Why do countries conduct vaccine-preventable disease surveillance?

**Pre-vaccine introduction**
- To describe disease burden to make decisions about vaccine introduction

**Impact of introduction**
- To monitor trends to show impact and cost-effectiveness of vaccine and vaccination program

**Long-term monitoring**
- To monitor changes in disease after introduction
- To document control, elimination, and eradication

**Across all phases**
- Identify outbreaks for immediate action for effective reactive vaccination campaigns
- Components of surveillance can be leveraged to monitor other VPDs and other diseases without vaccines
- Identify unreached populations not getting vaccinated for targeted delivery strategies
# Why do countries conduct rotavirus disease surveillance?

<table>
<thead>
<tr>
<th>Pre-vaccine introduction</th>
<th>Impact of introduction</th>
<th>Long-term monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To describe disease burden to make decisions about vaccine introduction</td>
<td>• To monitor trends to show impact and cost-effectiveness of vaccine and vaccination program</td>
<td>• To monitor changes in disease after introduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• To document control, elimination, and eradication</td>
</tr>
<tr>
<td>Across all phases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Identify outbreaks for immediate action for effective reactive vaccination campaigns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Components of surveillance can be leveraged to monitor other VPDs and other diseases without vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Identify unreached populations not getting vaccinated for targeted delivery strategies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
WHO’s role in vaccine-preventable disease (VPD) surveillance

• To generate and monitor VPD trends globally
• To lead, coordinate, and advocate for surveillance activities with countries and partners
• To set global norms and standards for surveillance including quality assurance and control systems
• To support countries with technical assistance and evidence-based policy decisions
• To build on surveillance platforms and inform immunization program monitoring and policy

Role of VPD laboratory networks

• To standardize laboratory procedures (e.g., rotavirus laboratory manual)
• To enhance global EQA and QA/QC programs to ensure high level of performance and reliable data
• To maintain Regional Reference Laboratories to support national laboratories and build national laboratory capacity
• To serve as a platform for sharing experiences between countries and regions
Many methods for monitoring VPDs

But really two main methods are used

National & Sentinel site

WHO-coordinated Global Sentinel VPD Surveillance Networks

- Syndromes and pathogens currently under surveillance
  - Diarrhea (for rotavirus and other enteric pathogens)
  - Invasive Bacterial Vaccine-Preventable Disease (IB-VPD)
    - Meningitis (for pneumococcus, Hib, and meningococcus)
    - Pneumonia/sepsis (for pneumococcus, Hib and typhoid)

- Coordinated by WHO with partners since 2008
Countries that conducted rotavirus surveillance in 2016

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not be full agreement. © WHO 2017. All rights reserved.

Rotavirus positivity among children enrolled in GRSN, by WHO Region, 2016

WHO Global Invasive Bacterial Vaccine Preventable Disease and Rotavirus Surveillance Network Bulletin, June 2017
Rotavirus positivity among children enrolled in GRSN, by WHO Region, 2016

Global Rotavirus Genotype Distribution by Year, 2010-2014
How is surveillance data being used?

- **Country decision making (e.g., Gavi VIGs)**
- **Reports and publications**
  - Bi-annual WHO global electronic bulletin (left)
  - Journal supplements of country manuscripts
    - 20 vaccine impact from AFRO (CID, 2016)
  - Two 2017 supplements in Vaccine: 24 pre-vaccine globally and 20 early vaccine impact from AFRO
- **Global models of rotavirus mortality and age distribution (U.S. CDC, Hopkins, LSTMH)**

Leveraging the surveillance platform

- **Vaccine impact studies**
  - Journal supplements
  - Global analysis
- **Vaccine safety monitoring**
- **Monitor other enteric pathogens**
  - Pipeline enteric vaccines: Shigella, ETEC, norovirus
  - Global Pediatric Diarrhea Surveillance (TAC) project
Prospective diarrhea surveillance in 35-40 countries in 2017-2019 to monitor etiology of severe pediatric diarrhea worldwide (including bloody and non-acute diarrhea)

~100 episodes per site per year will be tested by qPCR (TAC array)

