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Post-marketing surveillance of rotavirus vaccine safety

Immunization, Vaccines and Biologicals

World Health Organization

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Abbreviations and acronyms

ACIP	Advisory Committee on Immunization Practices (USA)
AEFI	adverse events following immunization
BCG	bacille Calmette-Guérin (vaccine)
CDC	Centers for Disease Control and Prevention (USA)
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
DPT	diphtheria-pertussis-tetanus vaccine
dsRNA	intracellular double-stranded RNA
EIA	enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GAD	glutamic acid decarboxylase
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
ICP	Inter-Country (Personnel) Team
IVB	Department of Immunization, Vaccines and Biologicals (WHO)
IVR	Initiative for Vaccine Research
RT-PCR	reverse transcription/polymerase chain reaction
VAERS	Vaccine Adverse Events Reporting System
WHO	World Health Organization

Preface

The Department of Immunization, Vaccines and Biologicals (IVB) of the World Health Organization has supported, through collaboration with various stakeholders and partners, the development of rotavirus vaccines aimed at preventing the morbidity and mortality worldwide associated with rotavirus gastroenteritis in infants. In 1998 there was great optimism when the first oral rotavirus vaccine was licensed in the United States of America (USA). (RRV-TV, Rotashield®, Wyeth Lederle Vaccines, USA). However, nine months later the vaccine was withdrawn due to an unexpected association with intussusception. Alternate rotavirus vaccines (Rotarix®, GlaxoSmithKline Biologicals (GSK) and Rotateq®, Merck Research Laboratories (Merck)) have been shown to be safe and effective in placebo-controlled Phase III clinical trials, each involving over 60 000 infants. However, their safety and performance outside the clinical trial setting and in a range of healthcare settings, has not been demonstrated. Therefore, post-marketing surveillance will be important for the detection of any rare or unexpected vaccine-related adverse events.

In view of the past experience with rotavirus vaccines, both with respect to the risk of adverse effects and varying efficacy in different settings, countries planning to introduce rotavirus vaccines are encouraged to develop a system of post-marketing surveillance for these vaccines. Such a system will require coordination between the national vaccine regulatory authority, the national immunization programme, and the relevant vaccine manufacturer(s), and may also involve collaboration with international partners. Currently there is substantial variability in the quality of post-marketing surveillance systems in different countries and in data regarding vaccine safety obtained from routine surveillance systems. As a result, these data may be difficult to interpret and be inadequate to guide vaccination policy. In recognition of these issues, the WHO Global Advisory Committee on Vaccine Safety (GACVS) and other expert groups have recommended a standardized approach to address potential safety issues to accompany the introduction of rotavirus vaccines, particularly in developing countries where the capacity to support post-marketing surveillance activities may be limited. The rationale for a standardized post-marketing surveillance approach is to enhance the quality of safety data available at the population level so that an adequate assessment of the safety of rotavirus vaccines can be established, and data can be comparable across countries and regions.

In response to the recommendation from the GACVS and other expert groups, IVB has developed this document — Post-marketing surveillance of rotavirus vaccine safety. The document provides background data regarding safety concerns of rotavirus vaccines and presents guidelines for routine post-marketing surveillance to assess the safety of rotavirus vaccines, with flexibility for adaptation at country level according to existing surveillance systems, health infrastructure and resources. A Technical Advisory Committee on post-marketing surveillance of rotavirus vaccine safety, established by IVB/IVR and the rotavirus subgroup of GACVS, is available to provide technical advice to enhance the quality of post-marketing surveillance activities aimed at assessing the safety and effectiveness of rotavirus vaccines.

The primary targets for this document are regulatory authorities and national immunization programmes in developing countries, with responsibility for routine post-marketing surveillance systems, often linked to immunization or pharmacovigilance programmes. However, to adapt it to the local setting, fieldwork and operational procedure details should be added with input from healthcare workers with expertise in diarrhoeal and surgical conditions, in particular, intussusception. The surveillance system and the information collected will also need to meet the standards and format required by the relevant national regulatory authority.

1. Introduction – potential safety concerns with rotavirus vaccines

Rotavirus infection is the leading cause of severe dehydrating gastroenteritis, and is responsible for >500 000 deaths per year worldwide in children <5 years of age (Parashar et al., 2003). Rotavirus infection is primarily spread via the faecal-oral route. The virus invades the small intestinal mucosa causing injury to the enterocytes and resulting in malabsorption and fluid loss. In a normal child rotavirus infection is self-limited, however diarrhoeal symptoms may persist due to secondary infection and/or lactose intolerance. The widespread deployment of efficacious rotavirus vaccines in developing countries is likely to contribute significantly towards attaining the United Nations Millennium Development Goals. The first oral rotavirus vaccine was licensed in the USA (Rotashield®, Wyeth) and was highly efficacious for the prevention of severe diarrhoea and hospitalization due to rotavirus infection (Joensuu et al., 1997; Perez-Schael et al., 1997; Bresee et al., 1999). However, Rotashield® was withdrawn nine months after introduction due to an increased risk of intussusception associated with the vaccine (Centers for Disease Control and Prevention, 1999; Prevention, 1999; Murphy et al., 2001; Bines, 2005; Justice et al., 2005; Bines, 2006). This was a major setback in efforts to reduce the global burden of rotavirus disease. Although the risk of development of intussusception associated with receipt of Rotashield® vaccine is estimated to be low (<1 in 10 000 vaccine recipients), this has had important implications for clinical trials of other rotavirus vaccine candidates (Murphy et al., 2001; Murphy et al., 2003). Recently developed rotavirus vaccines (Rotarix®, GSK and Rotateq®, Merck) have been shown to be safe and effective in placebo-controlled clinical trials, each of which included >60 000 infants. However, their safety and performance outside the clinical trial setting, in situations of routine use in a range of healthcare settings have not yet been demonstrated (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). When any new vaccine is introduced into a public-health programme, it is important to have in place a system to detect any unexpected adverse effects of vaccination that may not have been apparent in earlier clinical trials. In view of the past experience of adverse reactions associated with rotavirus vaccines, national vaccine regulatory authorities and immunization programmes are particularly encouraged to develop a system of post-marketing surveillance for rotavirus vaccines through which any rare or unexpected vaccine-related adverse events may be detected.

1.1 Intussusception

1.1.1 What is intussusception?

Intussusception is the most common cause of bowel obstruction in infants and young children with a peak incidence at four to ten months of age (Bines & Ivanoff, 2002). It occurs when one segment of the bowel becomes infolded within a more distal segment. If the resulting obstruction is not relieved, the vascular supply to the bowel becomes compromised resulting in bowel ischaemia and, if untreated, may be fatal. The symptoms and signs in children presenting with intussusception reflect the underlying pathophysiology. Intestinal obstruction causes vomiting, abdominal distension and abnormal or absent bowel sounds. The intussusception and associated oedema may be identified as a mass upon abdominal examination. Obstruction to the venous return or arterial supply of the intestine may result in rectal bleeding or the classic "redcurrant jelly" stool. Occasionally patients present in shock due to severe vascular compromise of the intestine. The diagnosis of intussusception is confirmed by radiology or by surgery, and is treated by air or hydrostatic reduction enema under x-ray or ultrasound guidance, or by surgery. About 10% of patients require an intestinal resection due to vascular injury to the intestine (Bines & Ivanoff, 2002).

In Australia, China, Hong Kong Special Administrative Region, and the USA, the average incidence of intussusception is <100 per 100 000 live births (Parashar et al., 2000; Nelson et al., 2002; Justice et al., 2005; Bines et al., 2006). A similar incidence is reported from Denmark, Israel, the Netherlands, Sweden and the United Kingdom (UK) (66–224 cases/100 000 < 1 year of age), and a lower incidence reported from Latin America (35–51 cases/100 000 < 1 year of age) (Carstensen et al., 1984; Reijnen et al., 1990; Eshel et al., 1997; Gay et al., 1999; Sardinas et al., 2001; Perez-Schael et al., 2003; Abate et al., 2004; O'Ryan et al., 2004). There are few data on incidence in developing countries, but such data as exist suggest that the incidence tends to be higher, for example a study in Viet Nam reported an incidence of >300 per 100 000 infants < 1 year (Bines et al., 2006). It is not known if infants in specific regions are at increased risk of intussusception due to genetic, cultural, dietary or environmental factors.

The causes of acute intussusception in the majority of cases are not known. In a small proportion of cases in infants an anatomical "lead point", such as a polyp, or Meckel's diverticulum, can be identified at surgery. The presence of mesenteric lymphadenitis in many infants with intussusception has focused attention on identifying a possible infectious agent. A number of viruses, bacteria and parasites have been identified in patients with intussusception, although there are few controlled studies aimed at identifying causative organisms (Bines& Ivanoff, 2002). Following the recognition of an association between intussusception and a rotavirus vaccine, the role of wild-type rotavirus infection and the development of intussusception has been investigated (Chang et al., 2001). Changes in the bowel wall thickness and characteristics observed on ultrasound of infants with acute rotavirus infection provide evidence that an association between natural rotavirus infection and intussusception is biologically plausible (Robinson et al., 2004). Rotavirus has been variably reported in the stool of patients with intussusception (3%–49%), but controlled studies do not suggest a significant association (Konno et al., 1978; Staatz et al., 1998; Bines et al., 2006;

Nakagomi et al., 2006). The lack of a seasonal association between rotavirus and intussusception hospitalizations is consistent with this observation (Chang et al., 2002; Bines et al., 2006). Adenovirus has been identified in the stool in over one-third of infants with intussusception in a case-controlled study in Australia and Viet Nam (Bines et al., 2006). Adenovirus has also been identified in the mesenteric lymph nodes of patients with intussusception (Clarke et al., 1969; Hsu et al., 1998).

In almost all studies, intussusception is reported more commonly in males (Bines & Ivanoff, 2002). Interestingly, a higher rate of a mobile caecum and ascending colon in the population of Nigeria has been proposed as an explanation for the high incidence of intussusception (Archibong et al., 1994). Differences in intussusception rate have been observed in different ethnic groups attending the same hospital in Israel and Kuwait, Malaysia, and Trinidad and Tobago, and a higher rate of intussusception following Rotashield® immunization was observed in Black and Hispanic infants than in Caucasian infants (Laidin & Goon, 1982; Issa et al., 1988; Eshel et al., 1997; Murphy et al., 2001). In addition to possible genetic factors, cultural factors, including age at weaning and/or the type of weaning foods, or the difference in opportunities for access to medical facilities, are alternative explanations for these observations (Laidin et al., 1982; Bines et al., 2006).

