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REVIEW ARTICLE

Significance of continuous rotavirus and norovirus surveillance in Indonesia

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Abstract

Background Diarrhea significantly contributes to the global burden of diseases, particularly in developing countries. Rotavirus and norovirus are the most dominant viral agents responsible for diarrheal disease globally. The aim of this review was to conduct a comprehensive assessment of rotavirus and norovirus study in Indonesia.

Data sources Articles about rotavirus and norovirus surveillance in Indonesia were collected from databases, including PubMed and Google Scholar. Manual searching was performed to identify additional studies. Furthermore, relevant articles about norovirus diseases were included.

Results A national surveillance of rotavirus-associated gastroenteritis has been conducted for years, resulting in substantial evidence about the high burden of the diseases in Indonesia. In contrast, norovirus infection received relatively lower attention and very limited data are available about the incidence and circulating genotypes. Norovirus causes sporadic and epidemic gastroenteritis globally. It is also emerging as a health problem in immunocompromised individuals. During post-rotavirus vaccination era, norovirus potentially emerges as the most frequent cause of diarrheal diseases.

Conclusions Our review identifies knowledge gaps in Indonesia about the burden of norovirus diseases and the circulating genotypes. Therefore, there is a pressing need to conduct national surveillance to raise awareness of the community and national health authority about the actual burden of norovirus disease in Indonesia. Continuing rotavirus surveillance is also important to assess vaccine effectiveness and to continue tracking any substantial changes of circulating rotavirus genotypes.

Keywords Diarrhea · Rotavirus · Norovirus · Indonesia · Surveillance

Introduction

Diarrheal diseases are among the leading causes of global disease burden with significant morbidity and mortality, especially in low income developing countries [1]. In 2010, it was estimated that there were about 1.7 billion episodes of diarrhea in children aged less than 5 years, of which, 36 million progressed to severe diseases [1]. In Indonesia, the incidence of diarrhea in all ages and in children aged less than 5 years is 3.5 and 10.2%, respectively [2]. In 2015, 5.0 billion episodes of diarrhea in all age groups are reported, as well as 21 diarrhea outbreaks with more than 1200 patients and 30 deaths [case fatality rate (CFR) 2.47%] [3].

Various bacteria, viruses, and parasites have been identified as the causes of diarrhea, mainly transmitted through contaminated food or water sources. A systematic review of articles published between 1990 and 2011 showed that rotavirus is the most dominant cause of diarrhea in children aged less than 5 years, followed by enteropathogenic *Escherichia coli* (EPEC) and caliciviruses (norovirus and sapovirus) [4]. Among pathogens commonly transmitted through contaminated food, norovirus is the most common. Norovirus causes 677 million diarrheal episodes, resulted in 213,000 deaths in all ages [5].

Since rotavirus and norovirus are the main viral pathogens causing diarrhea globally, we conducted a comprehensive review of the detection and surveillance of these viruses

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in Indonesia. Based on the available surveillance data, we identified the burden of the diseases in Indonesia as well as the circulating genotypes. Finally, we identified gaps in the previous surveillance to guide recommendations for improving the surveillance systems of these viruses in Indonesia.

Years of rotavirus surveillance and detection in Indonesia

Rotavirus is a non-enveloped, double-stranded RNA (dsRNA) virus belonging to the *Reoviridae* family. Its genome consists of 11 dsRNA segments encoding six structural proteins [viral proteins (VPs)] and six non-structural proteins (NSPs). The viral particle comprises three concentric protein layers. The outer layer is made of two neutralizing antigens, VP7 and VP4 proteins. These proteins are essential for binary classification of rotavirus into G- and P-genotype, respectively [6]. Rotavirus is the most important cause of hospitalization in children suffering from diarrhea. In 2013, it was estimated that 215,000 children aged less than 5 years died from rotavirus-associated diarrhea [7]. Rotavirus-associated diseases also emerged in immunocompromised patients, including pediatric and adult organ transplant recipients [8].

