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The rotavirus causing acute gastroenteritis in children of under 5-year of age in Indonesia 1972-2018: a review

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ABSTRACT

The reason of this review is the absence of thorough information of rotavirus infection that had been the major cause of severe diarrhea in children of under 5-years of age in Indonesia, despite numerous publications elaborating rotavirus infection in some geographic areas of Indonesia. A review was conducted towards 52 published articles covering rotavirus research in Indonesia during period of 1972-2018.A thirty three selected articles were match with review criteria which comprises rotavirus positive rate, clinical features, and severity of rotavirus infection, as well as genotypes of the rotavirus. Rotavirus has been known as the major cause of severe diarrhea among children under 5 years of age world wide including in Indonesia. The rotavirus positive rates were range from 31.1 to 90.9%, which variably to different subject's population, study criteria and methods, and time. Rotavirus can cause severe diarrhea with majority of infected children suffered from dehydration, vomiting, and fever. The first genotyping conducted in Indonesia in the early 1980s revealed the predominant genotypes were G3 and G4, followed by G2, and small proportion of G1 and mixed genotypes. However the following decades G1 and G2 were on the raise with G3 predominantly re-appeared on 2015. G9 was first identified in 2004, and occasionally detected until 2015. The P genotyping revealed P[4], P[6], and P[8] were the common genotypes detected. Mixed and untyped genotypes were also detected in various proportion. Rotavirus diarrhea is a vaccination preventable disease, after natural infection, the immune system will produce protective antibodies that will protect from infection of both homotypic and heterotypic, however homotypic infection will protect stronger. Therefore this review recommends continuous rotavirus genotypes surveillance in Indonesia.

ABSTRAK

Review ini untuk menjawab ketiadaan informasi yang komprehensif tentang infeksi rotavirus penyebab diare berat pada anak-anak berusia kurang dari 5 tahun di Indonesia, meskipun berbagai publikasi memberikan informasi mengenai infeksi rotavirus di beberapa wilayah di Indonesia. Review dilakukan pada 52 artikel tentang penelitian rotavirus di Indonesia periode tahun 1972-2018. Sebanyak 33 naskah sesuai dengan kriteria yang mencakup *rotavirus positive rate*, manifestasi klinis, derajat keparahan infeksi rotavirus, dan genotipe rotavirus. Rotavirus diketahui sebagai penyebab utama diare pada anak di dunia termasuk di Indonesia. *Rotavirus positive rate* berkisar antara 31,1 sampai 90,9%, bervariasi tergantung populasi subyek penelitian, waktu, metode dan kriteria penelitian. Rotavirus dapat menyebabkan diare berat, dengan mayoritas anak yang terinfeksi mengalami dehidrasi, muntah, dan demam. *Genotyping* yang pertama dilakukan di Indonesia pada awal 1980 menunjukkan adanya genotipe yang predominan adalah G3 dan G4, kemudian diikuti oleh G2, dengan sedikit proporsi genotipe G1 dan campuran. Meskipun demikian, studi pada dekade berikutnya menunjukkan naiknya proporsi G1 dan G2, dengan G3 yang kembali muncul dan menjadi predominan pada tahun 2015. G9 pertama kali teridentifikasi pada tahun 2004, dan kadang-kadang masih terdeteksi sampai tahun 2015. Sementara *P genotyping* mengungkap adanya genotipe P[4], P[6], dan P[8] yang paling sering teridentifikasi. Genotipe campuran, dan genotipe yang belum dapat teridentifikasi juga dijumpai dengan proporsi yang bervariasi. Diare karena rotavirus dapat dicegah dengan vaksinasi, setelah infeksi alamiah, sistem imun dapat memproduksi antibodi yang bersifat melindungi dari infeksi rotavirus yang *homotypic* maupun yang *heterotypic*, tetapi infeksi oleh rotavirus yang *homotypic* akan memberikan perlindungan yang lebih kuat. Oleh karenanya, review ini merekomendasikan adanya surveilens genotipe rotavirus yang berkelanjutan di Indonesia.