Global Pediatric Diarrhea Surveillance TAC card

<table>
<thead>
<tr>
<th>GI pathogen assay</th>
<th>Clinical Sample Control</th>
<th>Manufacture Positive Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus (CDC)</td>
<td>VP7_G1</td>
<td>VP7_G2</td>
</tr>
<tr>
<td>Rotavirus, NSP2 &amp; RotaTeq, VP8</td>
<td>VP7_G3 &amp; G4</td>
<td>VP7_G9</td>
</tr>
<tr>
<td>VP4_P[8]</td>
<td>VP7_G8 &amp; G10</td>
<td>VP7_G12</td>
</tr>
<tr>
<td>VP4_P[12] &amp; Ebeia</td>
<td>VP7_G12 &amp; GI</td>
<td>VP7_G12</td>
</tr>
<tr>
<td>VP7</td>
<td>VP7_G12 &amp; GI</td>
<td>VP7_G12</td>
</tr>
<tr>
<td>Astrovirus</td>
<td>Norovirus GI &amp; GI</td>
<td>Norovirus GI &amp; GI</td>
</tr>
<tr>
<td>Sapovirus</td>
<td>Norovirus GI &amp; GI</td>
<td>Norovirus GI &amp; GI</td>
</tr>
<tr>
<td>Shigella/EIEC (paH)</td>
<td>Adenovirus 40/41 &amp; Pan</td>
<td>Adenovirus 40/41 &amp; Pan</td>
</tr>
<tr>
<td>S. flexneri (non 6) &amp; S. flexneri 6</td>
<td>S. sonnei</td>
<td>S. sonnei Type 1 &amp; M.tb</td>
</tr>
<tr>
<td>S. Other (boyds, dysen, flex6)</td>
<td>S. dysen Type 1 &amp; M.tb</td>
<td>S. sonnei Type 1 &amp; M.tb</td>
</tr>
<tr>
<td>18S</td>
<td>Aeromonas</td>
<td>Aeromonas</td>
</tr>
<tr>
<td>B. fragilis &amp; C. difficile</td>
<td>Campylobacter jejuni/coll</td>
<td>Campylobacter jejuni/coll</td>
</tr>
<tr>
<td>Salmonella</td>
<td>V. cholerae</td>
<td>V. cholerae</td>
</tr>
<tr>
<td>EAEC_aeC &amp; aeaA</td>
<td>EPEC_aee &amp; bfaA</td>
<td>EPEC_aee &amp; bfaA</td>
</tr>
<tr>
<td>ETEC_STh &amp; STp</td>
<td>ETEC_LT</td>
<td>ETEC_LT</td>
</tr>
<tr>
<td>ETEC_CFa &amp; CS1</td>
<td>ETEC_CSF2 &amp; CS1</td>
<td>ETEC_CSF2 &amp; CS1</td>
</tr>
<tr>
<td>ETEC_CSF &amp; CS6</td>
<td>STEC_stx1 &amp; stx2</td>
<td>STEC_stx1 &amp; stx2</td>
</tr>
<tr>
<td>PhHV</td>
<td>PhHV</td>
<td>PhHV</td>
</tr>
<tr>
<td>Cyclospora &amp; Isospora</td>
<td>E. bieneusi &amp; E. intestinalis</td>
<td>E. bieneusi &amp; E. intestinalis</td>
</tr>
<tr>
<td>Cryptosporidium &amp; E.histolytica</td>
<td>Giardia &amp; Strongyloides</td>
<td>Giardia &amp; Strongyloides</td>
</tr>
<tr>
<td>Amycolstoma &amp; Necator</td>
<td>Ascans &amp; Trichures</td>
<td>Ascans &amp; Trichures</td>
</tr>
</tbody>
</table>
Enteric Pathogens TaqMan Array Card (TAC) Study: Phase 1 results

Operario, et al. (2017) Journal of Infectious Diseases

Strategic Vision for Global Rotavirus Surveillance

- Remaining data gaps
  - Focus rotavirus burden and vaccine impact on regions with gaps (esp. Asia)
  - Long-term impact, genotype changes after vaccine intro, new products
  - Leverage the network to include additional agents (GPDS)
- Sustainability
  - Build national and regional capacity with country ownership
  - Challenges with GAVI support and graduation
  - Develop smarter surveillance (Fewer specimens? Fewer sites?)
  - Coordinate with other surveillance networks
- Communicate and use the surveillance data
### Example of Disease-Specific Template from 2008: Hepatitis

