handling should be described (by GPs, hospital in-/outpatient service, transport of samples, etc.). Discuss the potential limitations related to the chosen case definition.

Case exclusion

For hospitalisations or consultations corresponding to the same AGE, diarrhoea or RV episode, only the first episode will be counted. Iterative hospitalisations or consultations for diarrhoea, AGE or RV AGE will be considered as different episodes if more than 14 symptom-free days have elapsed between two consultations, hospitalisations for diarrhoea, AGE or RV AGE.

Nosocomial RV AGE cases

A hospital-acquired RV AGE case is a case who developed AGE symptoms onset at least 72 hours (three days) after being admitted to or visiting hospital and who had no signs or symptoms of gastroenteritis at time of admission or hospital visit [5].

Each country/region to define if nosocomial RV AGE cases will be included or excluded from the impact study.

Other definitions

Age groups

If possible, six months age groups will be used for younger children.

Proposed age groups:

- 1–5 months
- 6–11 months
- 12–17 months
- 18–23 months etc. (until 60 months, then larger age steps to be defined)

Hospitalisation

The definition of hospitalisation should be stated and will depend on the hospital practices. Some examples of definitions are:

- admission for at least one overnight stay in the hospital
- admission for more than XX hours
- all admissions in the paediatric ward.

Each country/region to select a definition of 'hospitalisation' suitable to its context and discuss its potential limitations.

RV season onset, peak, end

The RV season onset, peak and end should be defined.

For studies having RV tests results available, the following definitions may be used:

- Onset: first of two consecutive weeks in a season during which the median percentage of specimens taken from patients with AGE that tested positive for RV is >= 10% [4].
- Peak: week with the highest proportion of RV positive test results [4].
- End: last of two consecutive weeks during which the median percentage of specimens was < 10%.

For studies not having laboratory tests results available, the start, peak and end can be defined according to the incidence or total number of cases of the selected outcome.

Each country to specify the definitions of start, peak, end of the season

Sources of case identification and data

Cases (numerator)

Cases can be identified through hospital, laboratory or practitioners based epidemiological surveillance systems or through existing registers such as:

- Hospital registers, e.g. discharge registers (ICD codes)
- Hospital microbiology laboratory registers (RV test)
- Practitioners databases
- Laboratory surveillance network
- Hospital surveillance network
- Practitioners surveillance network
- Hospital outbreaks for nosocomial cases
- Others

Denominator

- Population statistics data/ birth registers in hospital catchment areas
- Census

Vaccination coverage

- Vaccination coverage obtained from manual or electronic vaccination registries, vaccine sales, or specific uptake surveys in catchment areas

Additional information

- Interviews with experts: to gain information on RV testing specifics like criteria, tests used, changes over time, ICD coding practices, season particularities (e.g. AGE outbreaks, vaccine trials), criteria for taking stool samples, etc. These data may not be directly analysed, but will help understand possible variations in trend

Each country/region to describe the data sources that can be used for each aspect listed above and the potential limitations (exhaustivity, representativeness, selection bias, etc.).

Sample size

The studies will require sufficient power to detect the impact of RV vaccination, hence certain a sample size will be required.

The achievable power of each study should be calculated in advance, and the following aspects should be taken into consideration:

- the estimated size of their study population
- an alpha error of 0.05
- the expected vaccination coverage in the study population
- the expected rate of the selected outcome
- the number of strata included in any stratified analysis, each stratum specific analysis should be powered with the same above principles

If the achievable sample size is too low to assure representativeness of the data and meaningful results, the study should be reconsidered.

Each country/region to estimate the power of the study.

Data collection

Data will be extracted for the years XXXX-YYYY from selected databases, see appendix 1 for an example of the details of required variables. In the rest of this document, hospital discharge registers and hospital laboratory databases will be used as examples. Whether inpatients and outpatients can be differentiated should be clarified.

Cases

Hospital discharge registers

For all hospitalisations with ICD codes XXX-YYY (to be defined by each study site) the following information will be documented:

- Date of admission
- Date of discharge or length of hospital admissions for AGE
- First two ICD codes available for same individual in same hospitalisation episode (if more than one diagnosis)
- Date of birth or age or age group
- if possible, hospital ward to further assess severity (i.e. admission to intensive care)
- if possible, hospital discharge (e.g. transfer to another hospital, discharge to home, or death)

To assess differences in reporting, data collection and completeness over time in the hospital discharge registers, cases that are hospitalised for a different condition may be included in the analysis as a reference or comparison group. This comparison morbidity should be any paediatric disease with a stable incidence and reporting pattern over time that is not prone to outbreaks, and does not have any major, high-impact prevention and control measures. The eventual choice should be made for each setting, as it is important that there is a sufficient number in cases of the reference morbidity that allows assessing reporting patterns.

