Rotavirus

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Rotavirus, a member of the reovirus family, causes watery diarrhoea, vomiting and severe dehydration in young children. Rotavirus is common, accounting for 35–60% of acute severe diarrhoea in children < 5 years of age in countries without rotavirus vaccine, with the highest attributable percentage in infants (1, 2). Rotavirus diarrhoea is ubiquitous and, unlike bacterial diarrhoea, is not more prevalent in settings with poor water, sanitation and hygiene. Rotavirus has a case-fatality rate (CFR) of approximately 2.5% among children in developing countries who present to health facilities (2). This CFR is higher in areas without good access to health care. In 2013, rotavirus caused an estimated 215 000 deaths worldwide (3). Rotavirus is highly communicable; it is shed in the stool at high concentration, and transmission is through faecal-oral route, either person-to-person or through fomites in the environment. The incubation period is one to three days. There is a spectrum of clinical disease with the typical presentation being acute, watery, non-bloody diarrhoea often accompanied by vomiting and fever. Rotavirus peaks in cool, dry seasons in temperate climates but exhibits less pronounced seasonality in tropical settings.

Several rotavirus vaccines are licensed and commercially available, all of which have been efficacious in randomized controlled trials in high- and low-income settings. Two live oral rotavirus vaccines are marketed internationally: the monovalent (RV1) Rotarix® and the pentavalent (RV5) RotaTeq® (4). RV1 is given as two doses and RV5 is given as three doses; doses for both vaccines are separated by four weeks starting as early as 6 weeks of age. Vaccine efficacy ranges from 50% to > 90% against severe rotavirus diarrhoea, with moderate efficacy in lower-socioeconomic, higher-mortality countries. Nonetheless, because of higher rates of disease in these countries, the number of serious rotavirus infections prevented by vaccination is higher despite this lower efficacy. More recently, another live oral monovalent vaccine (ROTAVAC®) was licensed in India after it was found to be effective in a large clinical trial. This vaccine is given in three doses to infants (5).

Rotavirus vaccine introduction has decreased severe rotavirus gastroenteritis burden in many countries and rotavirus-associated mortality in several settings. Rotavirus vaccines have been associated with a slightly elevated risk of a rare, serious condition called intussusception, which can result in potentially fatal bowel obstruction. However, the increased incidence of intussusception is small relative to the overall positive impact of the vaccine. WHO recommends that rotavirus vaccine be included in all national immunization programmes, particularly those in high child mortality settings such as south Asia and sub-Saharan Africa, as part of a comprehensive package of diarrhoea prevention and treatment measures that include access to safe water and sanitation as well as early treatment with rehydration therapy.
RATIONAL EN OF SURVEILLANCE

For all countries, the primary objectives for rotavirus surveillance are to:

- Determine the epidemiology and burden of rotavirus hospitalizations
- Document the spectrum of clinical presentations and outcomes of rotavirus cases
- Determine the age and seasonal distribution of rotavirus hospitalizations
- Identify the prevalent, circulating strains of rotavirus.

For countries that have yet to introduce rotavirus vaccine, an objective is to:

- Generate information to facilitate and support the introduction of rotavirus vaccine.

For countries that have introduced rotavirus vaccine, objectives are to:

- Monitor impact of rotavirus vaccination on disease and changes in epidemiology and circulating strains after rotavirus vaccine implementation
- Estimate vaccine effectiveness by using surveillance as a platform for special studies.

An additional objective could include to:

- Monitor burden of other enteric pathogens, namely ETEC, Shigella and norovirus.

MINIMAL SURVEILLANCE

Active, case-based surveillance at sentinel hospitals with laboratory confirmation

Rotavirus surveillance should be case-based, requiring the collection of data on individual cases of diarrhoea among children < 5 years of age. Surveillance officers should actively look for cases in sentinel health facilities, usually a hospital. Hospitalized cases are the most severe cases of a wide spectrum of rotavirus illness, are relative easy to collect specimens from and represent a significant cost in health resources. Hospitals also often have laboratory capacity to diagnose rotavirus.