<table>
<thead>
<tr>
<th>Acute viral hepatitis</th>
<th>Acute viral hepatitis (continued)</th>
<th>Acute viral hepatitis (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale for surveillance</strong></td>
<td><strong>Recommended types of surveillance</strong></td>
<td><strong>Special aspects</strong></td>
</tr>
<tr>
<td>Some national regulations group acute viral hepatitis. Transmission is mainly by fecal-oral route for hepatitis A and F, and parenteral routes for hepatitis B, C, and D.</td>
<td><strong>Result of monthly reporting of aggregated data on suspected cases of each type of hepatitis and all notified cases with laboratory-confirmed acute viral hepatitis.</strong></td>
<td>Surveillance data on acute viral hepatitis from developing countries should be interpreted with caution. Differences in types of hepatitis (A, B, C, and D) based on clinical diagnosis are unreliable and serological tests are necessary for accurate diagnosis.</td>
</tr>
<tr>
<td><strong>Control measures for blood-related transmission include ensuring transfusion of blood and blood products are obtained from vaccinated donors and having a surveillance system for transfusion recipients.</strong></td>
<td><strong>Designated reporting data at all levels should report at a speed (e.g., weekly or monthly) even if there are zero cases (combined reporting).</strong></td>
<td><strong>Implications</strong></td>
</tr>
<tr>
<td><strong>Recommended case definition</strong></td>
<td><strong>All outbreaks should be investigated immediately and confirmed.</strong></td>
<td><strong>Monitoring</strong></td>
</tr>
<tr>
<td>Acute hepatitis typically manifests as fever, malaise, nausea, anorexia, abdominal pain and right upper quadrant tenderness, and jaundice. Chronic hepatitis may result from acute hepatitis with persistence of symptoms for more than 6 months.</td>
<td></td>
<td><strong>Rationale for surveillance</strong></td>
</tr>
<tr>
<td><strong>Laboratory criteria for diagnosis</strong></td>
<td><strong>Aggregated data:</strong></td>
<td><strong>Interpretation of surveillance data</strong></td>
</tr>
<tr>
<td>Hepatitis A: positive for IgM and HBSAg (3–6 weeks after the onset of symptoms).</td>
<td><strong>Number of hospitalizations related to hepatitis A:</strong></td>
<td><strong>Hepatitis A</strong></td>
</tr>
<tr>
<td>Non-A, non-B: negative for IgM and HBSAg and IgG and non-B (less than 6 months).</td>
<td><strong>Number of hospitalizations related to hepatitis B:</strong></td>
<td><strong>Hepatitis B</strong></td>
</tr>
<tr>
<td><strong>Note:</strong> All infections occurring early childhood may be acute hepatitis.</td>
<td><strong>Number of hospitalizations related to hepatitis C:</strong></td>
<td><strong>Hepatitis C</strong></td>
</tr>
<tr>
<td><strong>Laboratory criteria for diagnosis</strong></td>
<td><strong>Number of hospitalizations related to hepatitis D:</strong></td>
<td><strong>Hepatitis D</strong></td>
</tr>
<tr>
<td>Hepatitis B: positive for anti-HBc and positive for HBsAg.</td>
<td><strong>Number of hospitalizations related to hepatitis E:</strong></td>
<td><strong>Hepatitis E</strong></td>
</tr>
<tr>
<td>Non-A, non-B: negative for IgM and HBSAg and IgG and non-B (less than 6 months).</td>
<td><strong>Number of hospitalizations related to hepatitis F:</strong></td>
<td><strong>Hepatitis F</strong></td>
</tr>
<tr>
<td><strong>Note:</strong> All infections occurring early childhood may be acute hepatitis.</td>
<td><strong>Characteristics of acute hepatitis by geographical areas, age, month and age group:</strong></td>
<td><strong>Hepatitis G</strong></td>
</tr>
<tr>
<td><strong>Case classification</strong></td>
<td><strong>Proportion of cases with chronic liver disease, cirrhosis and/or one that are HBeAg positive or anti-HBV positive:</strong></td>
<td><strong>Hepatitis H</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Special aspects:</strong></td>
<td><strong>Hepatitis I</strong></td>
</tr>
<tr>
<td><strong>Rationale for surveillance</strong></td>
<td></td>
<td><strong>Hepatitis J</strong></td>
</tr>
<tr>
<td>Some national regulations group acute viral hepatitis. Transmission is mainly by fecal-oral route for hepatitis A and F, and parenteral routes for hepatitis B, C, and D.</td>
<td></td>
<td><strong>Hepatitis K</strong></td>
</tr>
<tr>
<td><strong>Control measures for blood-related transmission include ensuring transfusion of blood and blood products are obtained from vaccinated donors and having a surveillance system for transfusion recipients.</strong></td>
<td></td>
<td><strong>Hepatitis L</strong></td>
</tr>
<tr>
<td><strong>Recommended case definition</strong></td>
<td></td>
<td><strong>Hepatitis M</strong></td>
</tr>
<tr>
<td>Acute hepatitis typically manifests as fever, malaise, nausea, anorexia, abdominal pain and right upper quadrant tenderness, and jaundice. Chronic hepatitis may result from acute hepatitis with persistence of symptoms for more than 6 months.</td>
<td></td>
<td><strong>Hepatitis N</strong></td>
</tr>
<tr>
<td><strong>Laboratory criteria for diagnosis</strong></td>
<td></td>
<td><strong>Hepatitis O</strong></td>
</tr>
<tr>
<td>Hepatitis A: positive for IgM and HBSAg (3–6 weeks after the onset of symptoms).</td>
<td></td>
<td><strong>Hepatitis P</strong></td>
</tr>
<tr>
<td>Non-A, non-B: negative for IgM and HBSAg and IgG and non-B (less than 6 months).</td>
<td></td>
<td><strong>Hepatitis Q</strong></td>
</tr>
<tr>
<td><strong>Note:</strong> All infections occurring early childhood may be acute hepatitis.</td>
<td></td>
<td><strong>Hepatitis R</strong></td>
</tr>
<tr>
<td><strong>Laboratory criteria for diagnosis</strong></td>
<td></td>
<td><strong>Hepatitis S</strong></td>
</tr>
<tr>
<td>Hepatitis B: positive for anti-HBc and positive for HBsAg.</td>
<td></td>
<td><strong>Hepatitis T</strong></td>
</tr>
<tr>
<td>Non-A, non-B: negative for IgM and HBSAg and IgG and non-B (less than 6 months).</td>
<td></td>
<td><strong>Hepatitis U</strong></td>
</tr>
<tr>
<td><strong>Note:</strong> All infections occurring early childhood may be acute hepatitis.</td>
<td></td>
<td><strong>Hepatitis V</strong></td>
</tr>
<tr>
<td><strong>Case classification</strong></td>
<td></td>
<td><strong>Hepatitis W</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hepatitis X</strong></td>
</tr>
<tr>
<td><strong>Rationale for surveillance</strong></td>
<td></td>
<td><strong>Hepatitis Y</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hepatitis Z</strong></td>
</tr>
</tbody>
</table>