1.1.2 Diagnosis of intussusception

A definitive diagnosis of intussusception is based on the demonstration of invagination of the intestine on contrast enema (air or liquid), ultrasound or surgery. However, in some regions, access to radiological facilities and the necessary expertise to interpret paediatric radiographs may be limited. A clinical case definition for the diagnosis of acute intussusception in infants and children has been developed following recommendations of a meeting on the future of rotavirus vaccines held in February 2001 at the World Health Organization, Geneva, and through consensus of the Brighton Collaboration Intussusception Working Group (Bines et al., 2004). This definition provides a case definition that is suitable for use in studies conducted in different geographical regions with different health-care facilities and resources, and has been validated in a developed and developing country setting (Annex A) (Bines et al., 2006). The Brighton clinical case definition for intussusception has been endorsed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, and is available in French and Spanish (Brighton Collaboration, 2007).

1.1.3 History of intussusception and rotavirus vaccines

The first oral rotavirus vaccine licensed in the USA was the rhesus-human reassortant tetravalent vaccine (Rotashield®, RRV-TV: Wyeth Lederle Vaccines and Pediatrics, Marietta, PA, USA). This was a live-attenuated, oral vaccine consisting of three reassortant strains to be given orally in a 3-dose regimen. Pre-licensure trials demonstrated that the vaccine was highly efficacious for the prevention of severe diarrhoea and hospitalization due to rotavirus infection (Joensuu et al., 1997; Perez-Schael et al., 1997; Bresee et al., 1999). However, these trials also hinted at a possible association with intussusception. Five of 10 054 vaccine recipients (~0.5/1000) compared with 1 of 4633 controls (~0.2/1000) developed intussusception; however, this was not a statistically significant association (Rennels et al., 1998). As a result of this observation the Rotashield® package insert included intussusception as a potential adverse event.

The American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC) recommended universal immunization of all USA infants at 2, 4 and 6 months of age. The vaccine was licensed in August of 1998 and was available in October 1998. However, by July 1999, 15 cases of intussusception following vaccination had been reported to a passive surveillance system, the Vaccine Adverse Events Reporting System (VAERS), jointly operated by the US Food and Drug Administration (FDA) and the CDC, and the vaccination programme was suspended pending further investigation (Centers for Disease Control and Prevention, 1999). During the nine-month period of Rotashield® availability, more than 500 000 of the 3.8–4 million USA birth cohort had received at least one dose of vaccine (Smith et al., 2003). By September 1999, additional cases of intussusception had been reported in vaccine recipients and data were emerging to support a causal link between receipt of the vaccine and the development of intussusception (Centers for Disease Control and Prevention, 1999). In October 1999, the USA Advisory Committee on Immunization Practices and CDC withdrew its recommendation for Rotashield® and Wyeth Lederle Vaccines and Pediatrics voluntarily withdrew the vaccine from the USA market (Centers for Disease Control and Prevention, 1999).

A clear temporal relationship between receipt of the vaccine and the development of intussusception was demonstrated with cases of intussusception clustering between nine to 14 days following immunization with the first dose of the vaccine (odds ratio 21.7) (Murphy et al., 2001). The age at time of receipt of the first dose of Rotashield® appears to have influenced the risk of intussusception post-immunization. No cases of intussusception occurred in infants vaccinated at < 60 days of age despite 16% of all first doses received at that age (Simonsen et al., 2005). The risk therefore of intussusception following Rotashield® was highest in infants who received their first dose of vaccine after three months of age, perhaps coinciding with the "natural" high risk period for intussusception. However, this difference in risk according to age at first vaccination was not statistically significant.

Initial estimates suggested a risk of intussusception of 1 in 2500 vaccinees (Centers for Disease Control and Prevention, 1999; Murphy et al., 2001; Murphy et al., 2003). This led to projections that 1200 to 1600 excess cases of intussusception would occur if the entire USA birth cohort were immunized with Rotashield®. However, following a case-series and case-control analysis, estimates of intussusception risk were reduced to between 1 in 4500 and 1 in 9500 (Murphy et al., 2001). This reduction in risk was based on lower estimates of the baseline incidence of intussusception in infants in the USA (reduced from 51 to 34 cases per 100 000), and the reduced proportion of USA infants participating in the National Vaccine Program (Murphy et al., 2001; Murphy et al., 2003). Using a different methodological approach, a study examining hospitalizations for intussusception before and after Rotashield® availability failed to demonstrate an increase in hospitalizations in states with "high use" of Rotashield®. Based on these data, the risk of intussusception was estimated at ~ 1 excess case of intussusception per 32 000 infants during the immediate post-immunization period (Simonsen et al., 2001; Murphy et al., 2003).

The reasons for the association between the rhesus reassortant rotavirus vaccine and the development of intussusception are not known. It is not known if non-USA populations would have the same risk of intussusception following receipt of this vaccine. Two commercial rotavirus vaccines (Rotarix®, GSK and Rotateq®, Merck) completed Phase III clinical trials in 2005. Each of these trials was designed to include over 60 000 infants, in order to be able to assess the intussception risk. No association was identified between receipt of either vaccine and the development of intussusception (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). However, the safety and efficacy of these vaccines outside a clinical trial setting have not yet been demonstrated (Glass & Parashar, 2006). Any risks associated with these new rotavirus vaccines may only be identified after further trials or post-licensure surveillance studies.

The definition of baseline rates of intussusception and disease due to rotavirus will allow for estimation of potential attributable risks associated with vaccine, and this will enable a quantitative assessment of the potential risks and benefits of a vaccine programme. Local studies of intussusception can be used to shed light on causes of intussusception, and perhaps to identify new prevention and treatment methods.

1.2 Other gastrointestinal symptoms and signs

Although adverse event monitoring in the USA was focused on the development of intussusception during the period of RRV-TV availability, there were concerns that vaccination was also associated with a spectrum of other gastrointestinal illnesses. The Vaccine Adverse Events Reporting System (VAERS) in the USA reported that, after exclusion of intussusception cases, there was a higher proportion of reports of fever, bloody stool, vomiting, diarrhoea, abdominal pain, gastroenteritis, abnormal stool and dehydration in infants receiving RRV-TV, than reports relating to other vaccines (Haber et al., 2004). The median time interval between vaccination and illness onset was 3–7 days. Of the VAERS reports of children with potential adverse events following RRV-TV administration, 109 (24%) were diagnosed with intussusception, 36 (8%) were considered to have suspected intussusception, 33 (7%) an illness consistent with gastroenteritis or intussusception, 101 (22%) gastroenteritis, and 10 (2%) another gastroenterological diagnosis. The presence of bloody stool may potentially represent cases of spontaneously resolved intussusception. Only three reports indicated an enteric co-infection as the potential cause of the presence of blood in the stool. Post-marketing surveillance activities will be valuable in determining if other gastrointestinal symptoms occur as an adverse event following rotavirus immunization.

1.3 Shedding and transmission of vaccine virus strains

Natural rotavirus infection is primarily spread by the faecal-oral route. Upon infection, the virus replicates in the enterocytes causing cell damage. This results in a loss of intestinal absorptive surface, epithelial dysfunction and/or stimulation of secretions. The clinical symptoms of diarrhoea and dehydration reflect this pathophysiological mechanism (Estes, 2001; Widdowson et al., 2005). The detection of virus particles in the stool forms the basis of the diagnostic test for rotavirus infection. It is now recognized that rotavirus infection is not confined to the gut and that a significant proportion of patients with a high viral load (as detected by faecal shedding) have antigenemia and/or viremia (Blutt et al., 2003; Chiappini et al., 2005). Rotavirus has been detected in lymph nodes, liver, myocardium, lung and central nervous system in patients with rotavirus gastroenteritis, suggesting extraintestinal spread can

occur in some patients (Nuovo et al., 2002; Chiappini et al., 2005). Extraintestinal infection can be fatal, particularly in the immunocompromised (Nuovo et al., 2002). Rotavirus infection in immunocompromised patients may have a variable course, ranging from minor symptoms to severe and prolonged infection (Mori et al., 2002; Anderson et al., 2004). Whereas natural rotavirus infection is associated with antigenemia and viremia in gnotobiotic piglets, exposure to an attenuated human rotavirus strain (RRV-TV) did not have the same association. In addition, nasal shedding of the attenuated human rotavirus vaccine strain in vaccinated gnotobiotic piglets was greater than for the natural rotavirus infection, suggesting that some attenuated strains may be temperature sensitive (Wood & WHO IC Group, 2005).

The ability to infect human intestinal cells and shed vaccine strains in the stool varies according to the specific vaccine strain and its presentation. The Rotarix® (GlaxoSmithKline) vaccine is a monovalent vaccine derived from the most common human rotavirus strain G1P [8]. It replicates well in the intestine and is shed by more than 50% of patients after receiving the first vaccine dose (Glass et al., 2006). By contrast, Rotateq® (Merck) is a pentavalent vaccine based on a bovine strain (WC3), which does not grow as well in the human intestine, is infrequently shed in the stool and requires higher aggregate titres to achieve protection (Glass et al., 2006).

Although studies of the efficacy and safety of oral rotavirus vaccines are currently underway in infants with HIV, currently there are no clinical data that confirm the safety of rotavirus vaccines in immunocompromised individuals, including patients receiving immunosuppression or chemotherapy, or patients with infections such as HIV.

Oral poliovirus vaccine, another live-attenuated vaccine, was considered contraindicated for use in immunocompromised patients and their close household contacts due to the risk of transmission and its ability to cause severe illness (Lee, 2006). However, there are no published data to guide recommendations for rotavirus vaccine administration to the immunocompromised patient or their family. Post-marketing surveillance studies will be important to identify any potential risk of transmission to immunocompromised patients and the severity of illness in these patients.

1.4 Implications of antigenemia and viraemia after acute rotavirus infection

Extra-intestinal identification of rotavirus has been reported in lymph nodes, myocardium, liver and the central nervous system (Chiappini et al., 2005). The clinical symptoms in patients with extra-intestinal rotavirus infection are thought to be consistent with internal virus spread, and a number of potential mechanisms have been proposed (Ushijima et al., 1994; Iturriza-Gomara et al., 2002; Blutt et al., 2003; Kehle et al., 2003). One possible explanation is the passage of infectious rotavirus particles via lymphocytes in the circulation (Lynch et al., 2001). This may provide an explanation for the fever and exanthematous rash observed in some patients with acute rotavirus gastroenteritis (McCormack, 1982).