The global minimum standard for rotavirus surveillance is one sentinel site per country with laboratory confirmation. Depending on personnel and laboratory resources, some countries may choose to include additional sentinel sites. When considering which sites to include for rotavirus surveillance, sites are expected to hospitalize a minimum of 100 children for diarrhoea each year, but preferably 250–500 cases, prior to vaccine introduction. Based on a conservative estimate of 30% of severe diarrhoea cases being attributable to rotavirus, a pre-vaccine introduction annual enrolment of 250–500 diarrhoea cases would provide 75–150 cases of rotavirus annually per site. Ideally, sites would undertake surveillance for two full years prior to vaccine introduction to assess annual and seasonal variations in disease burden, identify rotavirus genotypes circulating before vaccine introduction, and establish a stable baseline for post-vaccine introduction impact evaluations. After vaccine introduction, surveillance should be maintained long-term, though countries can consider decreasing the intensity of surveillance after vaccine impact has been demonstrated, approximately two to five years after the year of vaccine introduction. Countries can decrease intensity by having fewer sentinel sites or a lower percentage of diarrhoea cases tested for rotavirus (such as testing every fifth case).

ENHANCED SURVEILLANCE

In addition to the minimum recommended surveillance of active case-based surveillance at sentinel hospitals, other types of rotavirus surveillance can be done to meet some of the surveillance objectives in certain settings.

- Laboratory surveillance. Laboratory-based surveillance, in which rotavirus cases are identified in laboratories and reported to public health authorities, can be considered in countries where samples from cases of acute gastroenteritis are already routinely collected and tested for rotavirus. Laboratory-based testing can assess circulating strains of rotavirus and general disease trends.
CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED CASE DEFINITION FOR CASE FINDING
Acute (<14 days) watery diarrhoea, defined as three or more loose or watery stools in a 24-hour period in a child < 5 years of age who is admitted for treatment of diarrhoea to a hospital ward or emergency unit at a participating surveillance facility. Children with bloody diarrhoea and nosocomial infections are excluded.

CONFIRMED CASE DEFINITION
A suspect case in whose stool the presence of rotavirus is demonstrated by means of an enzyme immunoassay (EIA) or polymerase chain reaction (PCR)-based methods.

SPECIAL CONSIDERATIONS
If diarrhoea surveillance is also intended to identify other enteric pathogens, then some components of the suspect and confirmed case definition might change. For example, bloody diarrhoea might be included.

LINKAGE TO OTHER SURVEILLANCE PLATFORMS
Rotavirus surveillance can potentially link with other types of surveillance. Integrated Disease Surveillance and Response (IDSR) collects aggregate numbers of cases of diarrhoea with dehydration in children < 5 years of age. With the addition of laboratory testing, IDSR surveillance could potentially meet some of the objectives of rotavirus surveillance. When stools are already being collected in a facility for surveillance of other diseases (such as polio), consider leveraging existing systems of stool specimen collection, transport and virological laboratory testing for rotavirus surveillance.

CASE INVESTIGATION
Surveillance staff in sentinel hospitals screen cases of diarrhoea and identify those meeting suspect case criteria. Surveillance staff should complete case investigation forms for all cases meeting the suspect case definition. Suspect cases should have a stool specimen collected within 48 hours of admission to avoid detection of nosocomially acquired pathogens. Detection of individual rotavirus cases does not require immediate notification of public health authorities.
SPECIMEN COLLECTION

Whole stool is the preferred specimen. Collect a minimum of 1 mL of stool for basic confirmatory testing; 2 mL or more may be needed for additional testing, such as genotyping. A stool specimen should be obtained within 48 hours of hospital admission to avoid detection of nosocomially acquired infections. Avoid using rectal swabs or swabs placed in bacterial media, which are not optimal for rotavirus detection or characterization.

Stool specimens should be placed in sterile screw-top containers, properly labelled. Samples can be stored temporarily at 4–8°C for up to one month. Ice packs can be used to keep samples cool. Freeze-thaw cycles should be avoided where possible. If prolonged storage is necessary, store at -70°C, as evidence suggests that ability to characterize rotaviruses declines during storage for years at -20°C.