Each country/region to specify which 'reference morbidity' it will use to assess differences in reporting.

Practitioner registers

For all patients consulting for gastroenteritis (according to the case definition used) the following information will be documented:

- Date of consultation
- Date of onset of symptoms
- Birth date or age group
- Stool sample collection

Laboratory registries

Information on all AGE tested for RV

- Total number of RV tests
- Date of admission or consultation or onset of symptoms
- Date tested for RV (or date sampled, or date of result)
- Result of RV test (positive/ negative/ other)
- Birth date or age or age group

Vaccination coverage

Number of children vaccinated, by birth cohort, by vaccine type and number of doses.

- Children born between XXXX and YYYY
- Children vaccinated against RV between XXXX and YYYY (dose number in series for used vaccine)

If administrative data used

- Number of vaccine doses sold/distributed
- Number of children belonging to the age group for which the vaccine is recommended

Countries/regions to specify sources of vaccination coverage.

Denominator

Number of children < X years resident in the study sites' catchment areas by year and by age groups. If the study population is considered to be stable during a year, the annual census could provide the denominator.

Additional information

Interviews with RV experts (clinicians, epidemiologists) to gather information on:

- Year of introduction of specific RV diagnostic kit in the hospital or at practitioners level
- RV tests used during the study period (sensitivity/specificity/change of test)
- Criteria for AGE hospitalisations
- Changes in criteria for acute gastroenteritis hospitalisations
- Criteria for RV testing
- Changes in criteria for RV testing
- Vaccine trials conducted in the hospitals' catchment area (years, population)
- Vaccination coverage in the hospitals' catchment area by year if known
- Changes in coding dictionary
- Changes in coding practices
- Any season with big outbreak of RV in the catchment area
- Any season with AGE outbreaks in the catchment area (community or hospital)
- Changes in other AGE pathogens in the catchment area
- Changes in the data sources (e.g. proportion of laboratory/hospitals reporting)

Each country/region to define which datasets will be used and which information will exactly be collected

Data management

The way the data will be managed should be laid out before the study start, and the following issues need to be decided in advance:

- Who enters data
- Who validates data
- Who links databases
- How are data extracted
- Who extracts data
- Who centralises data
- Who analyses data
- Software used

Each country/region to lay out how study data will be managed.

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.

Statistical analysis

Data checking

- Identification and elimination of duplicate records (each study site to indicate variables used to identify duplicate records)
- Identification of inconsistencies (each study site to indicate procedures to identify inconsistencies)
- Checking of datasets for missing information. If the following variables are missing, cases will be excluded:
  - Date of birth/age available (minimum necessary is month and year)
  - For laboratory outcome, laboratory testing date (minimum necessary is month and year)
  - For hospitalisations outcome, date of hospital admission
  - For primary care outcome, date of consultation

Data description

- Description of missing observations for each variable
- Description of records

The aim is to compare the RV related outcome in the pre- and post-vaccination period. For this, the indicators mentioned below will be described and compared between the two time periods.

Hospitalisations

- Total number of admissions for AGE by week and age group
- Rate of admissions for AGE by week and age group
- Total number of admissions for RV AGE by week and age group
- Rate of admissions for RV AGE by week and age group
- Rate by age group, sex, median length of stay

Practitioner consultations

- Total number of consultations for gastroenteritis by week and age group
- Rate of consultations for gastroenteritis by week and age group

Laboratory tests

- Total number of RV tests performed by week and age group
- Total number of tests positive for RV by week and age group
- Proportion of positive tests by week and age group
- If the source of the specimens is available, results should be reported by source (e.g. outpatient vs. inpatients, practitioner vs. hospital)

Graphs

- Distribution of number of RV related outcome by week and age group
- Distribution of number (%) of AGE or diarrhoea tested for RV per week and age group
- Distribution of number of RV+ by week and age group
- Proportion of RV+ tests by week and age group
- Age distribution of cases (according to the outcome selected) by pre post-vaccination period

Smoothing: moving averages will be used to smooth the data. The number of weeks used to describe seasonal patterns may be identified. A fifty-two week moving average may be used to describe long-term trends.