Rotavirus antigens have been identified in the sera of children hospitalized with severe gastroenteritis, suggesting the presence of non-infectious rotavirus or viral proteins (antigenemia) or infectious particles in the sera (viremia) (Blutt et al., 2003; Chiappini et al., 2005; Fischer et al., 2005). In a study of children with acute gastroenteritis, 22/33 (66%) of children with rotavirus detected in the stool had rotavirus antigen detected in the serum by enzyme immunoassay (EIA) (Blutt et al., 2003). Rotavirus antigen was detected only in acute sera suggesting that this was a transient finding. The study also found that nine of the 14 antigen-positive sera samples had rotavirus intracellular double-stranded RNA (dsRNA) detected by reverse transcription/ polymerase chain reaction (RT-PCR) suggesting that intact infectious particles may be present in the serum of patients with acute rotavirus infection (Chiappini et al., 2005). This is further supported by a study in gnotobiotic piglets who developed rotavirus diarrhoea after exposure (orally or intravenously) to serum from a rotavirus-infected pig (Azevedo et al., 2005). In gnotobiotic piglets infected with rotavirus, the occurrence of antigenemia was dependent on the magnitude of virus replication in the gut as evidenced by the level of rectal shedding (Azevedo et al., 2005).

The specific serotype or regions of the rotavirus may influence the ability to result in antigenemia and viraemia. Extra-intestinal spread was studied in neonatal mice infected with either simian rotavirus (SA11-C4) or rhesus rotavirus (RRV) (Mossel & Ramig, 2003). Whereas SA11-C4 was confined to the gut, RRV was found in intestine, mesenteric lymph node and peripheral tissues. G1 strains appear to have a unique tropism for blood. Where viral shedding showed the major strain to be G1, G1 rotavirus has been readily detected in the sera (Sim, 2006). Villous atrophy in gnotobiotic piglets was induced by virulent rotavirus, but not attenuated rotavirus (Ward, 1996). The authors suggest that virulent rotavirus created significant damage to enterocytes enhancing the penetration of the mucosal barrier into the blood stream. In particular, rotavirus VP8 protein and NSP4, a non-structural protein, are capable of disrupting tight junctions resulting in increased paracellular transit (Nava et al., 2004; Ramig, 2004).

In summary, data are emerging to support the observation that acute rotavirus infection is associated with antigenemia and viremia in a proportion of immunocompetent patients. However, there is a positive correlation between high levels of viral shedding in the gut and the presence of antigenemia. The levels of viral shedding required for antigenemia (reported to date) exceeds the level likely to be observed in healthy infants following vaccination using the currently available rotavirus vaccines. The lack of villous atrophy in gnotobiotic piglets receiving an attenuated rotavirus vaccine (RRV) compared to a virulent rotavirus is also suggestive that there may be less risk of transmission of antigen or viral particles with current rotavirus vaccines compared to natural infection (Ward 1996).

The identification of antigenemia and viremia following vaccination requires expertise in molecular biological techniques and is more suited to a specific Phase IV study rather than routine post-marketing surveillance systems.

1.5 Potential effect of malnutrition on vaccine safety

Although the efficacy of oral vaccines is lower in poor hygiene settings where malnutrition is common, the effect of protein energy malnutrition or micronutrient deficiency on vaccine safety has not been reported (Linhares et al., 2002; Wood & WHO IC Group., 2005). Protein energy malnutrition and specific micronutrient deficiencies are associated with delays in small intestinal recovery following natural rotavirus infection (Zijlstra et al., 1997), but it is not known if the delay in intestinal repair observed in malnutrition states result in an increase in the incidence or severity of vaccine-related adverse events. The major clinical trials of rotavirus vaccines reported to date have been performed in sites where malnutrition is uncommon. Studies are currently underway in Africa and Asia in areas with a higher incidence of malnutrition.

To identify a possible effect of protein energy malnutrition on vaccine safety, details of children with potential adverse events identified in post-marketing surveillance activities should include a record of age, weight and length that can be converted to region/ethnic-related percentile values or z-scores. Identification of specific micronutrient deficiencies would require a description of clinical features and laboratory measures of micronutrient status as part of a specific Phase IV surveillance activity.

1.6 Other potential rare adverse events

Rotavirus infection has been associated with central nervous system (CNS) disease by a number of groups (Nishimura et al., 1993; Goldwater et al., 2001; Lynch et al., 2001; Wong, 2001; Iturriza-Gomara et al., 2002; Kehle et al., 2003). In a United Kingdom study, PCR-genotyping together with cDNA sequencing demonstrated the same G1P[8] strain in paired faecal and cerebrospinal fluid samples from a child with gastroenteritis associated with meningitis and seizures (Iturriza-Gomara et al., 2002). The same G1 strain was identified in cerebrospinal fluid, sera and faecal samples of a patient in Japan with chronic gastroenteritis, seizures and encephalopathy (Ushijima et al.. 1994). It has been proposed that infectious viral particles in the bloodstream cross the blood-brain barrier to spread into the cerebrospinal fluid (Lynch et al., 2001). Alternative explanations include replication of virus in neuronal cells or lymphatics allowing transfer into the CSF (Goldwater et al., 2001; Mossel & Ramig., 2003). These episodes have been rare and are likely to be associated with infections causing high viral shedding or with specific serotypes (such as G1). To date there have been no reports of CNS disease associated with rotavirus vaccines.

In the Phase III trial of the G1P[8] human rotavirus vaccine Rotarix® (GSK) there was an excess of deaths due to pneumonia in infants receiving the rotavirus vaccine, 16 vaccine recipients and six placebo recipients (p=0.05) (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). However, there was no significant difference in pneumonia-related deaths reported within the first 31 days after vaccination or other pneumonia related serious adverse events including hospitalizations.

As rotavirus contains peptide sequences similar to T-cell epitopes in the islet autoantigens, glutamic acid decarboxylase (GAD) and tyrosine phosphatase, there has been concern that rotavirus infection may trigger or exacerbate islet cell auto-immunity in genetically susceptible children, leading to diabetes (Honeyman et al., 2000). However, conflicting results have been reported from studies investigating this hypothesis (Honeyman et al., 2000; Blomqvist et al., 2002). It is considered unlikely that there is only one exogenous determinant of Type 1 diabetes, but rather a complicated interaction between a series of environmental factors and between environmental factors and genetic disease resulting in the development of Type 1 diabetes (Knip & Akerblom, 1999).

Kawasaki disease in a vaccine trial following receipt of Rotateq® has been described in a small number of infants (n=5 vaccinated group compared with n=1 placebo) (WHO, 2007). However, it is unclear whether this rate in the vaccinated group is higher than expected in the normal population. Further studies are needed to investigate this potential association.

A high number of rotavirus infections have been reported to be associated with an increased risk of celiac disease in early childhood in genetically susceptible individuals (Stene et al., 2006). It has been suggested that the combination of transient increases in intestinal permeability associated with rotavirus infection and increased gut mucosa tissue transglutaminase, facilitate the deamination of cereal proteins into more immunogenic epitopes. It is hypothesized that in individuals with genetic susceptibility (HLA-DQ2 or DQ8) this insult may lead to an abnormal immunological response resulting in the development of celiac disease.

Post-marketing surveillance is likely to be an effective method for further investigating these rare observations. Identification of CNS disease or other rare events that may be related to vaccination should be clearly documented with reference to the time interval between vaccination and the onset of illness, clinical presentation, supportive diagnostic studies, and outcomes.

2. General surveillance methods

The primary purpose of post-marketing surveillance of vaccine safety is to identify adverse events, and in particular rare or unanticipated adverse events, that may be associated with specific vaccines, to distinguish those that are causally related to vaccination and to estimate their incidence. Surveillance systems should be set up to ensure that all suspected adverse events are reported, and the relevant information about them is collected and analysed appropriately. Post-marketing surveillance may be achieved through "routine" monitoring (often linked with national immunization programmes and/or pharmacovigilance programmes) or through Phase IV studies which are specially designed to assess vaccine effectiveness and safety. Post-marketing surveillance may involve either passive or active surveillance methods; active surveillance involves an active search for selected adverse events or active follow-up of vaccinees for a defined period. In most settings routine surveillance is based on passive or spontaneous reporting. By contrast, active surveillance is usually done in the context of Phase IV studies that are designed to address a specific research question or questions related to vaccine effectiveness or potential adverse events.

Passive reporting systems play an important role in the detection of vaccine-related adverse events, but they do have important limitations. Some of the limitations are under-reporting of adverse events, incomplete data on cases, diagnoses not verified, and limited duration of follow-up after vaccination. Adverse events identified in a passive surveillance system cannot be used to measure true incidence rates due to reporting bias and lack of accurate numerators and denominators. While passive surveillance is a valuable tool to identify a potential adverse event related to vaccination, it often provides insufficient data to establish causality. Where relevant and possible, potential signals of vaccine-related adverse events generated through passive surveillance should be followed up, with appropriate research investigations, to try to establish whether or not the association between vaccination and the event is causal.

The surveillance system proposed in this document focuses on routine surveillance with two components: an active hospital/health facility-based surveillance and a stimulated passive surveillance based primarily on spontaneous reporting. Common elements of surveillance are outlined below while the passive and active surveillance components are described in further detail in the next two sections.

2.1 Adverse events to be reported

Reportable events should be stated with clear case definitions for reporting. Surveillance should focus on conditions following vaccination that are classified as "serious".

A **serious adverse event** is defined as: any untoward medical occurrence that results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is life-threatening.

Potential **serious** adverse events of special relevance for rotavirus vaccines include:

- Intussusception;
- other gastrointestinal symptoms and signs;
- hospitalization for unexplained medical events following vaccination;
- unexplained death following vaccination;
- other rare events thought to be related to rotavirus vaccination or otherwise causing concern, including pneumonia or central nervous system signs and symptoms.

Non serious adverse events following rotavirus vaccination (with or without other concurrent vaccines) should be reported, as recommended under the existing surveillance system for adverse events following immunization (AEFI). Where a national AEFI system does not yet exist, standard WHO guidelines for AEFI surveillance may be followed to establish one (refer to *Surveillance of adverse events following immunization – Field guide for managers of immunization programmes,* accessible at http://www.who.int/immunization_safety/publications/aefi/en/.

A number of standardized AEFI case definitions have been developed by the Brighton Collaboration (an international voluntary network of health professionals) to improve the quality and comparability of vaccine safety data — (http://www.brightoncollaboration.org). The Brighton Collaboration clinical case definition for acute intussusception in infants is used in this protocol to identify cases of intussusception (Annex A). The use of Brighton Collaboration case definitions for other adverse events is encouraged where these are available. While these case definitions are less suited for initial reporting of cases, data collected should allow cases to be analysed according to the different levels of certainty in the case definitions.