If stool samples are also tested for bacterial or parasitic pathogens by conventional methods, the specimens should be transported to the lab within two hours of collection and placed on appropriate media. Specimens should then be stored in a freezer at -20°C or colder until testing is performed.

LABORATORY TESTING

CONFIRMATION METHODS

EIAs are most commonly used for rotavirus detection in stool. Several EIA kits (Premier™ Rotaclone®, ProSpecT™ and RIDASCREEN®) are available. Follow the manufacturer’s procedures for each kit. The sensitivity of EIAs has been found to be 75–82% with 100% specificity (6). Thus, occasional false negatives are possible, particularly at lower viral loads, though the clinical significance of rotavirus at concentrations below the threshold of EIA detection is unclear (7).

ADDITIONAL TESTING

Confirmatory testing of EIA results may be done by testing for the presence of the VP6 gene using RT-PCR or NP6 and NSP3 genes by real-time reverse transcription PCR (RT-PCR). Rotavirus strain characterization is done by using RT-PCR to identify both G and P types. A subset of rotavirus-positive stools obtained from routine surveillance should be chosen for strain characterization. It is recommended that a minimum of 50–60 randomly selected specimens per year be genotyped from each country. The randomly selected sample should be proportional to the age and seasonal distribution of cases. Only specimens > 3mL should be chosen to avoid running out of material. All non-typeable isolates should be sent to an appropriate reference laboratory for sequencing.

LABORATORY QUALITY CONTROL AND ASSESSMENT

A standard proficiency panel of rotavirus-positive and -negative stool samples can be obtained from the global or regional rotavirus laboratories. Labs should also arrange to send some rotavirus-positive stool specimens to a regional laboratory for independent confirmation of results. External Quality Assessment (EQA) and Quality Control (QC) of the laboratory should be completed annually.

LABORATORY NETWORKS

Participation in a rotavirus surveillance network is voluntary. The Global Rotavirus Laboratory Network has more than 100 participating laboratories throughout the world (8). The network focuses on conducting high quality diagnostic testing for rotavirus diarrhoea and characterizing the most prevalent strain genotypes in different countries and regions. The network promotes standardization of data collection and laboratory quality and control through a global external quality assessment programme coordinated by WHO.
RECOMMENDED DATA ELEMENTS

- Minimal case-based data elements
  - Geographic information (district, province, hospital—depending on local surveillance setting)
  - Demographics
    - Unique case identifier
    - Sex
    - Date of birth (or age in months if date of birth not available)
  - Clinical data
    - Date of admission
    - Number of days of diarrhoea (to define acute diarrhoea)
    - Date of onset of diarrhoea
    - Maximum number of diarrhoea episodes in 24-hour period, at peak of illness
  - Vaccination history
    - Source of vaccination information (vaccination card, medical records, clinic logbook, maternal recall, other)
    - Rotavirus vaccine received. If yes:
      - Type of rotavirus vaccine (Rotarix, RotaTeq, Rotavac, other)
      - Number of doses received
      - Dates received
  - Specimen
    - Was stool specimen collected from the case?
    - Stool specimen ID (to be provided if stool specimen ID differs from unique case ID)
    - Date of stool collection from case
  - Laboratory data
    - EIA test done on stool specimen
      - Type of lab where EIA testing was performed. (hospital laboratory, private laboratory, national laboratory, regional reference laboratory, unknown)
    - Date of EIA test on stool specimen
    - EIA results for stool specimen (positive, negative, indeterminate)
    - Genotyping done (on a subset of specimens)
      - Name of the lab where genotyping was performed
      - Type of lab where genotyping was performed
      - Date when genotyping was performed
      - Genotyping result (G-type)
      - Genotyping result (P-type)
  - Outcome of case at discharge (discharged alive, alive with sequelae, died, transferred, left/discharged against medical advice, unknown)
  - Date of discharge or death