In Indonesia, rotavirus was first visualized using electron microscopy in fecal specimens of infants and children with acute diarrhea in Yogyakarta collected during the year 1978–1979 [9]. Rotavirus was identified in 38% of the collected specimens [9]. Rotavirus was also detected from fecal specimens collected from children with diarrhea during August 1979 to September 1981 in Jakarta and Medan [10]. Strain characterization was performed by electropherotyping [11]. A subsequent study successfully detected the rotavirus serotype by using monoclonal antibodies against VP7 protein [12].

To further investigate the burden and impact of rotavirus diseases, the Asian Rotavirus Surveillance Network (ARSN) was established [13]. As a member of ARSN, the Indonesian Rotavirus Surveillance Network (IRSN) conducted a hospital-based surveillance based on World Health Organization (WHO) standard protocol [14–16]. Rotavirus surveillance was also conducted by other institutions or research laboratories (Table 1) [17–27]. Rotavirus detection was based on enzyme immunoassay and characterization of rotavirus genotypes was performed by reverse transcriptase polymerase chain reaction (RT-PCR) [15, 16].

These studies indicated a high incidence of rotavirus disease in children aged < 5 years in Indonesia. Rotavirus detection rate in these studies was about 40–50% (Table 1), in line with a recent analysis of worldwide studies from 2000 to 2013 (37–40%) [7]. It is worth noting that the difference of detection rate between studies may be due to the difference of detection assays used and the surveillance period. Even though rotavirus was detected year-round, the incidence tends to be higher from June to August [14, 15]. Rotavirus-positive children were at risk of developing severe clinical symptoms such as vomiting and dehydration [15, 23]. Outbreaks have been reported from Papua and East Nusa Tenggara [19, 22], underlying the urgency to control the diseases.

Rotavirus genotyping demonstrated that G1P[8], G1P[6], and G2P[4] strains were the most predominant strains circulating in Indonesia [15, 16, 25, 26], in line with findings of worldwide studies [28]. However, alterations of dominant strains in Indonesia were observed [16], supporting the importance of continuous surveillance in the country. Surveillance in Indonesia has identified novel genotypes such as G12 strain [29]. Results of the observation highlight the importance of updating genotyping assays to cope with the rapid evolution of the virus that might result in typing failure [30].

Collectively, the surveillance system provides valuable data about the epidemiology and impact of rotavirus disease in Indonesia [15]. Furthermore, it raises awareness about the magnitude of rotavirus disease burden. Together with the genotyping studies, government and public health experts could assess the prospect of introducing rotavirus vaccine into the national program to reduce the burden of diseases in Indonesia. It is expected that inclusion of rotavirus vaccines in the National Immunization Program will prevent 480,000 diarrhea cases in outpatient clinics, 176,000 hospitalizations, and 8000 deaths of Indonesian children [31].

Decline of rotavirus diarrhea following rotavirus vaccine introduction

Two commercially available oral rotavirus vaccines, Rotarix and RotaTeq, were licensed in 2006 and recommended for use by the World Health Organization in all countries, particularly those with a high incidence of severe rotavirus-associated gastroenteritis [32]. Clinical trials of these vaccines demonstrated high efficacy against severe rotavirus disease in developed, high- and upper middle-income countries. However, a lower efficacy was observed in developing, lower middle-income countries [33].

These vaccines are live-attenuated vaccines that differ in their antigenic composition. Rotarix (GlaxoSmithKline Biologicals, Belgium) is a monovalent vaccine (RV1), containing G1P[8] strains derived from human rotavirus. RotaTeq (Merck, USA) is a pentavalent vaccine (RV5), derived from human-bovine reassortant viruses containing five most dominant strains, i.e. G1, G2, G3, G4, and P[8] [34]. Both vaccines are available in Indonesia. However, they are not included in the National Immunization Program due to