Keywords:
rotavirus;
children of under 5-years of age;
Indonesia;
genotype;
dehydration;

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INTRODUCTION

Rotavirus group A was the major cause of severe diarrhea of under 5-years of age children in both developed and developing countries, especially before the implementation of vaccines.[1] Rotavirus infection caused severe acute diarrhea in young children of under 5 of age, can lead to death if adequate treatments were not available.[1] In 2000, the WHO and Coordinated Global Rotavirus Surveillance Network estimated that the annual rotavirus detection rate and the global mortality related to rotavirus infection among children of under 5-years of age were 42.5% (95% CI: 37.4%-47.5%) and 528,000 (range, 465,000-591,000) respectively.[1] After the introduction of rotavirus vaccination in more than 60 countries, the global rotavirus detection rate and the predicted mortality declined slightly over time to 37.3% (95% CI: 34.2%-40.5%) and 215,000 (range, 197,000-233,000), respectively.[1] In Southeast Asia region, the burden of rotavirus infection remained high.[2] It was estimated that the number of rotavirus death was 32,263(54.6%) in 2000.[1] This is before vaccine was available.

In Indonesia, rotavirus infection among children of under 5-years old is a public health challenge. While in the developed countries rotavirus infection rate decreased after the introduction of rotavirus vaccination,[1] in Indonesia is not the case. Several studies in Indonesia reported high detection rate of rotavirus from chlidren with diarrhea that reached 74.3%, as well as rotavirus outbreak which still occurred in 2018.[2,3] This may caused by the fact that although rotavirus infection is a vaccination preventable disease, the vaccination has not been a mandatory program in Indonesia. As the consequence, national health budget does not cover the cost of rotavirus vaccination, and parents must pay the vaccine for their children. This stimulated some research centers to conduct clinical trials to develop more affordable rotavirus vaccine.

A determinant of vaccine effectiveness was the distribution of genotypes in a respective area.[4] In Indonesia, although numerous studies were reported genotypes of rotavirus from several provinces, however, there is no national data of rotavirus detection rates neither its genotypes. This review aimed to fill this blank, to provide a thorough information of rotavirus detection rate, clinical features, severity of the infecton, and the genotypes in Indonesia.

MATERIALS AND METHODS

The study population and selection process

All published article containing “rotavirus” and “Indonesia” found in PubMed and Google are the population of this study. During the period of 1972-2018, 52 published articles were match with one or more of the basic criteria of this review which including rotavirus positive rate, severity, clinical features, and molecular epidemiology of rotavirus infection. After excluding 15 titles (three reviews, one comment, one case report, five articles of no data required in basic critera, four articles of vaccine or intervention or evaluation, one article of electrophoretic typing), 37 articles provided data of rotavirus detection rate, clinical features, with or without data of rotavirus genotyping (FIGURE 1). As this review focus is rotavirus infection in under 5-year-old children, four more titles were excluded (FIGURE 1). The 33 articles containing data which including rotavirus positive rate, severity and clinical features of disease, and genotyping distribution of rotavirus infection in under 5-year-old indonesian children were the subjects for this review.