2.2 Who should be involved in reporting?

It will be important to include both public and private health-care providers and health facilities in reporting. Designated AEFI surveillance personnel in the existing system should be involved in the stimulated passive surveillance (see below) of potential adverse events following rotavirus vaccination, and trained as necessary. In addition, efforts should be made to expand to the private sector if relevant.

Active surveillance will require clearly-defined surveillance sites, such as specific hospitals and clinics. Each surveillance site will require a surveillance monitor who will perform active search for cases and follow up to complete reporting forms.

Systems should be put in place to detect any duplicate reporting of cases. In addition, designation of a responsible AEFI surveillance officer/investigator is recommended for each site (e.g. clinician to review cases when detected). The role of the surveillance officer is to review completed forms for completeness and to advise on additional data to be collected or investigations to be done. A central monitor who maintains contact with all site monitors, and provides support and guidance to assist in their work, will be important to the success of surveillance activities. The central monitor can be the national focal point responsible for AEFI monitoring. If a different person is designated as the central monitor for active surveillance, he/she should liaise closely with the national AEFI focal point and ensure all data collected are regularly shared. Specific details of who is involved will have to be decided at country level according to the infrastructure and resources available. In all cases, the roles and responsibilities of all key persons involved in reporting should be clearly defined and documented, and appropriate training on the surveillance protocol should be provided.

2.3 Reporting methods (flow)

It will be important that serious events as defined above are reported on a timely basis to ensure that potential signals of vaccine adverse effects are continuously monitored and analysed appropriately. In order to ensure that all serious events are appropriately investigated and complete data made available to the central database, suspected serious events that may be detected through the passive surveillance system should be reported immediately to the site monitor in the nearest active surveillance site for follow-up (with copy to the next reporting levels in the passive system). Follow-up for additional information and the appropriate investigation will require coordination between the active surveillance monitor and the responsible health-care worker who notified the case. Reporting of cases through active surveillance is described in the next chapter. As few developing countries have experience with active post-marketing surveillance systems, adequate resources (including personnel, training and funding) will need to be identified. Overall, post-marketing surveillance will need to be supported with adequate case investigation capacity to ensure intussusception and other serious adverse events are appropriately worked up.

2.4 Issues specific to intussusception

Data defining the incidence and prevalence of intussusception should be presented with reference to the known specific population at risk; such as cases of intussusception/1000 infants (aged < 1 year) or /1000 children aged < 2 years; cases of intussusception/1000 live births and/or cases of intussusception/1000 infants administered rotavirus vaccine in the same age group in the specific region or country in a defined time period. In view of the data suggesting the importance of age at receipt of the first rotavirus vaccine and the risk of intussusception, cases of intussusception should be presented according to the age at presentation and compared to baseline data on the natural history of presentation of intussusception in that population. Age groups should be defined according to the data available (1 month intervals or <60 days versus > 60 days). Time from receipt of vaccination to presentation with intussusception should be recorded. If possible, the gender and race/ethnicity of cases should be described and the clinical presentation, outcomes and seasonality of cases should be summarized. All analysis should be performed separately for all sites as well as for all sites combined.

The Brighton Collaboration clinical case definition for acute intussusception in infants and children provides a set of standardized clinical criteria that have been validated in a developed and developing country setting (Bines et al., 2006). The definition divides clinical events into a classification according to the level of evidence for diagnostic certainty (Bines et al., 2004); level 1 of diagnostic certainty is defined as a confirmed or definite case of intussusception (Annex A). However to capture all clinically suspected events of intussusception, it is recommended that data should be collected and reported on all suspected cases, irrespective of whether the Brighton Collaboration case definition has been met.

2.5 Data-sharing

Communication between the key surveillance stakeholders in each country, regulatory authorities, immunization programmes, and pharmacovigilance centres where they exist, is critical. It is also important that information regarding serious adverse events is transmitted from the national level to the global level and to vaccine manufacturers in a timely manner, to enhance detection of signals for further investigation. Serious events should be reported to the relevant vaccine manufacturer as soon as they are notified to the national level. In addition, countries are encouraged to submit reported data on adverse events to the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring).

3. Active surveillance

3.1 Selection of surveillance population and participating hospitals

The choice of population may be influenced by several factors. Ideally, the population should be demographically and geographically well described. However in limited resource settings accurate data describing the surveillance population may be lacking. In areas where baseline population data are not available or are incomplete and where further investigation is required, collection of data on adverse events may still be valuable in identifying safety concerns and targeting limited resources. Data should be available on the number of births, infants aged less than one year, and the age and sex distribution of the population. Immunization practices should be well described in the study population. In particular, the schedule for administration for rotavirus vaccines, type of vaccine used, and the uptake rate of rotavirus vaccines, should also be well defined.

An important objective of these guidelines is to facilitate the determination of the incidence of intussusception following rotavirus vaccination. Therefore, the discussion on active surveillance focuses on the detection of intussusception. Similar principles can be applied for the active surveillance of all potential serious adverse events.

Wherever possible, the baseline incidence of intussusception should be known for the study population prior to introduction of rotavirus vaccines. The baseline incidence of intussusception prior to the introduction of rotavirus vaccines should be based on recent local data, as temporal changes in the incidence of intussusception, unrelated to vaccination, have been reported in a number of regions (Fischer et al., 2004; Justice et al., 2005). As intussusception is diagnosed and treated in a hospital or clinic setting, post-marketing surveillance for intussusception should be conducted at hospitals and clinics expected to provide care for nearly all cases of intussusception in the study population. Selection of sites for active surveillance should be based on hospitals or clinics that have the capacity to diagnose and treat intussusception, or a reliable system to transport the patient to a reference hospital. This capacity includes experienced staff to recognize symptoms associated with intussusception, radiological and/or ultra-sonography for diagnosis, and paediatric, surgical and radiological staff for treatment. Skills in adequate record-keeping practices are necessary for the recording and linkage of laboratory and clinical data.

A survey of all hospitals and clinics that may manage infants with intussusception may be needed to ensure that the hospitals selected for inclusion in the surveillance activity capture sufficient patients. The locations of the hospitals can be mapped and the number of children presenting with intussusception during the previous year can be determined. A study population that has good access to a single hospital or a small number of hospitals is ideal. All government and private hospitals serving the defined population should be included. If possible, each group of institutions should serve a population of known size, and for which the age-specific denominator is known. This will allow for calculation of disease rates at the conclusion of the period of surveillance.

The population should have good access to medical and surgical care within the surveillance area. Access to a hospital may be determined by measuring the distance to the hospital from different areas under surveillance, taking into account any areas with poor roads or none, a lack of public transport, and natural barriers such as rivers. Also, residents in the surveillance site should be those most likely to seek medical or surgical care in the hospitals or clinics selected as surveillance sites. It may be necessary for sites wishing to conduct active surveillance to conduct a survey of health-care service utilization at the beginning of the study. Knowledge of the attitudes and practices of the population and primary health-care services concerning symptoms that may occur in infants, may be vital for the design of surveillance studies aimed at understanding disease burden and for comparison between different settings. The *WHO generic protocol for a community-based survey on utilization of health-care services for gastroenteritis in children* (WHO/V&B/02.15) can be used to guide a survey on health-care service utilization for surveillance activities.

3.2 Duration of surveillance

The duration of surveillance should be for at least 12 months after the last dose administered to account for potential seasonal variability in the presentation of adverse events such as intussusception or other gastrointestinal symptoms. As there is annual variability in the incidence of intussusception, a surveillance period of > 12 months would be ideal for an attempt to document incidence of intussusception following rotavirus vaccination, taking into account background seasonal trends.

3.3 Case-finding

3.3.1 Intussusception

Children with suspected or confirmed intussusception admitted to or cared for at participating sites, should be identified by the designated surveillance monitor for each site within 24 hours of presenting to the hospital (or during their hospital stay if they are not admitted or stay less than 24 hours). Depending on the facility, the methods of case-finding may vary. In hospitals where all children with suspected intussusception are admitted to the paediatric or surgical ward, surveillance personnel may be assigned to review daily admission logs and review admissions with ward nurses each day. In settings where children are primarily seen as outpatients and treated without admission, involvement of health care-staff in radiology might be more efficient. Since most sites will care for children in a variety of settings, surveillance personnel in charge of active surveillance at each site will be required to include daily surveillance of hospital admission logs, wards, radiology services, and perhaps surgical services and emergency centres (Scheifele DW et al., 2003). The optimal settings in which to

concentrate surveillance can be guided by review of retrospective hospital admission data to audit the completeness of case-finding. Sites should ensure that a high proportion (>80%) of expected, eligible patients, are detected and 7enrolled — based on retrospective data. Monthly reviews of data should be used to assess the sensitivity of the system and to guide changes in methods.

3.3.2 Other serious adverse events

No active search of cases is recommended for other serious adverse events. However, it may be helpful for the monitor to set up a network of communication within the surveillance site that ensures other serious events known to occur following rotavirus vaccination (or where the vaccine is unclear) will be flagged to his/her attention for follow-up and reporting if relevant. In addition, serious adverse events detected by passive surveillance should be notified to the respective active surveillance monitor, and should be followed up actively for collection of data and investigation when needed (see also Chapter 4).

3.4 Case definition

3.4.1 Intussusception

Data on each case of intussusception should be recorded if the child meets the criteria below.

- Their age is ≤24 months at the time of diagnosis of intussusception (patient becomes ineligible on the day of their second birthday).
- The subject is diagnosed with intussusception based on:
  - level 1 of diagnostic certainty using the Brighton Collaboration clinical case definition (Annex A);
  - the subject is suspected of having intussusception based on Level 2 or Level 3 of diagnostic certainty using the Brighton Collaboration clinical case definition (Annex A);
  - the subject is suspected of having intussusception but there is insufficient information to establish the diagnosis according to the Brighton Collaboration clinical case definition (these latter patients will be defined as unconfirmed cases of intussusception and analysed accordingly as other adverse events).
- The subject is diagnosed with intussusception during the defined surveillance period (sites should attempt to conduct surveillance for 1–2 years).
- A child will be defined as a potential rotavirus vaccine-related intussusception case if he/she has received a rotavirus vaccine prior to the episode of intussusception.

If a diagnosis of intussusception has been excluded on the basis of clinical assessment and/or appropriate investigations defined in the Brighton Collaboration clinical case definition (Annex A), the case should be reported as another potential adverse event using the case data form (Annex C).