Table 1 Rotavirus (RV) detection and surveillance in Indonesian population

No.	Regions	Study periods	Types of study	Population	No of cases tested[a]	RV positive samples (%)	Methods	References
1	Yogyakarta	June 1978–June 1979	Hospital-based surveillance	Children age 0–12 years hospitalized due to acute diarrhea	334	126 (38%)	EM	[9]
2	Jakarta and Medan	August 1979–September 1981	NS	Children with diarrhea	41	16 (39%)	RPH	[10]
3	Jakarta	March 1997–August 1999	Community- and hospital-based surveillance	Pediatric and adults patients reporting diarrhea	539	202 (37.5%)	EIA	[17]
4	Jakarta	March 1997–June 1999	Hospital-based surveillance	Inpatient and outpatient reporting diarrhea	402	170 (42.3%)	EIA	[18]
5	Yogyakarta and Purworejo	August 2001–April 2004	Hospital-based surveillance	Children < 3 years admitted due to diarrhea	1321	705 (53%)	EIA	[13, 14]
6	Kupang, East Nusa Tenggara	August 2002	Outbreak investigation	Acute diarrhea cases during outbreak period ($n = 2600$)	27	13 (48%)	EIA	[19]
7	NS	February 2004–February 2005	Hospital-based surveillance	Children < 6 years of age with acute diarrhea	1660	755 (45.5%)	EIA or RT-PCR	[20]
8	Palembang, Jakarta, Bandung, Yogyakarta, Denpasar, Mataram	January–December 2006	Prospective surveillance in 6 teaching hospitals	Children aged < 5 years with acute diarrhea (inpatient and outpatient)	2240 (inpatients) and 176 (outpatients)	1345 (60%) and 73 (41%)	EIA	[15]
9	Jakarta, Yogyakarta, Denpasar, Makassar, Mataram	January–April 2007	Hospital-based surveillance	Children < 5 years old with acute diarrhea	421	257 (61%)	RT-PCR	[21]
10	Bandung, Yogyakarta, Mataram, Denpasar	2006, 2009, 2010	Hospital-based surveillance	Children aged < 5 years with acute diarrhea	4235	2220 (52.4%)	EIA	[16]
11	Bintuni Bay, Papua	September–October 2008	Outbreak investigation in five villages	242 toddlers admitted to hospitals with massive diarrhea	15	10 (67%) or 12 (80%)	EIA or RT-PCR, respectively.	[22]
12	Denpasar	April 2009–December 2011	Hospital-based surveillance	Children aged < 5 years with acute diarrhea	656	327 (49.8%)	EIA	[23]
13	Bandung	April 2009–December 2012	Hospital-based surveillance	Infants aged ≤ 6 months with acute diarrhea	134	60 (44.8%)	EIA	[24]
14	Surabaya	April–December 2013	Hospital-based surveillance	Children 1–60 months hospitalized due to acute diarrhea	220	88 (40%)	IC	[25]

Table 1 (continued)

No.	Regions	Study periods	Types of study	Population	No of cases tested[a]	RV positive samples (%)	Methods	References
15	Yogyakarta	February–August 2009	Hospital-based surveillance	Children aged < 5 years with acute diarrhea	104	57 (54.8%)	EIA	[26]
16	Pekanbaru, Riau	January–July 2015	Hospital-based surveillance	Children aged 0–60 months	71	42 (59.2%) or 44 (62.0%)	EIA or RT-PCR, respectively	[27]

[a]For case–control studies, only number of tested cases were presented

NS not specified, *IC* immunochromatographic assay, *EIA* enzyme immunoassay, *RT-PCR* reverse transcriptase polymerase chain reaction, *EM* electron microscopy, *RPH* reversed passive hemagglutination kits

financial constraints [35]. Currently, there are no available data about the vaccination coverage and the impact of rotavirus vaccination in Indonesia.

By the end of 2013, Rotarix and RotaTeq had been included in the national immunization programs of more than 50 countries worldwide and showed a significant impact to reduce rotavirus diseases [33]. In these countries, rotavirus vaccines proved to be safe and effective in reducing rotavirus-associated diarrhea cases, hospitalizations, and deaths [33]. Interestingly, following a widespread implementation of rotavirus vaccination, a change in the epidemiology of viral gastroenteritis has been observed. With the decline of rotavirus disease, human norovirus infection has become more prevalent, especially in countries where universal rotavirus vaccination has been introduced. Reports from Bolivia [36], Brazil [37, 38], Nicaragua [39], Finland [40, 41], and the United States [42, 43] indicated that norovirus has become more prevalent than rotavirus in causing gastroenteritis in children. As an example, during 2009–2010, norovirus was detected in 21% of young children with acute gastroenteritis, while rotavirus was detected in 12% of children at the same period in the United States [43]. Although more comprehensive global epidemiological studies are needed, these initial reports clearly indicate that norovirus had emerged as the most predominant cause of gastroenteritis in children during post-rotavirus vaccination era.