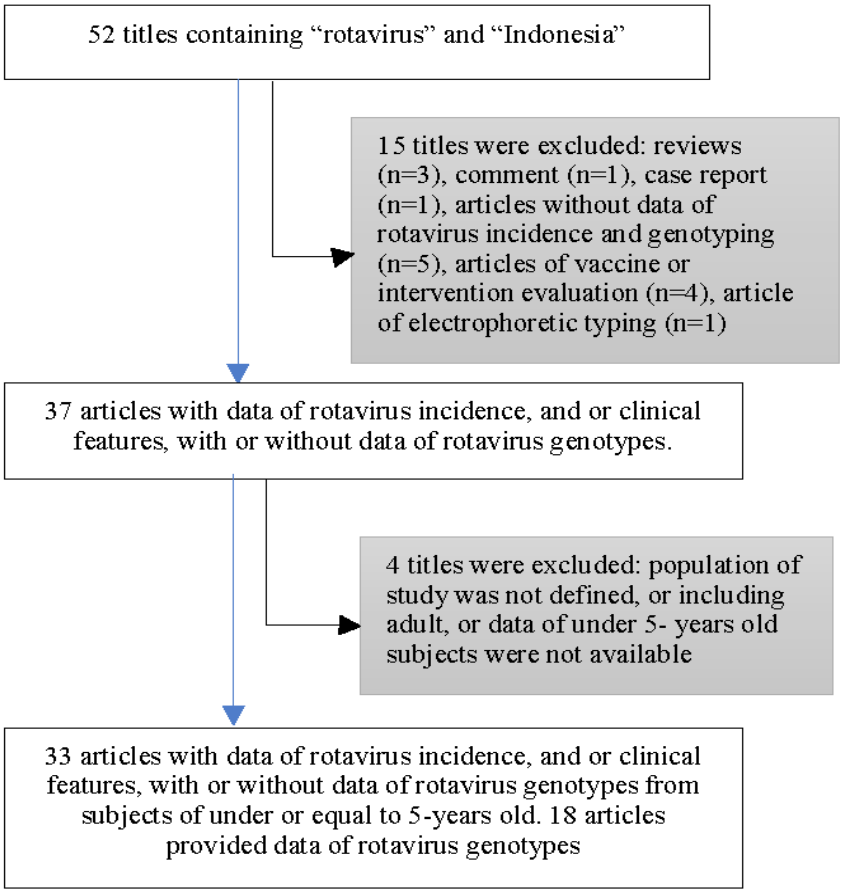

FIGURE 1. Diagram of data analysis to review the articles

Data analysis

All articles included in this analysis have subjects' population of under 5-year-old children, otherwise would be stated. Data of detection rate, severity, and clinical features of rotavirus infection, as well as the genotyping of rotavirus were tabulated and summarized. Data of rotavirus positive rate were supplied from 33 articles; their population, study design, study period, location as well as laboratory methods were described, whereas the positive rate of rotavirus infection was presented as percentage of rotavirus positive among total sampel tested.

Clinical features summarized in this review were including diarrhoea, vomiting, fever, bloody stool, stool mucous and other clinical signs. The data of rotavirus infection among 7 different age groups (0-2, 3-5, 6-11, 12-23, 24-35, 36-47, and 46-80 months) were also summarized. Data of dehydration level were analysed to project the severity of rotavirus infection. One study described G genotypes in early 1980s, and 18 recent studies (conducted after the year of 2000) published the rotavirus genotypes (G and P) from which 16 studies provided data of G and P genotypes, one study provided only G genotyping data, one study provided P genotypes data only, and 13 titles published data of G and P combination genotypes circulating in Indonesia.

RESULTS

Rotavirus research has been conducted in several sites in Indonesia, with various design and results. This review focus on several studies of

rotavirus infection in gastroenteritis disease among children of under 5-years of age that had been conducted in numerous region of Indonesia including Medan, Riau, Palembang, Jakarta, Bandung, Purworejo, Yogyakarta, East Java/Surabaya, Makasar, Denpasar, Mataram, Lampung, Belu (East Nusa Tenggara), and Bintuni (Papua) during 1972-2018. The last three studies were outbreak investigation affecting hundreds to thousands of local population.

TABLE 1. The detection of rotavirus infection among under 5-year-old children with acute gastroenteritis in Indonesia from 33 studies during 1972-2018.