3.4.2 Other serious adverse events

Other serious adverse events of interest are listed in section 2.1. Symptoms and signs relating to other potential serious adverse events should be described in detail, and the clinical diagnoses should be recorded so that events can be coded and analysed appropriately. If available, standardized case definitions (such as those of the Brighton Collaboration) should be used.

3.5 Non-eligibility for reporting

A child is not eligible for reporting as a potential adverse event case if rotavirus vaccination has definitely not been received. However, if the medical event is temporally related to another vaccine, a standard AEFI report, as recommended for existing guidelines, should be submitted.

3.6 Immunization data

Documentation of immunization details is mandatory for each case of intussusception. This includes details (vaccine product/manufacturer, lot number, expiry date) of all vaccines received (and diluents where relevant) and the date and time received. Any symptoms reported following prior immunization should be documented as part of the vaccination history. Data on the type of rotavirus vaccine administration, and the time interval between receipt of the vaccine and the onset of symptoms and diagnosis of illness must be documented. Administration of any pharmacological agents or traditional medicines coinciding with immunization or in the post-immunization period should be detailed. A history of any medications prior to the current immunization should also be documented. The case data form (Annex C) provides a sample format for collection of this information.

3.7 Completion of case data form

For each case of a suspected adverse event, a case data form (Annex C) should be completed. This case data form should be completed through medical chart abstraction and an interview with the patient's family. It is designed to confirm that a case meets the eligibility criteria and to collect data regarding some details of the current episode of illness, including diagnosis, treatment and outcome, physical examination findings on admission, laboratory values, information on surgical and radiographic procedures performed, and pathological findings. In addition, this form will include follow-up information, such as the length of hospital stay, the outcome, and the discharge diagnoses and International Classification of Diseases (ICD-10) codes applied to the record. Finally, questions regarding feeding, recent illnesses and medical history can be added, to develop hypotheses for etiology and predisposing factors that might be tested in follow-up epidemiological studies. Monitors will often need to contact primary health-care providers to access accurate immunization records, including details of the specific vaccine(s) administered and the exact date(s) of administration (see Annex C).

3.8 Reporting of cases

Site monitors should inform respective site surveillance officers/investigators and the central monitor daily of any suspected case of intussusception as well as any other serious adverse event that is detected. Site monitors should also complete a case report form for each adverse event case in as timely a fashion as possible, and forward the completed form to their respective surveillance officer/investigator. While some elements of the form may take longer to complete, the aim should be to provide an initial case report form within 24 hours of case detection. A follow-up form (or forms) should then be provided as data become available, always ensuring that the same case identification number is used. Ideally, an electronic system linking surveillance sites (and the central level) should be set up for reporting. Where this is not possible, completed forms, without patient identifiers but with a unique reference number, should be sent to the designated central monitor for review of data completeness and entry into a central computerized data- management system. Monthly reports of adverse event data collected should be communicated to all stakeholders at national and sub-national levels.

3.9 Case identification

Adverse event cases should be identified solely by a unique case number in all materials that are used for reporting and analysis of surveillance data, including all materials that are sent to any site other than the site at which the data are collected. No patient identifiers should be used in the analyses, nor should any identifying information be used in any reports or publications that may arise from the surveillance activity or follow-up studies.

3.10 Specimen collection, handling and analysis

Except when necessary as part of the investigation of a reported case, the collection of clinical specimens for each case is not required. Sites may choose to collect such specimens to investigate specific research questions regarding the etiology or risk factors for intussusception in their population. A guide to the collection, handling and analysis of stool, blood and intestinal specimens has been included in Annex E, to provide assistance for further studies.

4. Stimulated passive surveillance

Passive reporting in post-marketing surveillance contributes, when appropriate, to the detection of adverse event signals that require further investigation and research. Passive reporting can also be particularly useful in the detection of delayed adverse events. Stimulated passive surveillance should be based on the existing surveillance system for AEFI in each country; countries that do not yet have an AEFI surveillance system in place may refer to the generic WHO protocol from WHO Western Pacific Regional Office *Immunization safety surveillance. Guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization* which is accessible at http://www.who.int/immunization_safety/publications/aefi/en/).

Stimulation of the passive system to improve reporting may be achieved through various means, such as:

- providing easy access to reporting forms (e.g. prepaid forms, online forms);
- providing regular training and retraining on the surveillance system for staff;
- ensuring sufficient staff are designated and resources are allocated for reporting and supervision;
- establishing a system of sending regular reminders;
- acknowledging receipt of forms and providing regular feedback (e.g. summary reports, newsletters) to sustain interest of reporters;
- monitoring performance;
- facilitating the participation of surveillance officers in scientific and other (e.g. professional association) meetings.

Most importantly there should be regular review of incoming data and active follow- up and investigation of serious events. Where an active system has been set up, such cases should be notified to the respective active surveillance monitors for more efficient and complete follow-up.

4.1 Who should report?

Reporters at all levels, including peripheral health units, both district, regional and national, should be trained on the specific adverse events of interest in the post-marketing surveillance of rotavirus vaccines. Relevant reporting forms and case definitions (appropriate to the reporting level) should be made available. In particular, district level upwards should, where possible, designate a responsible officer who can determine if a reported event meets the reporting criteria for rotavirus vaccines.

Serious adverse events should be referred immediately (upon detection) to the active surveillance monitor for appropriate follow-up.

It is critical that private physicians and clinics be included in the passive surveillance system. AEFI surveillance systems should be strengthened by establishing links to private health-care services and to physicians in secondary and tertiary facilities through steps such as:

- education and advocacy (e.g. through meetings, continuing medical education activities, etc.);
- providing clear guidelines on reporting and relevant documents, including reporting forms;
- providing feedback on surveillance (including events reported, outcomes and actions taken);
- creating or using existing networks (e.g. professional medical associations) to optimize involvement of key individuals in clinical services (public and private) in the investigation of serious events or further research of suspected associations.

4.2 When to report?

All ***serious*** reportable events should be reported immediately to the appropriate active surveillance monitor for active follow-up, and concurrently to the next level within the passive system.

Non serious events (e.g. mild to moderate local or systemic events) following rotavirus vaccination (with or without other vaccines) should be reported according to the existing AEFI surveillance system for each country. It should be noted that newly- established AEFI systems may include reporting of all adverse events to create a culture of reporting. The information for rotavirus vaccine (as for any other vaccine(s) received) should be complete and accurate; this includes vaccine product/manufacturer, lot number, date and time of vaccination, and site and route of administration.

4.3 How to report?

Whenever possible, the initial report of serious adverse events to the active surveillance monitor should be made on the detailed case report form (see sample form in Annex C) entering as much information as possible. Where this is not possible, the initial report may be made using the existing AEFI report form. The active surveillance monitor should ensure that the more detailed report form is completed once case details are obtained on follow-up.

5. Analysis and interpretation of data

5.1 Data analysis

The reporting rate of total and specific adverse events should be calculated based on the known population of vaccinated children and be expressed in age groups. All analysis should be performed for all sites as well as for all sites combined. Data should be presented with a numerator and denominator and not in percentages alone. Special efforts should be made to obtain denominator data for the number of children who have received rotavirus vaccine by age at vaccination; ideally this should be grouped by one month intervals to allow maximum flexibility in analysis of safety data. In some regions denominator data may not be easily accessible and therefore approximations may be necessary. The source of the denominator should be reported (i.e. Ministry of Health, manufacturers data) and calculations of estimates described.

Adverse event episodes should be calculated according to the vaccine characteristics (dose, type, vaccine lot) and the time interval between receipt of vaccine and the onset of the adverse event. Patient characteristics, including age at onset and diagnosis (monthly intervals if possible), sex and ethnicity should be described. Co-administration with other vaccines, medications and traditional therapies, should be reported in analyses. Data for rotavirus vaccine co-administered with other vaccines should be compared to the data for the individual vaccines in the same population. Regional and seasonal distribution of cases with and without rotavirus vaccination should be described.

All reported cases of suspected intussusception should be presented according to the classification outlined below.

- Events that meet the criteria for intussusception.
- Level 1: As specified in the case definition for intussusception.
- Level 2: As specified in the case definition for intussusception.
- Level 3: As specified in the case definition for intussusception.
- Events that do not meet the case definition for intussusception.
- Intussusception reported with insufficient evidence to meet the case definition.

The rate of intussusception-associated hospitalizations should be calculated based on the known population of children ≤ 24 months of age (and for finer age groups if possible). The rate of intussusception occurring in relationship to rotavirus vaccination should be compared with respect to the known baseline incidence of intussusception in the population.

The incidence of cases in the surveillance population can be presented in tables or figures with reference to the baseline data in the surveillance population or in unvaccinated infants. Examples of data presentation are provided in Figures 1 and 2.

5.2 Causality assessment

Causality assessment requires consideration of the strength of association, consistency, specificity, biologic plausibility, coherence, experimental evidence and analogy (WHO, 2001). The clearest and most reliable way to determine whether an adverse event is causally related to vaccination is by comparing rates of the event in vaccinated and non-vaccinated groups in a randomized clinical trial. Observational studies, such as the self-controlled case series, may also be helpful in assessing risk in a vaccinated population (Murphy et al., 2001). Causality associations cannot usually be confirmed from reports of individual cases without definitive laboratory studies; nonetheless causation may be suspected if there is definite evidence of an increased risk of the event in vaccinated persons.

However, establishing a systematic review of serious adverse events to determine the likelihood of a causal association between an event and the vaccine received can contribute to the analysis of data collected in routine post-marketing surveillance. It can assist in distinguishing true adverse reactions from coincidental events, increase credibility in the surveillance programme, and assist in making decisions on further action needed. Such causality assessment will be most effective if done in a comprehensive and standard manner consistent with international pharmacovigilance criteria — refer *WHO Aide Memoire: AEFI causality assessment* accessible at http://www.who.int/immunization_safety/publications/aefi/en/).

Where it does not already exist, an expert advisory committee may be established to: (a) review individual cases of intussusception or other serious or unusual AEFIs in order to assess the causal link between the event and the vaccine; (b) monitor reported AEFI data for potential signals of previously unrecognized adverse events.

It is recommended that the committee has broad expertise, including a paediatrician, a gastroenterologist, a microbiologist/virologist, and an epidemiologist. In addition, representatives of the national immunization programme and the national vaccine regulatory authority should participate in the meetings of the committee to review cases. Designated immunization programme officers may be invited to participate in meetings of the committee to review AEFI cases reported in their region/district. A sample standardized causality assessment form is provided in Annex D and may be modified as needed for use by the committee.