Norovirus: an emerging and under-recognized human pathogen

Human norovirus is a linear, single-strand, positive RNA virus that is ~ 7.6 kb in length and belongs to the family of *Caliciviridae*. It is classified into at least six genogroups [genogroup 1 (G1) to GVI] and more than 40 genotypes. The prototype of human norovirus, Norwalk virus, is designated as GI, genotype 1 (GI.1). Human norovirus GII.4 is the most frequent cause of human infection, followed by GI and rarely, GIV. The other genogropus, GIII, GV, and GVI are bovine, murine, and canine norovirus, respectively [44, 45]. As an RNA virus, norovirus displays a great genetic diversity, particularly due to the error-prone nature of RNA-dependent RNA polymerase (RdRp) and recombination between two related strains [46].

Norwalk virus is the first viral agent identified as the cause of gastroenteritis in human. The virus was visualized in 1972 from specimens collected during an outbreak of acute gastroenteritis in Norwalk, Ohio, the United States, and hence its name [47]. However, its significance as human pathogen was under-recognized due to lack of a routine detection method [45]. In addition, efforts to develop robust norovirus cell culture models that mimick the entire life-cycle in infected cells have been unsuccessful, hampering

studies on the molecular biology and development of specific anti-viral drugs [48]. Along with the rapid development of diagnostic methodology based on quantitative real-time PCR and its wide-spread availability, understanding of norovirus epidemiology and its disease burden have largely improved, particularly in developing countries [49].

The global burden of norovirus gastroenteritis

Norovirus diseases mainly affect children aged less than 5 years and older adults (greater than 65 years) in which it causes a high rate of hospitalization and death [49]. Norovirus can infect general population, causing outbreaks and acute sporadic gastroenteritis, and also chronic infection in immunocompromised individuals (Fig. 1).

Norovirus outbreaks

Norovirus is the leading cause of acute gastroenteritis outbreaks globally. Indeed, most of our recent understandings about molecular epidemiology of norovirus come from the analysis of global outbreak samples [49]. Several factors contribute to the high incidence of norovirus outbreaks, such as low infectious dose; prolonged fecal shedding that facilitate secondary transmission; viral stability in the environment; and lack of cross-protective and long-lasting immunity [45].

Norovirus is responsible for about 50% of all gastroenteritis outbreaks reported worldwide [50]. In some countries, the incidence is even higher. As an example, an analysis of fecal specimens taken from more than 300 outbreaks of non-bacterial gastroenteritis in the United States demonstrated that more than 90% of these outbreaks were attributable to norovirus [51, 52].

In a systematic analysis of norovirus outbreaks, the food service (e.g. restaurant) was the most common outbreak setting (35%), followed by health care (e.g. hospitals and long-term care facilities) (27%); leisure places (e.g. cruises, hotels and recreational activities) and school/daycare facilities (27%) [53]. For nosocomial outbreaks, the most frequently reported route of transmission was person-to-person transmission (18.5%). However, the majority of the transmission route of the nosocomial outbreaks (77.8%) is still unknown [54]. Most importantly, a systematic analysis of published hospital outbreaks identified norovirus as the most common cause of a hospital wards closure [55]. Altogether, the data underscore that the impact of norovirus disease should not be underestimated. Therefore, appropriate prevention and control measures are urgently required to prevent the occurrence of any future norovirus outbreaks.

Especially in healthcare settings, a highly virulent GII.4 norovirus strain has been recognized as the most common strain responsible for global norovirus outbreaks. The GII.4 strain is more likely to be associated with person-to-person transmission [56, 57]. However, some of GII.4 outbreaks were attributable to foodborne transmission [58]. A systematic review indicates that GII.4 outbreaks were associated with more severe clinical outcomes, independent of other factors [59]. New variants of GII.4 strain frequently emerged in cycles of 2–7 years, replacing the previously dominant variant to cause pandemic [57]. As an RNA virus, the high mutation rate facilitates the virus to escape from the host's immune system, leading to a constantly susceptible population and widespread newly emerging strains [46]. Interestingly, recent reports from Japan and China identified a novel strain, GII.17 norovirus, as the major cause of outbreaks and potentially replaces the previously dominating GII.4 strain [60].