Vaccination impact analysis

The methods used for the comparison of pre-vaccination and post-vaccination periods will depend on what data are available and should be specified according to the data available in each study setting.

Analysis proposed	Data needed	Assumptions	Limitations
Reduction in total number of cases, risks or rates, by age group	From XXXX onwards (depending on definition of pre-introduction)	Assumes stable reporting in pre-introduction years	Low power as possibly few data points and high variability between RV epidemic seasons.
Modelling	At least seven years of retrospective data	Assumes stable reporting in pre-introduction years	More data points post-introduction could provide more power for the analysis.

Seasonal characteristics

- Median onset of RV season pre-vaccination (range), onset in year of vaccination starts and the years after, delay onset pre-vaccination years/post-vaccination years
- Median peak of RV season pre-vaccination (range), peak in year of vaccination starts and the years after, delay peak season pre-vaccination/post-vaccination year
- Median end of RV seasons pre-vaccination (range), end in year of vaccination start and the years after, delay end season pre-vaccination /post-vaccination year
- Median duration of RV seasons pre-vaccination (range), duration in year of vaccination starts and the years after. The median week of peak and duration of RV season between pre- and post-vaccination eras may be compared.

Graph: median, maximum, minimum percent of RV + test results in pre-vaccination, vaccine introduction, and post-vaccination periods.

The impact may be computed as:

- the reduction in the mean number of cases (or rate) in the post-vaccination period compared to the pre-vaccination period, expressed as a proportion of the number of cases (or rates) in the pre-vaccination period and corresponding 95% CI
- if rates are available, as the incidence rate ratio and its corresponding 95% CI

Each country/region to specify the effect measure used.

Modelling

If enough retrospective data is available and the sample size is big enough, modelling may be considered. See Luquero et al [9, 10], Grijalva [11], Tate et al [4].

- Weekly AGE and RV+ hospitalisations in pre-vaccination period, smoothed (X weeks moving average) and by age group
- Analysis of secular trend and periodicities, testing of different functions including linear, quadratic, logarithmic and exponential, then identify the one that suits the available data best through the least square method
- Identification of cycles and seasonality by removing trend, then use of Fourier transformation for identifying (statistically significant) cyclic components
- Predictive model incorporating trend and periodicities (95% CI)
- Compare expected and observed trends for the year of vaccine introduction and available post-vaccination period

Discussion: impact study limitations and bias

Power limited by sample size

If achieved sample sizes do not meet the planned sample size, large confidence intervals will limit the possible interpretation of obtained results.

Pre-existing vaccination coverage

Rotavirus vaccination may have started earlier in some regions or a country, and a certain coverage may have been achieved before the vaccine's universal introduction in a country. If so, there would be pre-existing immunity in the target population which could lead to an underestimation of the impact of the vaccine.

Some sites/hospitals may have been involved in RV vaccine clinical trials, which could also have contributed to an increase in VC in their catchment area.

This may be difficult to compute and take into account.

Limitations related to the study design

In studies comparing pre and post intervention, the main limitation is that the effect measured can be due to other factors not related to the intervention: rotavirus seasonality, changes in reporting, in medical practices, in health seeking behaviour, etc. Efforts to collect information on all the potential factors that can explain the changes should be described.

Case identification

ICD or other codes used for case identification

There are limitations linked to the use of ICD codes for outcome determination. In a US study, ICD RV classification was found to have a low sensitivity (47%), leading to underestimation of the burden of RV-hospitalisations [12].

Laboratory definitions

The potential limitations arising from the laboratory tests should be mentioned: sensitivity, specificity.

Selection bias

The ICD classification or practitioners´ diagnosis or stool testing procedures may be influenced by the knowledge of rota vaccination status. Furthermore, coding practices may change following vaccine introduction.

Reporting variability

It is possible that the reporting of the rotavirus related outcome may not be constant over time, and that there is a variation in the completeness of reporting.

In order to account for this for hospitalised related outcomes, another ICD disease class could be described to see whether there is a difference to AGE-related reporting over time.

If possible, impact estimates should be adjusted for these variations (e.g. changes in proportion of cases reported).

Each country/region to describe the potential limitations applying to their setting (including representativeness of the data source used, the completeness, etc.).

Communication of results

A report and or scientific article may be written to summarise the results.

Each country/region to describe their communication strategy: publications, oral communications, etc.