Figure 1 : Age of children diagnosed with intussusception
in the two years before introduction of a rotavirus vaccine (shaded bars)
and in the 2-year surveillance period after introduction
of a rotavirus vaccine (solid line)
(Example - not actual data)

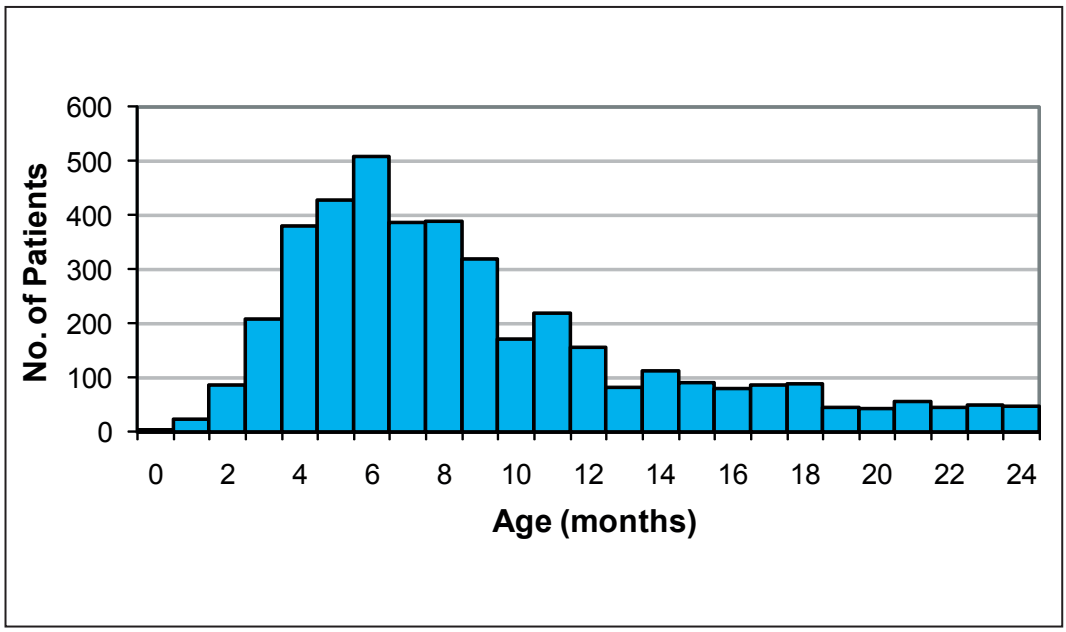
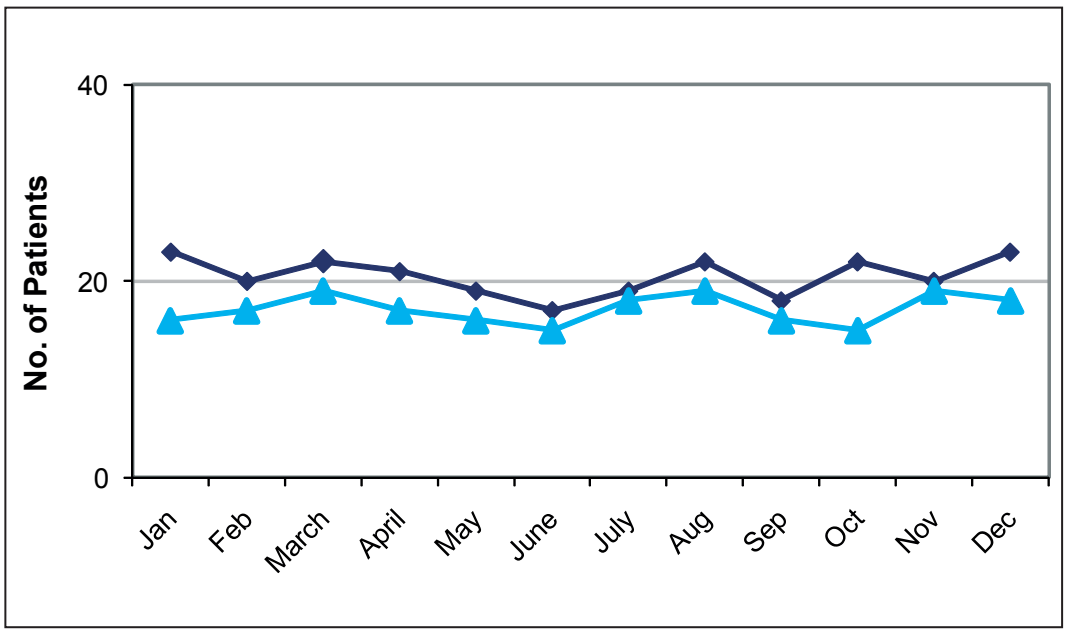


Figure 2 : Seasonal distribution of cases of intussusception in vaccinated
(blue line) and unvaccinated (yellow line) infants during
the 2-year surveillance period
(Example - not actual data)



6. References

Abate H et al. (2004). *A multi-center study of intussusception in Latin America: First year results*. Cancun, Mexico, ICP.

Advisory Committee on Immunization Practices (1999). Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*, **48**(RR-2):1–20.

American Academy of Pediatrics (1998). Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. American Academy of Pediatrics. *Pediatrics*, **102**(6):1483–1491.

Anderson EJ, Weber SG (2004). Rotavirus infection in adults. *The Lancet Infectious Diseases*, **4**(2): 91–99.

Archibong AE et al. (1994). Intestinal obstruction in southeastern Nigerian children. *East African Medical Journal*, **71**(5): 286–289.

Azevedo MS et al. (2005). Viremia and nasal and rectal shedding of rotavirus in gnotobiotic pigs inoculated with Wa human rotavirus. *Journal of Virology*, **79**(9):5428–5436.

Bines J (2006). Intussusception and rotavirus vaccines. *Vaccine*, **24**(18):3772–3776.

Bines J, Ivanoff B (2002). *Acute intussusception in infants and children: a global perspective*. Geneva, World Health Organization (WHO/V&B/02.19).

Bines JE (2005). Rotavirus vaccines and intussusception risk. *Current Opinion in Gastroenterology*, **21**(1):20–25.

Bines JE et al. (2004). Clinical case definition for the diagnosis of acute intussusception. *Journal of Pediatric Gastroenterology and Nutrition*, **39**(5):511–518.

Bines JE et al. (2006a). Risk factors for intussusception in Vietnam and Australia: adenovirus implicated, not rotavirus. *The Journal of Pediatrics*, **149**(4):452–460.

Bines JE et al. (2006b). Validation of clinical case definition for acute intussusception in infants in Viet Nam and Australia. *Bulletin of the World Health Organization*, **84**(7):569–575.

Blomqvist M et al. (2002). Rotavirus infections and development of diabetes-associated autoantibodies during the first 2 years of life. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*, **128**(3):511–515.

Blutt SE et al. (2003). Rotavirus antigenaemia and viraemia: a common event? [see comment]. *Lancet*, **362**(9394):1445–1449.

Bresee JS et al. (1999). Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. *Vaccine*, **17**(18):2207–2222.

Brighton Collaboration (2007). Intussusception with 2007 addendum. http://www.brightoncollaboration.org/internet/en/index/definition___guidelines/document_download.html

Carstensen H et al. (1984). [Lavage as an effective and careful method of treating children]. *Läkartidningen*, **81**(34):2941–2944.

Chang EJ et al. (2002). Lack of association between rotavirus infection and intussusception: implications for use of attenuated rotavirus vaccines. *The Pediatric Infectious Disease Journal*, **21**(2):97–102.

Chang HG et al. (2001). Intussusception, rotavirus diarrhea, and rotavirus vaccine use among children in New York state. *Pediatrics*, **108**(1):54–60.

Chiappini E et al. (2005). Viraemia is a common finding in immunocompetent children with rotavirus infection. *Journal of Medical Virology*, **76**(2):265–267.

Clarke EJ Jr. et al. (1969). Adenovirus infection in intussusception in children in Taiwan. *JAMA : the journal of the American Medical Association*, **208**(9):1671–1674.

Eshel G et al. (1997). Intussusception: a 9-year survey (1986–1995). *Journal of Pediatric Gastroenterology and Nutrition*, **24**(3):253–256.

Estes MK (2001). Rotaviruses and their replication. In: DM a. H, Knight PM, eds. *Fields Virology*, Philadelphia, Lippincott-Raven, 1747–1785.

Fischer TK et al. (2004). Intussusception in early childhood: a cohort study of 1.7 million children. *Pediatrics*, 114(3):782–785.

Fischer TK et al. (2005). Health care costs of diarrheal disease and estimates of the cost-effectiveness of rotavirus vaccination in Vietnam. *The Journal of Infectious Diseases*, **192**(10):1720–1726.

Gay N et al. (1999). Rotavirus vaccination and intussusception. *Lancet*, **354**(9182):956.

Glass RI, Parashar UD (2006). The promise of new rotavirus vaccines. *The New England Journal of Medicine*, **354**(1):75–77.

Glass RI et al. (2004). The future of rotavirus vaccines: a major setback leads to new opportunities. *Lancet*, 363(9420):1547–1550.

Goldwater PN et al. (2001). Rotavirus encephalopathy: pathogenesis reviewed. *Journal of Paediatrics and Child Health*, **37**(2):206–209.

Haber P et al. (2004). An analysis of rotavirus vaccine reports to the vaccine adverse event reporting system: more than intussusception alone? *Pediatrics*, **113**(4):e353–e359.

Honeyman MC et al. (2000). Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes*, **49**(8):1319–1324.

Hsu HY et al. (1998). Viral etiology of intussusception in Taiwanese childhood. *The Pediatric Infectious Disease Journal*, **17**(10):893–898.

Intussusception among recipients of rotavirus vaccine — United States, 1998–1999. (1999). *MMWR. Morbidity and mortality weekly report*, **48**(27):577–581.

Issa MA et al. (1988). The pattern of intussusception in Kuwait. A review of 244 cases. *International Surgery*, **73**(3):198–201.

Iturriza-Gomara M et al. (2002). Rotavirus gastroenteritis and central nervous system (CNS) infection: characterization of the VP7 and VP4 genes of rotavirus strains isolated from paired fecal and cerebrospinal fluid samples from a child with CNS disease. *Journal of Clinical Microbiology*, **40**(12):4797–4799.

Joensuu J et al. (1997). Randomized placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. *Lancet*, **350**(9086):1205–1209.