**Special aspects:**

- **Hepatitis A**
  - Hepatitis A coverage in infants by year and geographical areas.
  - Number of acute viral hepatitis cases and incidence rates by year and geographical areas.
  - Number of acute viral hepatitis cases and incidence rates by month and age group.
- **Hepatitis B**
  - Proportion of cases with chronic liver disease, cirrhosis and/or one that are HBeAg positive or anti-HBV positive.
- **Hepatitis C**
  - Monitoring and monitoring of the prevention of transmission of hepatitis C.
- **Hepatitis D**
  - Monitoring and monitoring of the prevention of transmission of hepatitis D.
- **Hepatitis E**
  - Monitoring and monitoring of the prevention of transmission of hepatitis E.
- **Hepatitis F**
  - Monitoring and monitoring of the prevention of transmission of hepatitis F.
- **Hepatitis G**
  - Monitoring and monitoring of the prevention of transmission of hepatitis G.
- **Hepatitis H**
  - Monitoring and monitoring of the prevention of transmission of hepatitis H.
- **Hepatitis I**
  - Monitoring and monitoring of the prevention of transmission of hepatitis I.
- **Hepatitis J**
  - Monitoring and monitoring of the prevention of transmission of hepatitis J.
- **Hepatitis K**
  - Monitoring and monitoring of the prevention of transmission of hepatitis K.
- **Hepatitis L**
  - Monitoring and monitoring of the prevention of transmission of hepatitis L.
- **Hepatitis M**
  - Monitoring and monitoring of the prevention of transmission of hepatitis M.
- **Hepatitis N**
  - Monitoring and monitoring of the prevention of transmission of hepatitis N.
- **Hepatitis O**
  - Monitoring and monitoring of the prevention of transmission of hepatitis O.
- **Hepatitis P**
  - Monitoring and monitoring of the prevention of transmission of hepatitis P.
- **Hepatitis Q**
  - Monitoring and monitoring of the prevention of transmission of hepatitis Q.
- **Hepatitis R**
  - Monitoring and monitoring of the prevention of transmission of hepatitis R.
- **Hepatitis S**
  - Monitoring and monitoring of the prevention of transmission of hepatitis S.
- **Hepatitis T**
  - Monitoring and monitoring of the prevention of transmission of hepatitis T.
- **Hepatitis U**
  - Monitoring and monitoring of the prevention of transmission of hepatitis U.
- **Hepatitis V**
  - Monitoring and monitoring of the prevention of transmission of hepatitis V.
- **Hepatitis W**
  - Monitoring and monitoring of the prevention of transmission of hepatitis W.
- **Hepatitis X**
  - Monitoring and monitoring of the prevention of transmission of hepatitis X.
- **Hepatitis Y**
  - Monitoring and monitoring of the prevention of transmission of hepatitis Y.
- **Hepatitis Z**
  - Monitoring and monitoring of the prevention of transmission of hepatitis Z.
Objectives of the Updated Standards