Population	Study design	Sample tested	Positive Rotavirus n(%)	Detection Methods	Period of study	Location	Reference
Under 5-years old children	Multi sites, hospitals based surveillance	97	45(46.4)	ELISA	1972-1975	Jakarta and Medan	Urasawa S. *et al*,[5]
Under 2-years old children	Hospital based surveillance	292	116(39.7)	Morphology with electron microscope and staining	1978-1979	Yogyakarta	Soenarto Y. *et al*,[6]
Under 2-years old children	Hospital based study (serotyping)	111	111(100)	Neutralizing monoclonal antibodies (EIA)	1978-1979	Yogyakarta	Bishop RF *et al*,[7]
Under 3-years old children	Hospital based surveillance	59	32(54.2)	ELISA	1984	Medan	Razali A. *et al*,[8]
Under 2-years old children	Hospital based surveillance	1184	408(34.5)	Ab sensitized latex	1993-1997	Surabaya	Wasito EB. *et al*,[9]
Under 5-years old children	Hospital and PHCs based surveillance	339	160(47.2)	EIA	1997-1999	Jakarta	Subekti D. *et al*,[10]
Under 5-years old children	Multi sites, hospitals based surveillance	577	302(52.4)	EIA	2001-2002	Yogyakarta and Purworejo (ARSN)	Bresee J. *et al*,[11]
Under 5-years old children	Multi-sites, hospitals based surveillance	577	300-301 (52)	EIA, RT-PCR	2001-2003	Yogyakarta and Purworejo (ARSN)	Nelson EAS. *et al*,[12]
Under 2-years old children	Hospital based surveillance	98	35(35.7)	ELISA	2003-3004	Jakarta	Tjitrasari T. *et al*,[13]
Under 5-years old children	Multi-sites, hospitals based surveillance	1321	705(53.4)	EIA, RT PCR	2001-2004	Yogyakarta and Purworejo (ARSN)	Wilopo SA. *et al*,[14]
Under 5-years old children	Multi-sites, hospitals based surveillance	2031	804(39.6)	EIA, RT-PCR, semi-nested RT-PCR	2004-2005	4 referral hospitals in Indonesia (NAMRU case series)	Putnam SD. *et al*,[15]

Under 5-years old children	Multi-sites, hospitals based surveillance	2440	1418 (58.1)	EIA, RT-PCR	2006	Palembang, Jakarta, Bandung, Yogyakarta, Denpas-ar, and Mataram	Soenarto Y. *et al*,[16]
Under 5-years old children	Hospital based surveilance	513	326(64)	EIA, RT-PCR	2006	Palembang	Widowati T. *et al*,[17]
Under 5-years old children	Hospital based surveilance	353	116(32.7)	EIA, RT-PCR	2006-2007	Yogyakarta	Widowati T. *et al*,[18]
Under 5-years old children	Multi-sites, hospitals based surveillance	421	257(61)	RT-nested multiplex PCR	2007	Jakarta, Yogyakarta, Denpasar, Makasar, and Mataram	Radji M. *et al*,[19]
Under 5-years old children	Hospital based surveilance	99	66(67)	EIA, RT-PCR	2007	Jakarta	Kadim M. *et al*,[20]
Under 5-years old children	Hospital based surveilance	104	57(54.8)	EIA, RT-PCR	2009	Yogyakarta	Nirwati H. *et al*,[21]
Under 5-years old children	Multi-sites, hospitals based surveillance	4235	2220(52.4)	EIA, RT-PCR	2006, 2009, 2010	Bandung, Yogyakarta, Denpasar, Mataram	Nirwati H. *et al*,[22]
Under 5-years old children	hospitals based surveillance	656	327(49.8)	EIA	2009-2011	Denpasar	Salim H. *et al*,[23]
Under 41-months old	Outbreak investigation	15	10(67)	EIA, RT-PCR	2008	Bintuni (Papua)	Pratiwi E. *et al*,[24]
Under 5-years old children	Hospital based surveillance	329	210(63.8)	EIA, RT-PCR	2010	Mataram	Parwata WSS. *et al*,[25]
Under 6-months old chil-dren	Hospital based surveillance	134	60(44.8)	EIA	2009-2012	Bandung	Prasetyo D. *et al*,[26]
Under 5-years old children	Hospital based surveillance	945	427(45.2)	EIA	2009-2012	Bandung	Prasetyo D. *et al*,[27]
Under 5-years old children	Hospital based surveillance	945	427(45.2)	EIA	2009-2012	Bandung	Ermaya YS. *et al*,[28]
Under 5-years old children	Hospital based surveillance	220	88(40.0)	ELISA, RT-PCR	2013	Surabaya	Sudarmo SM. *et al*,[29]
Under 5-years old children	Multi-sites, hospitals based surveillance	586	242(41.3)	EIA, RT-PCR	2013	Bandung, Yogyakarta, Denpasar, Mataram	Gdara F.O. *et al*,[30]
Under 5-years old children	Hospital based surveillance	71	44(62.0)	EIA, RT-PCR	2015	Riau	Djojosugito FA. *et al*,[31]