Justice F et al. (2005). Changing epidemiology of intussusception in Australia. *Journal of Paediatrics and Child Health*, **41**(9–10):475–478.

Kehle J et al. (2003). First case of confirmed rotavirus meningoencephalitis in Germany. *The Pediatric Infectious Disease Journal*, **22**(5):468–470.

Knip M, Akerblom HK (1999). Environmental factors in the pathogenesis of type 1 diabetes mellitus. *Experimental & Clinical Endocrinology & Diabetes*, **107**(Suppl. 3):S93–S100.

Konno T et al. (1978). Human rotavirus infection in infants and young children with intussusception. *Journal of Medical Virology*, **2**(3):265–269.

Laidin AZ, Goon HK (1982). Intussusception among infants and children in Malaysia. *The Medical Journal of Malaysia*, **37**(2):150–156.

Lee P-I (2006). Rotavirus vaccines (correspondence). *The New England Journal of Medicine*, **354**(16): 1747–1751.

Linhares AC et al. (2002). Nutritional status in relation to the efficacy of the rhesus-human reassortant, tetravalent rotavirus vaccine (RRV-TV) in infants from Belem, Para state, Brazil. *Revista do Instituto de Medicina Tropical de São Paulo*, **44**(1):13–16.

Lynch M et al. (2001). Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review [see comment]. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, **33**(7):932–938.

McCormack JG (1982). Clinical features of rotavirus gastroenteritis. *The Journal of Infection*, **4**(2):167–174.

Mori I et al. (2002). Prolonged shedding of rotavirus in a geriatric inpatient. *Journal of Medical Virology*, **67**(4):613–615.

Mossel EC, Ramig RF (2003). A lymphatic mechanism of rotavirus extraintestinal spread in the neonatal mouse. *Journal of Virology*, **77**(22):12352–12356.

Murphy BR et al. (2003). Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. *The Journal of Infectious Diseases*, **187**(8):1301–1308.

Murphy TV et al. (2001). Intussusception among infants given an oral rotavirus vaccine. *The New England Journal of Medicine*, **344**(8):564–572.

Murphy TV et al. (2003). The first rotavirus vaccine and intussusception: epidemiological studies and policy decisions. *The Journal of Infectious Diseases*, **187**(8):1309–1313.

Nakagomi T et al. (2006). A high incidence of intussusception in Japan as studied in a sentinel hospital over a 25-year period (1978–2002). *Epidemiology and Infection*, **134**(1):57–61.

Nava P et al. (2004). The rotavirus surface protein VP8 modulates the gate and fence function of tight junctions in epithelial cells. *Journal of Cell Science*, **117**(Pt. 23):5509–5519.

Nelson EA et al. (2002). Incidence of rotavirus diarrhea and intussusception in Hong Kong using standardized hospital discharge data. *The Pediatric Infectious Disease Journal*, **21**(7):701–703.

Nishimura S et al. (1993). Detection of rotavirus in cerebrospinal fluid and blood of patients with convulsions and gastroenteritis by means of the reverse transcription polymerase chain reaction. *Brain & Development*, **15**(6):457–459.

Nuovo GJMD et al. (2002). Histologic distribution of fatal rotaviral pneumonitis: an immunohistochemical and RT in situ PCR analysis. *Diagnostic molecular pathology : the American journal of surgical pathology, part B*, **11**(3):140–145.

O'Ryan M et al. (2004). A novel rotavirus vaccine RIX4414 is not associated with intussusception. In: *Proceedings of the forty-fourth annual general meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy*, Washington DC, G1129a.

Parashar UD (2006). Rotavirus and severe childhood diarrhea. *Emerging Infectious Diseases*, 12(2):304–306.

Parashar UD et al. (2000). Trends in intussusception-associated hospitalizations and deaths among US infants. *Pediatrics*, **106**(6):1413–1421.

Parashar UD et al. (2003). Global illness and deaths caused by rotavirus disease in children. *Emerging Infectious Diseases*, **9**(5):565–572.

Perez-Schael I et al. (1997). Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. *The New England Journal of Medicine*, **337**(17):1181–1187.

Perez-Schael I et al. (2003). Intussusception-associated hospitalization among Venezuelan infants during 1998 through 2001: anticipating rotavirus vaccines. *The Pediatric Infectious Disease Journal*, **22**(3):234–239.

Prevention CfDCa (1999). Withdrawal of rotavirus vaccine recommendation. *MMWR. Morbidity and mortality weekly* report, **48**(43):1007.

Ramig RF (2004). Pathogenesis of intestinal and systemic rotavirus infection. *Journal of Virology*, **78**(19):10213–10220.

Reijnen JA et al. (1990). Atypical characteristics of a group of children with intussusception. *Acta Paediatrica Scandinavica*, **79**(6–7):675–679.

Rennels MB et al. (1998). Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. *The Pediatric Infectious Disease Journal*, **17**(10):924–925.

Robinson CG et al. (2004). Evaluation of anatomic changes in young children with natural rotavirus infection: is intussusception biologically plausible? *The Journal of Infectious Diseases*, **189**(8):1382–1387.

Ruiz-Palacios GM et al. (2006). Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *The New England Journal of Medicine*, **354**(1):11–22.

Sardinas MA et al. (2001). Lack of association between intussusception and oral polio vaccine in Cuban children. *European Journal of Epidemiology*, **17**(8):783–787.

Scheifele DW et al. Immunization Monitoring Program, Active: a model of active surveillance of vaccine safety. Semin Pediatr Infect Dis. 2003;**14**(3):213-9.

Sim WH (2006). *Rotavirus:exploring the implications of viraemia*. Department of Paediatrics, The University of Melbourne, Melbourne, Australia:38.

Simonsen L et al. (2001). Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception. *Lancet*, **358**(9289):1224–1229.

Simonsen L et al. (2005). More on RotaShield and intussusception: the role of age at the time of vaccination. *The Journal of Infectious Diseases*, **192**(Suppl. 1):S36–S43.

Smith PJ et al. (2003). The first oral rotavirus vaccine, 1998–1999: estimates of uptake from the National Immunization Survey. *Public Health Reports*, **118**(2):134–143.

Staatz G et al. (1998). [Intestinal infection, the most frequent cause of invagination in childhood: results of a 10-year clinical study]. *Klinische Pädiatrie*, **210**(2):61–64.

Stene LC et al. (2006). Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *The American Journal of Gastroenterology*, **101**(10):2333–2340.

Ushijima H et al. (1994). Detection and sequencing of rotavirus VP7 gene from human materials (stools, sera, cerebrospinal fluids, and throat swabs) by reverse transcription and PCR. *Journal of Clinical Microbiology*, **32**(12):2893–2897.

Vesikari T et al. (2006). Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *The New England Journal of Medicine*, **354**(1):23–33.

Ward RL (1996). Mechanisms of protection against rotavirus in humans and mice. *The Journal of Infectious Diseases*, **174**(Suppl. 1):S51–S58.

WHO Guidelines on clinical evaluation of vaccines. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924:35–101).

Widdowson MA et al. (2005). Rotavirus disease and its prevention. *Current Opinion in Gastroenterology*, **21**(1):26–31.

Withdrawal of rotavirus vaccine recommendation (1999). *MMWR. Morbidity and mortality weekly report*, **48**(43):1007.

Wong V (2001). Acute gastroenteritis-related encephalopathy. *Journal of Child Neurology*, **16**(12):906–910.

Wood D, WHO IC Group (2005). WHO informal consultation on quality, safety and efficacy specifications for live attenuated rotavirus vaccines. Mexico City, Mexico, 8–9 February 2005. *Vaccine*, **23**(48–49):5478–5487.

World Health Organization (2001). Causality assessment of adverse events following immunization. *Weekly Epidemiological Record*, 76(12):85–89.

World Health Organization (2007). Global Advisory Committee on Vaccine Safety 12–13 June 2007 *Weekly Epidemiological Record*, 82 (28/29):252–259.

Zijlstra RT et al. (1997). Protein-energy malnutrition delays small-intestinal recovery in neonatal pigs infected with rotavirus. *Journal of Nutrition*, **127**(6):1118–1127.

Annex A:
Brighton collaboration clinical case definition for the diagnosis of acute intussusception in infants and young children

Level 1 of diagnostic certainty

Surgical criteria: the demonstration of invagination of the intestine at surgery

and/or

Radiological criteria:

the demonstration of invagination of the intestine by either air or liquid contrast enema; **or**

the demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features[1] that is proven to be **reduced** by hydrostatic enema on **post-reduction ultrasound; and/or**

Autopsy criteria: the demonstration of invagination of the intestine.

Level 2 of diagnostic certainty

Clinical criteria:

- two major criteria (see criteria for diagnosis below); **or**
- one major criterion[2] and three minor criteria (see criteria for diagnosis below).

Level 3 of diagnostic certainty

Clinical criteria:

- four or more minor criteria (see criteria for diagnosis below).

For any level

In the *absence* of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (such as volvulus, congenital pyloric stenosis).

1 Target sign or doughnut sign on transverse section and a pseudo-kidney or sandwich sign on longitudinal section.

2 If one major criterion is the passage of blood per rectum that is mixed in a diarrhoeal stool, then consideration should be given to infectious etiologies.

Major and minor criteria used in the case definition for the diagnosis of intussusception

Major criteria:

1) **Evidence of intestinal obstruction**

- History of bile-stained vomiting ***and either***
- examination findings of acute abdominal distension and abnormal or absent bowel sounds ***or***
- plain abdominal radiograph showing fluid levels ***AND*** dilated bowel loops.

2) **Features of intestinal invagination**

One or more of the following:

- abdominal mass;
- rectal mass;
- intestinal prolapse;
- plain abdominal radiograph showing a visible intussusceptum or soft tissue mass;
- abdominal ultrasound showing a visible intussusceptum or soft tissue mass;
- abdominal CT scan showing a visible intussusceptum or soft tissue mass.

3) Evidence of intestinal vascular compromise or venous congestion

- Passage of blood per rectum; ***or***
- passage of a stool containing "redcurrant jelly" material; ***or***
- blood detected on rectal examination.

Minor criteria:

- Predisposing factors: age <1 year and male sex;
- abdominal pain;
- vomiting[1];
- lethargy[2];
- pallor[2];
- hypovolemic shock;
- plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern.

[1] If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion.

[2] Lethargy and pallor typically occur intermittently in association with acute spasms of abdominal pain. In patients with severe or prolonged intussusception, lethargy and pallor may become a constant feature associated with a deterioration in cardiovascular status and impending hypovolemic shock.