- Provide updated global guidance on standards for VPD surveillance based on current thinking in the field
  - Include outbreak investigation and some response description
  - Not an SOP on how to set up surveillance since that is very country-specific
- Key resource for countries
  - Countries/regions will modify based on needs
  - Relevant to countries in different situations (e.g., level of resources and capacity, disease control, vaccine introduction)

Intended audience

- Immunization Program Managers
- Surveillance Officers
- Ministries of Health
- Partners in the field of surveillance/outbreak investigation
- WHO
  - Feeding into IDSR revision in AFRO
VPDs to be included in new guidelines

Diarrheal Diseases
- Cholera
- Rotavirus (and enteric pathogens)

Acute jaundice/fever
- Hepatitis A, B, E
- Yellow Fever

Invasive Diseases/Meningitis-Encephalitis
- *Haemophilus influenzae* type b (Hib)
- Pneumococcal disease
- Meningococcal meningitis
- Japanese encephalitis
- Typhoid

Fever/Rash
- Measles
- Rubella
- Dengue
- Varicella

Acute Flaccid Paralysis
- Poliomyelitis
- (Japanese Encephalitis)

Respiratory
- Influenza
- Pertussis

Diphtheria

Mumps

Tetanus (neonatal and non-neonatal)

Birth Defect
- CRS
- Human Papilloma Virus (HPV)

Diseases which will have entire chapter but may be briefly mentioned and referenced out
- Anthrax
- Ebola
- Malaria
- Rabies
- Tick-borne encephalitis
- Tuberculosis
- Zika

Rationale and Objectives of surveillance

Rotavirus

- To determine rotavirus disease burden and the epidemiology to facilitate and support the introduction of rotavirus vaccination
- To monitor impact of vaccination on disease and changes in epidemiology and circulating strains, after implementation
- To observe the spectrum of clinical presentations and outcomes of rotavirus cases
- To determine the age and seasonal distribution of hospitalizations associated with rotavirus in the population of children under 5 years of age under surveillance
- To identify the prevalent strains of rotavirus in the population under surveillance to aid in vaccine development
- To estimate vaccine effectiveness, potentially using surveillance as a platform for special studies
- To monitor burden of other enteric pathogens, namely ETEC, Shigella and norovirus
Approaches to surveillance

- Case-based
- Sentinel hospitals
- Syndromic surveillance of acute gastroenteritis
- Global minimum standard for rotavirus surveillance
  - One sentinel site per country with aggregated data reporting and laboratory confirmation
  - Depending on personnel and laboratory resources, some countries may choose to include additional sentinel sites or expand case definition and laboratory testing

Case definitions and classification

- Suspect case definition
  - Acute (e.g. ≤ 14 days) watery diarrhoea defined as three or more loose or watery stools in a 24-hour period and no blood in them in a child under 5 years of age who is admitted for treatment of diarrhoea to a participating hospital. Children with bloody diarrhoea are excluded.
- Final Case Classification
  - A confirmed case is a suspect case in whose stool the presence of rotavirus is demonstrated by means of an enzyme immunoassay (EIA)
**Laboratory testing**

Rotavirus

- Specimen collection: Whole stool (1-2 mL) within 48 hours of admission
- Confirmatory testing: Enzyme Immunoassays (EIAs)
- Additional testing
  - Confirmatory testing of by testing for the presence of VP6 gene using RT-PCR
  - Strain characterization is done by using RT-PCR to identify both G and P types
  - Subset of 50-60 randomly selected rotavirus-positive stools obtained from routine surveillance should be chosen for strain characterization per year
  - All non-typeable isolates should be sent to an appropriate laboratory for sequencing

**Rotavirus surveillance, other topics**

- Clinical/epidemiological description and vaccine characteristics
- Case investigation, contact tracing, and reporting
- Data collection, reporting and use
- Data analyses/use for decision making (including evaluation of vaccine impact)
- Case management
- Evaluation of surveillance
- Outbreak response
- Special considerations (including intussusception, other enteric pathogens)
Summary

• Maintain rotavirus and expanded pediatric diarrhea surveillance to fill key data gaps
• Sustainability and funding for support of surveillance
• Please review surveillance guidelines within next month and send comments to me

Acknowledgements

Sentinel hospitals
Ministries of Health
WHO country offices
WHO regional offices
Global, Regional and National Reference laboratories
Partners (CDC, Gavi, BMGF, University of Virginia)
Thank you

Adam L. Cohen, WHO  |  cohen@who.int
20, Avenue Appia
1211 Geneva
Switzerland