Ethical approval

Depending on the nature and the national regulations of the country, an ethical approval may be needed.

Each country/region to investigate and specify the ethics committee requirements that may apply to the study.

Roles and responsibilities

The roles and responsibilities of the members of the investigation team should be described: principal investigator, assistant, 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
- financial support for laboratory tests
- application fee to ethical committee
- others

Each country/region to describe the budget lines.

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Appendix 1 Example variables needed for analysis

Variable name	Type	Values and coding	Description
Hospital/ area identification	Unique ID		Necessary
Individual case information			
caseage [#]	Numeric (binary)	0 = No 1 = Yes	Indicates case with acute gastroenteritis
caseagerv [#]	Numeric (binary)	0 = No 1 = Yes	Indicates case with acute RV gastroenteritis
caserv [#]	Numeric (binary)	0 = No 1 = Yes	Indicates lab-confirmed RV case
dateadm	Date	DD/MM/YYYY	Date of hospital admission
datedisch	Date	DD/MM/YYYY	Date of hospital discharge
los	Numeric (categorical)	1-XX	Length of stay in hospital (can be computed from previous two variables)
ward1	Numeric (categorical)	0 = General medicine 1 = Intensive care 8 = Don't know	Ward patient remained in
ward2	Numeric (categorical)	0 = General medicine 1 = Intensive care 8 = Don't know	Second ward patient remained in
testrv	Numeric (binary)	0 = No 1 = Yes	Patient was tested for RV
testrvdate	Date	DD/MM/YYYY	Date of RV test
testrv	Numeric (categorical)	0 = Negative 1 = Positive 9 = unknown/ inconclusive	RV test result
			Need to confirm patient belongs to catchment area?
Aggregated information			
testrvtot			Total number of RV tests performed in this season
testrvpos			Total number of RV tests that were positive in this season

[#] *all by definition hospitalised*

This table will need to be adapted to each country/region and each database that will be used

Appendix 2 ICD-10 codes considered for the study

(NOS = not otherwise specified)

Bacterial origin

A00 Cholera

A01 Typhoid and paratyphoid fevers

A02 Other salmonella infections

A02.0 Salmonella enteritis

A02.1 Salmonella septicaemia

A02.2 Localised salmonella infections

Salmonella:

arthritis+ (M01.3*)

meningitis+ (G01*)

osteomyelitis+ (M90.2*)

pneumonia+ (J17.0*)

renal tubulo-interstitial disease+ (N16.0*)

A02.8 Other specified salmonella infections

A02.9 Salmonella infection, unspecified

A03 Shigellosis

A04 Other bacterial intestinal infections

A05 Other bacterial foodborne intoxications, not elsewhere classified

Parasitic origin

A06 Amoebiasis

A07 Other protozoal intestinal diseases (incl. giardiasis, cryptosporidiosis, etc.)

Viral origin

A08 Viral and other specified intestinal infections

A08.0 Rotaviral enteritis

A08.1 Acute gastroenteropathy due to Norwalk agent

A08.2 Adenoviral enteritis

A08.3 Other viral enteritis

A08.4 Viral intestinal infection, unspecified

Viral:

enteritis NOS

gastroenteritis NOS

gastroenteropathy NOS

Other specified and of presumed infectious origin

A08.5 Other specified intestinal infections

A09 Diarrhoea and gastroenteritis of presumed infectious origin

The following manifestations were excluded from the AGE case definition after discussion with colleagues in Finland:

Manifestations presumed of non-infectious origin*

K52 Other noninfective gastroenteritis and colitis

K52.9 Noninfective gastroenteritis and colitis, unspecified

Diarrhoea, Enteritis, Ileitis, Jejunitis, Sigmoiditis,

=> specified as noninfective, or NOS in countries where the conditions can be presumed to be of non-infectious origin

Excludes: colitis, diarrhoea, enteritis, gastroenteritis:

infectious (A09)

unspecified, in countries where the condition can be presumed to be of infectious origin (A09)

functional diarrhoea (K59.1)

neonatal diarrhoea (noninfective) (P78.3)

psychogenic diarrhoea (F45.3)

*Presumed non-infectious origin ICD-codes have been handled differently by some investigators: Harris et al [13] included them as they are "often associated with infectious causes" as mentioned in another article by Ryan M et al [14], Fourquet et al excluded all non-infectious and several infectious and parasitic gastroenteritis codes (e.g. cholera, typhoid, non-enteritis salmonella, amoebiasis) [15].