Annex B:
Case Log Form

Surveillance site: _____

Case No	Name	Hospital record no.	Address	Date of birth	Date of onset of suspected adverse event	Type of event	Date of rotavirus vaccination	1st, 2nd, or 3rd dose	Confirm case? (Yes/No)	Form complete? (Yes/No)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										

Annex C:
Post-marketing surveillance for rotavirus vaccines
Case Data Form

Case identification | **Case No.**

Date of birth: ____/____/____ Age: ___ year ___ months Sex: ___ M ___F

Clinic/Hospital information Date of notification: ____/____/____

Name of person reporting: _____Position: _____

Name of Clinic/Hospital:_____

Address: _____ City: _____ State: _____

Telephone: _____Email: _____

Description of event

Date of onset of symptoms: ____/____/____

Date of hospital clinic admission: ____/____/____

Type of event: ❑ Intussusception ❑ Gastrointestinal ❑ Respiratory

❑ Nervous system ❑ Other:_____

Vaccination history

Rotavirus vaccine	1st dose	2nd dose	3rd dose
Date of administration			
Type of vaccine Manufacturer			
Vaccine lot number			
Vaccine expiry date			
Other relevant data			

Other vaccines	Neonatal dose	1st dose	2nd dose	3rd dose	Other doses
Polio					
BCG					
DPT					
Haemophilus type B					
Hepatitis B					

❑ **LEVEL 1: CASE DEFINITION** *(≥ 1 criterion)*	❑ Surgery ❑ Air/Liquid contrast enema ❑ Ultrasound with reduction verification ❑ Autopsy
❑ **LEVEL 2: CASE DEFINITION** *(2 major, or 1 major and 2 minor criteria)* **MAJOR CRITERIA** ❑ **Intestinal obstruction** ⇒	❑ Bile-stained vomiting ❑ Acute abdominal distension ❑ Abnormal or absent bowel sounds ❑ Abnormal Xray: Fluid level + dilated loops
❑ **Features of intestinal invagination**⇒	❑ Intestinal mass ❑ Rectal mass ❑ Intestine prolapse ❑ Plain abdominal Xray showing IS mass ❑ CT scan showing IS mass
❑ **Intestinal vascular compromise or venous congestion** ⇒	❑ Passage of blood per rectum ❑ Passage of "redcurrant jelly" stool ❑ Blood on rectal examination
MINOR CRITERIA ❑ **LEVEL 3: CASE DEFINITION** *(≥4 minor criteria)*	❑ Age < 1 year and male sex ❑ Abdominal pain ❑ Vomiting ❑ Lethargy ❑ Pallor ❑ Hypovolemic shock ❑ Plain Xray: abnormal non-specific bowel gas pattern
OTHER SYMPTOMS ❑ Diarrhoea ❑ Irritability ❑ Fever – temp:_____°C ❑ Rash ❑ Urticaria	❑ Headache ❑ Focal neurological signs ❑ Paralysis ❑ Seizures ❑ Other:
RELEVANT PAST HISTORY ❑ Abdominal surgery: Describe_____ ❑ Allergies ❑ CNS Disease ❑ Immunodeficiency	❑ Vaccine-related adverse events ❑ Prematurity ❑ Medications or traditional therapies used in the last 3 weeks: describe type, dose, dates _____ _____

Treatment

Intussusception:

❑ Air/hydrostatic enema reduction Date: ____/____/____

❑ Surgery: Date: ____/____/____

- ❑ Reduction alone
- ❑ Resection Site:_____ Length:_____
- ❑ Lead point or other pathology identified

Describe: _____

Site of intussusception: _____

Complications: _____

Intensive care:

Date of admission: ____/____/____ Date of discharge/death: ____/____/____

Other treatments: _____

Other potential adverse events:

Final diagnosis: _____ Date: ____/____/____

Other treatments: _____

Describe treatment: _____

Case outcome:

Patient status: ❑ Fully recovered ❑ Recovered with sequelae

❑ Dead ❑ Unknown

❑ Pending Date of discharge/death: ____/____/____

Describe treatment: _____

Annex D:
Sample form for causality review by an expert committee[1]

Note: A copy of the reporting form (and any follow-up information) for each specific AEFI to be reviewed by committee should be appended to this cover page.

[1] The sample form was adapted from a form developed by the Canadian Advisory Committee on Causality Assessment.

Identification: _____ Vaccine(s): _____

1. Primary reason for reporting: _____ **Code**: ☐☐

1.1 Agreement with report:

Agree ☐1

Disagree ☐2 ..... Error of coding? Yes ☐1 No ☐2 New coding ☐☐

..... Is the event severe? Yes ☐1 No ☐2

Insufficient data ☐3 ..... To be reviewed again? Yes ☐1 No ☐2

2. These questions are related to the primary reason for reporting only:

2.1	Frequency of occurrence of the adverse event	NPR* ☐4	Rare ☐1	Intermediate ☐2	Common ☐3
2.2	Similar events known to occur with other disease		Yes ☐1	No ☐2	
2.3	Event is known to be related to this vaccine		Yes ☐1	No ☐2	
2.4	Event is explainable by the biological properties of the vaccine		Yes ☐1	No ☐2	Unknown ☐3
2.5	Vaccine-event interval compatible with the event	n/a ☐4	Typical ☐1	Compatible ☐2	Incompatible ☐3
2.6	The patient had similar symptoms in the past	n/a ☐4	Yes ☐1	No ☐2	Unknown ☐3
2.7	Concomitant or preceding drug therapy		Yes ☐1	No ☐2	Unknown ☐3
2.8	Concomitant or preceding condition	Rel.* ☐4	Yes ☐1	No ☐2	Unknown ☐3
2.9	Other contributing factors		Yes ☐1	No ☐2	Unknown ☐3

* Rel: assessment of causality to be done in context of relevant condition. * NPR: not previously reported.

3. Conclusion with regard to the primary reason for reporting:

3.1 The association is:

☐1 Very likely — certain

☐2 Probable

☐3 Possible

☐4 Unlikely

☐5 Unrelated

☐6 Unclassifiable

3.2 Possible new entity ☐

3.3 Insufficient data ☐

3.4 The case would benefit from a second review: Yes ☐1 No ☐2

4. Comments: _____

_____

5. Recommendations: _____

_____

[1] The sample form was adapted from a form developed by the Canadian Advisory Committee on Causality Assessment.

Annex E :
Methods for collection and analysis of specimens obtained from subjects with intussusception

Although collection of clinical specimens is not required for intussusception diagnosis, their collection and testing for infectious agents may be helpful in defining local causes of intussusception (and therefore contributing to causality assessment) or for other research questions. Methods for collection are provided below.

Stool. Within 24 hours following enrolment, a sample of the patient's stool should be collected. Every effort to collect stool samples prior to barium or air enema or surgery should be made, as the effect of barium on the sensitivity of the tests is unknown. Additionally, since children may not produce stool for some time following bowel surgery, collection prior to surgery is recommended to limit the opportunity for nosocomial infection. Stool samples should be collected and stored as whole stool specimens. Stools may be collected in diapers/nappies or by other methods, and should be transferred to and stored in sterile screw-top containers.

If stool specimens are available from tests ordered as part of the patient's routine care, they can be used provided they have been processed in accordance with these guidelines (as above). Stool specimens placed in media or fixatives, such as Cary-Blair media or formalin, are not acceptable for this surveillance protocol. All specimens should be labelled with pre-printed labels containing the patient's identification number and date of collection. Information regarding specimens should be documented on the Specimen Log (Annex F).

Intestinal or lymph-node specimens collected at surgery or post-mortem. Patients requiring surgical resection should have a specimen of intestine and mesenteric lymph node collected for analysis. At post-mortem a specimen of the affected intestine and corresponding lymph nodes should be collected. Specimens can be divided with one sample placed in a container of formalin fixative for histological analysis, and another sample placed in a sterile screw-top container and transported for virological analysis. Information regarding specimens collected should be documented on the specimen log (Annex F). Special immunohistochemical stains for viral agents of gastroenteritis may be available through research or public-health laboratories. For further consultation contact the WHO Collaborating Centres (http://whqlily.who.int).

Blood specimens. Within 24 hours following enrolment, a specimen of blood can be collected for virological and/or serological testing. Testing of these specimens may require special research laboratories. For further consultation contact the WHO Collaborating Centres (http://whqlily.who.int).

Specimen handling

Stool. Stool specimens should be collected in sterile containers as bulk stools in as large a quantity as is practical (at least 10 grams) and, optimally, transported to the laboratory within 30 minutes of collection. If transport to the laboratory has to be delayed, stool samples should be refrigerated until transport. Stools should not remain at room temperature for more than 30 minutes.

Intestinal specimens. Specimens of intestine and/or mesenteric lymph nodes can be divided to allow analysis by both histological and virological methods. A sample of tissue is placed in formalin as in routine histological studies. Another sample of tissue can be placed in a sterile screw-top container with storage buffer (for example RNAse) and stored in a refrigerator at –70°C.

Blood. A sample of whole blood is collected and centrifuged to obtain serum. Serum is then stored in a screw-top container at –70°C.

All collection materials should be pre-labelled with the appropriate pre-made label that includes the patient's ID number, patient's initials and date of collection, and stored in a pre-designated site. All specimens that are received will be logged on the specimen log (Annex F). In hospitals where there are separate laboratories for anatomical pathology and microbiology, separate specimen logs may be required in each laboratory.

Specimen testing

Stool. A wet preparation of the stool should be examined by microscopy to identify white or red blood cells or parasites. The stool should be cultured using routine microbiological methods to identify enteric pathogens, including Salmonella, Shigella, Campylobacter, and Yersinia. Stool specimens should be tested for evidence of rotaviruses, astroviruses, and enteric and non-enteric adenoviruses, with commercial enzyme immunoassay kits using standard methods. In addition, stools could be tested for the presence of enteroviruses and caliciviruses using RT-PCR and Southern blot hybridization or nucleotide sequencing.

Intestinal specimens. Surgical and post-mortem specimens should be fixed and processed using routine histological techniques. In addition, specimens can be tested for evidence of rotavirus and other viruses using RT-PCR.

Blood. Blood can be used to test for evidence of rotavirus viremia using a combination of ELISA and RT-PCR methods. Sera can be checked for specific viral antibody to known and/or unknown pathogens using the ELISA method.

Annex F :
Post-marketing surveillance for rotavirus vaccines – Specimen log

Please use separate forms for each type of specimen (e.g. stool, serum, pathology samples)

Site: _____

ID	Subject initials	Date of specimen collection	Date arrived in laboratory	Comments

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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