Acute sporadic gastroenteritis

Beside outbreaks, norovirus is also an important agent of sporadic gastroenteritis. A systematic review of published studies between 1990 and 2008 documented that norovirus was responsible for 12% of severe gastroenteritis in children aged less than 5 years worldwide, requiring

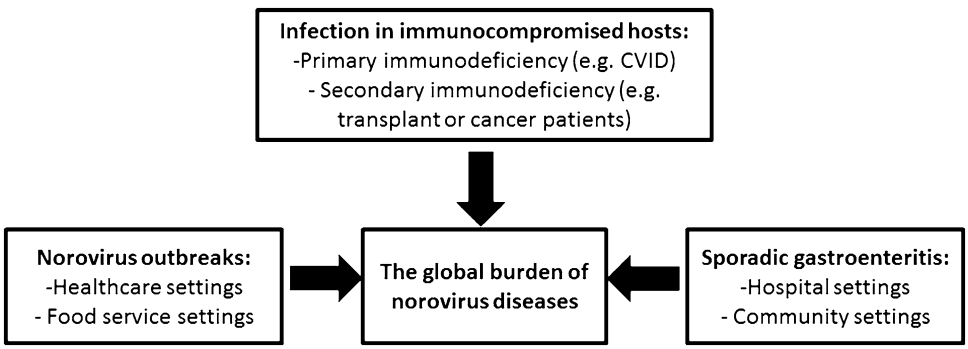

Fig. 1 The global burden of norovirus gastroenteritis. *CVID* common variable immune deficiency

emergency department visit and hospitalizations. Across all ages, norovirus accounted for 12% of mild and moderate diarrhea [61]. More recent estimates indicate that it accounted for 18% cases of acute gastroenteritis in children aged less than 5 years and mixed ages [62]. This estimation suggests that norovirus is the most common cause of diarrhea across all ages. In children aged less than 5 years during pre-rotavirus vaccination era, it is the second leading cause of severe diarrhea, following rotavirus.

Infection in immunocompromised host

Due to the use of immunosuppressant agents, transplant recipients are at high risk of contracting norovirus infection. The prevalence of norovirus-associated diarrhea in hematopoietic stem cell transplant (HST) and solid organ transplant (SOT) recipients have been reported to be 18% [63]. However, more thorough studies are required to confirm this finding. Importantly, norovirus infection in these patients was associated with more severe morbidity, such as prolonged viral shedding and recurrences of diarrhea episodes [63]. Therefore, a reduction or withdrawal of immunosuppressant agents should be considered for transplant patients at risk of norovirus infections in order to enhance the immune response in fighting the infection [64]. Patients with primary immunodeficiency, such as common variable immune deficiency (CVID), were also highly susceptible to develop chronic infections, leading to severe complications such as intestinal villous atrophy and malabsorption [65]. Due to a prolonged phase of infection and an increase of viral mutation, immunocompromised and transplant patients may serve as potential norovirus reservoirs in the human population [66].

Relevance of norovirus surveillance in Indonesia

In contrast to rotavirus, norovirus surveillance and detection in Indonesian population, as well as in several other developing countries, are very limited (Table 2). This suggests that norovirus received comparatively less concern than rotavirus, despite its significance in global contribution of all acute gastroenteritis cases. We found only four hospital-based surveillances identifying norovirus as the cause of acute gastroenteritis in Indonesia with a limited surveillance period and a relatively limited number of clinical samples tested [17, 18, 25, 67]. Moreover, the surveillances were only conducted in two regions, three of which were conducted in the capital city of Jakarta. This is probably due to the requirement of RT-PCR for norovirus detection which is not widely available in Indonesia. Therefore, we can conclude that nationwide studies focused more on rotavirus diseases rather than any other type of viruses [14–16].