- Additional data elements for case-based data
  - Clinical characteristics
    - Presence of bloody diarrhoea (only if using expanded case definition)
    - Presence of vomiting. If present:
      - Maximum number of vomiting episodes in 24-hour period at peak of illness
      - Duration of vomiting in days
    - Maximum body temperature
  - Treatment
    - Dehydration (mild, moderate, severe)
    - Rehydration given. If yes:
      - Type of rehydration therapy given. Examples: oral rehydration solution (ORS)/oral rehydration therapy (ORT), intravenous fluids, other (specify)
  - Laboratory
    - If case was laboratory-confirmed for other organism, please specify (may need to determine if other organisms are systematically tested)
REPORTING REQUIREMENTS AND RECOMMENDATIONS

Monthly number of rotavirus cases should be reported to the Ministry of Health. If no cases of diarrhoea are identified at the sentinel site, this should specifically be indicated in the report (“zero reporting”). Aggregate reporting (numbers only) is sufficient for routine reporting even if case-based surveillance is conducted. There are no global reporting requirements for rotavirus.

RECOMMENDED DATA ANALYSES

» Minimal data analysis

- Percentages of diarrhoea-associated hospitalizations caused by rotavirus by age groups 0–2 months, 3–5 months, 6–8 months, 9–11 months, 12–17 months, 18–23 months, 24–59 months, and all children <5 years
- Numbers and percentages of hospitalizations for diarrhoea and for rotavirus diarrhoea by month of year
- Number of deaths associated with rotavirus diarrhoea and in-hospital case fatality rate
- Calculation of the above data by year and site of surveillance

» Enhanced analyses for some surveillance settings

- Description of clinical and epidemiologic characteristics of cases
- Distribution of genotypes
- Examination of seasonal trends using weekly or monthly detection rates. Note: weekly analysis will only be possible with sufficient numbers of cases.
  - Seasonality – peak of rotavirus activity should be defined as the two consecutive weeks (if analysing weekly data) or the month (if analysing monthly data) with the greatest number of rotavirus detections
  - Onset of rotavirus season – the week in which the number of rotavirus detections first exceeds the mean number of rotavirus detections per week for the entire year
  - Duration of rotavirus season – the number of weeks during which the detections exceed the weekly mean
- For population-based surveillance, the rates of hospitalizations and deaths associated with diarrhoea and rotavirus per 1,000 children < 5 years old per year, in the surveillance population overall and by age groups

- Number of hospitalizations for all diarrhoea in children < 5 years of age (this can be gathered through logbooks or a review of hospital administrative data)
- Percentage of total hospitalizations caused by diarrhoea in children < 5 years of age (this can be gathered through logbooks or a review of hospital administrative data)
- Distribution of diarrhoeal hospitalizations by etiology, including rotavirus diarrhoea (if testing for other etiologies is routinely done)

USING DATA FOR DECISION-MAKING

» Rotavirus surveillance data are used primarily to support national vaccination strategies. Rotavirus is not targeted for global elimination or eradication.

» Evaluation of vaccine impact. Analysis of surveillance data after rotavirus vaccine introduction can be done in two principal ways. First, to measure the impact of rotavirus vaccine on disease reduction, evaluate the trends of rotavirus disease burden before and after vaccine introduction. This is done by comparing annual rates of rotavirus disease before and after vaccine introduction, ideally when population-based surveillance data are available. If the surveillance population is relatively stable, counts of rotavirus cases or proportion of rotavirus-positive cases by year can show a reduction in disease after vaccine introduction. Second, it is possible to estimate indirect effects of vaccine introduction by monitoring for reductions in rates of diarrhea and rotavirus among unvaccinated age groups before and after vaccine introduction.