In these four studies, norovirus prevalence was about 18–30% (Table 2), in accordance with the findings of global studies [62]. One study identified norovirus as co-viral agent with rotavirus infection. Seventeen out of 88 rotavirus-infected patients (19.3%) were co-infected with human norovirus [25]. Unfortunately, all previous studies (Table 2) did not report the genogroup and genotype of the infecting human norovirus. Consequently, genotyping data of norovirus circulating in Indonesia are not yet available. These findings clearly demonstrated the lack of national studies on the epidemiological burden and genetic diversity of human norovirus circulating in Indonesia.

Some countries have developed surveillance system to monitor norovirus incidence and outbreaks. NoroNet, led by the National Institute for Public Health and the Environment

Table 2 Norovirus (NoV) detection and surveillance in Indonesian population

No.	Regions	Study periods	Types of study	Population	No of cases tested	NoV positive samples (%)	Methods	References
1	Jakarta	March 1997–June 1999	Hospital-based surveillance	Inpatient and outpatient reporting diarrhea	218	45 (20.6%)	RT-PCR	[18]
2	Jakarta	March 1997–August 1999	Community- and hospital-based surveillance	Pediatric and adults patients reporting diarrhea	278	49 (18.0%)	RT-PCR	[17]
3	Jakarta	October 1997–September 1999	Hospital-based study	Infants (0–1 year) and young children (aged 5–12 years) presenting acute diarrhea	102	31 (30%)	RT-PCR	[67]
4	Surabaya	April–December 2013	Hospital-based surveillance	Children 1–60 months hospitalized due to acute diarrhea	88	17 (19.3%)[a]	RT-PCR	[25]

[a]As co-infection with rotavirus. *RT-PCR* reverse transcriptase polymerase chain reaction

of the Netherlands (Rijkinstituut voor Volksgezondheid en Milieu, RIVM), is a collaborative network of international institutes maintaining a database of norovirus nucleotide sequences [60]. In the United States, the Centers for Disease Control and Prevention (CDC) established CaliciNet on 2009 [68]. Both systems have proven successful in identifying the transmission routes and the emergence of norovirus' new strain variants [58, 60, 69]. A reporting system to detect norovirus outbreaks was also established by the United Kingdom Department of Health through the Hospital Norovirus Outbreak Reporting System (HNORS). In this system, outbreak data are collected and summarized using a standardized paper and stored in a web-based database [70]. This system was successful in increasing norovirus outbreak reports in hospitals. It also provided data about the burden and economic impact of norovirus outbreaks in hospitals [70]. An efficient detection and surveillance system may be able to reduce the health and societal cost expenses due to norovirus infections and outbreaks [71].

Conclusions

Continuous surveillance is required to enhance our understanding of the burden and impact of rotavirus and norovirus gastroenteritis in Indonesia. During post-rotavirus vaccination era, improvement of active surveillance in Indonesia is necessary to assess the effectiveness of rotavirus vaccines and to enhance the early detection of any changes of circulating rotavirus genotypes [16]. Continuous strain monitoring is pivotal to anticipate the emerging of novel or rare genotypes not included in the current vaccines, such as G12 [72]. The emergence of these genotypes may be due to vaccine-induced selective pressure. Subsequently, it may change the epidemiology of circulating rotavirus genotypes and influence the overall impact of rotavirus vaccines. The information is, therefore, useful for rotavirus vaccine development.

In addition, it is also necessary to include other patients in the surveillance, such as immunocompromised patients. In these patients, the incidence of rotavirus infection is considerably high and a prolonged diarrheal illness has been observed. These observations support the need of surveillance in these patients [8].

In contrast to rotavirus surveillance, norovirus surveillance in Indonesia is very limited. With the decline of rotavirus diseases following vaccine introduction, norovirus may emerge as a major cause of diarrhea in Indonesian children. Therefore, norovirus surveillance is crucial to investigate the burden of the disease and to characterize the genotypes. The surveillance system is of great importance to anticipate the emergence of novel, potentially pandemic strains such as GII.17 viruses [60]. The data of surveillance could serve as the basis for vaccine development [49].

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Compliance with ethical standards

Ethical approval Not needed.

Conflict of interest The authors declare no conflict of interest.

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