» Evaluation of vaccine effectiveness. Rotavirus vaccine effectiveness can be estimated through test-negative case-control studies. Details on how to do this are described elsewhere in WHO guidance and scientific publications (9, 10). These are often done in the setting of diarrhoea or rotavirus surveillance in which confirmed rotavirus gastroenteritis cases serve as the cases and confirmed rotavirus-negative gastroenteritis cases serve as the controls. This design is possible because of the high specificity of the rotavirus EIA test. It also decreases potential selection biases since all children are prospectively enrolled prior to confirmation of rotavirus infection or vaccination status. However, considerable effort is needed to appropriately document the vaccination status of enrolled children.
SURVEILLANCE PERFORMANCE INDICATORS

Table 1
Surveillance performance indicators for rotavirus

<table>
<thead>
<tr>
<th>SURVEILLANCE ATTRIBUTE</th>
<th>INDICATOR</th>
<th>TARGET</th>
<th>HOW TO CALCULATE (NUMERATOR / DENOMINATOR)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completeness of Reporting</td>
<td>Consistent reporting throughout year</td>
<td>At least 10 months with reporting (including zero reporting)</td>
<td>Number months reporting per year</td>
<td>Ideal is 12 months and confirmed zero reporting if no cases</td>
</tr>
<tr>
<td>Case Ascertainment</td>
<td>Minimum number of cases reported annually</td>
<td>≥ 80 suspected diarrhoea cases/year</td>
<td>Number of diarrhoea cases reported per site per year</td>
<td>Ideal is ≥ 100 diarrhoea cases/year</td>
</tr>
<tr>
<td>Specimen Collection</td>
<td>Proportion of suspected cases with specimens collected within 2 days of admission</td>
<td>≥ 80%</td>
<td># of suspected cases with specimen collected within 2 days of admission / # of suspected cases x 100</td>
<td>Specimen is stool; ideal is ≥ 90%</td>
</tr>
<tr>
<td>Completeness of Laboratory Testing</td>
<td>Proportion of specimens tested for rotavirus by EIA</td>
<td>≥ 80%</td>
<td># of cases with specimens tested for rotavirus by EIA / # of cases with specimens x 100</td>
<td>Ideal is ≥ 90%</td>
</tr>
</tbody>
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Please note that there is no minimum number of cases that should test positive for rotavirus since that number varies widely among countries and depends on rotavirus vaccine use.

CLINICAL CASE MANAGEMENT

The treatment of rotavirus gastroenteritis is rehydration, either oral or intravenous. Country-specific guidelines or Integrated Management of Childhood Illness (IMCI) guidelines can be followed for the management for rotavirus. No special antiviral treatment exists. In high childhood mortality settings, zinc supplementation has been shown to reduce the duration and severity of diarrhoea, and prevent subsequent diarrhoeal episodes. No antimicrobial treatment for rotavirus is recommended. However, if syndromic surveillance for acute gastroenteritis is being done and a bacterial cause of diarrhoea such as Shigella dysentery is found, antimicrobial treatment is warranted.

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CONTACT TRACING AND MANAGEMENT

Contact tracing is not routinely done for rotavirus.

SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

Rotavirus is an endemic disease that usually does not occur in large-scale outbreaks that require intervention. Other causes of diarrhoea, such as norovirus, cholera and enterotoxigenic Escherichia coli (ETEC) can occur in outbreaks. These outbreaks might be detected by syndromic surveillance for diarrhea, though sentinel surveillance is not an adequate way to detect outbreaks. Laboratory capacity developed for rotavirus surveillance can possibly be expanded to identify outbreaks of other causes of diarrhoea.

SPECIAL CONSIDERATIONS FOR ROTAVIRUS SURVEILLANCE

- A previously available rotavirus vaccine was associated with an increased risk of intussusception. Intussusception surveillance to monitor the safety of rotavirus vaccines will be important in some countries after rotavirus vaccine introduction, and is described elsewhere (11). Sentinel surveillance sites used for rotavirus surveillance can be considered for intussusception surveillance if appropriate.
- Surveillance for acute gastroenteritis can incorporate testing not only for rotavirus, but also for other enteric pathogens including ETEC, Shigella and norovirus, all of which have vaccines in the pipeline. Expanding surveillance to detect other enteric pathogens can require a broader suspect case definition that includes bloody and persistent (≥ 14 days) diarrhoea.
REFERENCES CITED