Under 5-years old children	Multi-sites, hospitals based surveillance	4013	1950(48.6)	EIA, RT-PCR	2010-2015	Bandung, Yogyakarta, Denpasar, Mataram	Mulyani*et al*, 2018 [32]
Under 5-years old children	Multi-sites, hospitals based surveillance	406	223(54.9)	EIA, RT-PCR	2015	Yogyakarta, Mataram	Nirwati H. *et al*,[33]
Under 5-years old	Hospital based surveillance	134	42(31.3)	ICT, RT-PCR, PAGE, NGS	2015-2016	Surabaya	Utsumi T. *et al*,[34]
Under 5-years old	Outbreak investigation	11	10(90.9)	ICT, RT-PCR, genome sequencing	2018	Belu (East Nusa Tenggara)	Utsumi T. *et al*,[3]
Under 5-years old	Hospital based surveillance	432	137(31.7)	ICT, Multiplex RT-PCR, genome sequencing	2015-2018	East Java	Athiyyah AF. *et al*,[35]
Under 5-years old	PHCs and hospital based investigation during outbreaks	74	53(74.3)	ICT, RT-PCR	2016, 2018	Lampung	Ana E.F. *et al*,[2]

PHC= Primary Health Care facility, unk= unknown as data was not published, ARSN= Asian rotavirus surveillance network, EIA=Enzyme immunoassay, ELISA=enzyme-linked immunosorbent assay, ICT= immunochromatography, NGS= Next Generation Sequencing, PAGE= Polyacrylamide gel electrophoresis, RT-PCR=reverse transcription-polymerase chain reaction.

The detection rate of rotavirus infection in Indonesia

The detection rate of rotavirus infection among gastroenteritis children of under 5-years of age was range from 31.3% to 90.9% in Indonesia during the year 1972-2018. The lowest detection (31.3%) was observed in a hospital-based study conducted in Surabaya in 2015, while the highest detection rate (90.9%) was identified in an outbreak investigation in Belu, East Nusa Tenggara, with only 11 samples collected from the affected community.[3,34] In the decade prior to the implementation of molecular diagnostics, the detection rate of rotavirus positive gastroenteritis in this population were recorded at 34.5%-54.2%, and similarly the rotavirus detection rate was identified with wide variation at 31.3-90.9% when serology test was combined with molecular diagnostics (TABLE 1). It is important to mention that these various positive rate of rotavirus infection were reported among studies with diverse criteria of subjects' population, and diagnostic methods.

Among children of under 5-years of age, the rotavirus positive rate was also diverge by age groups. Rotavirus detection rate occurred soon after birth, and increased sharply after 2-months of age, with a peak of detection rate was recorded at 5 months until 2-years of age. Afterward, rotavirus infections declined and occasionally occurred until the age of 5 years (FIFURE 2). All the study show the similar pattern, except Razali *et al*.[8] which show a peak a bit earlier and decreased early as well, however the study was conducted on a small subjects population (n=32) aged 3 to 36 months.

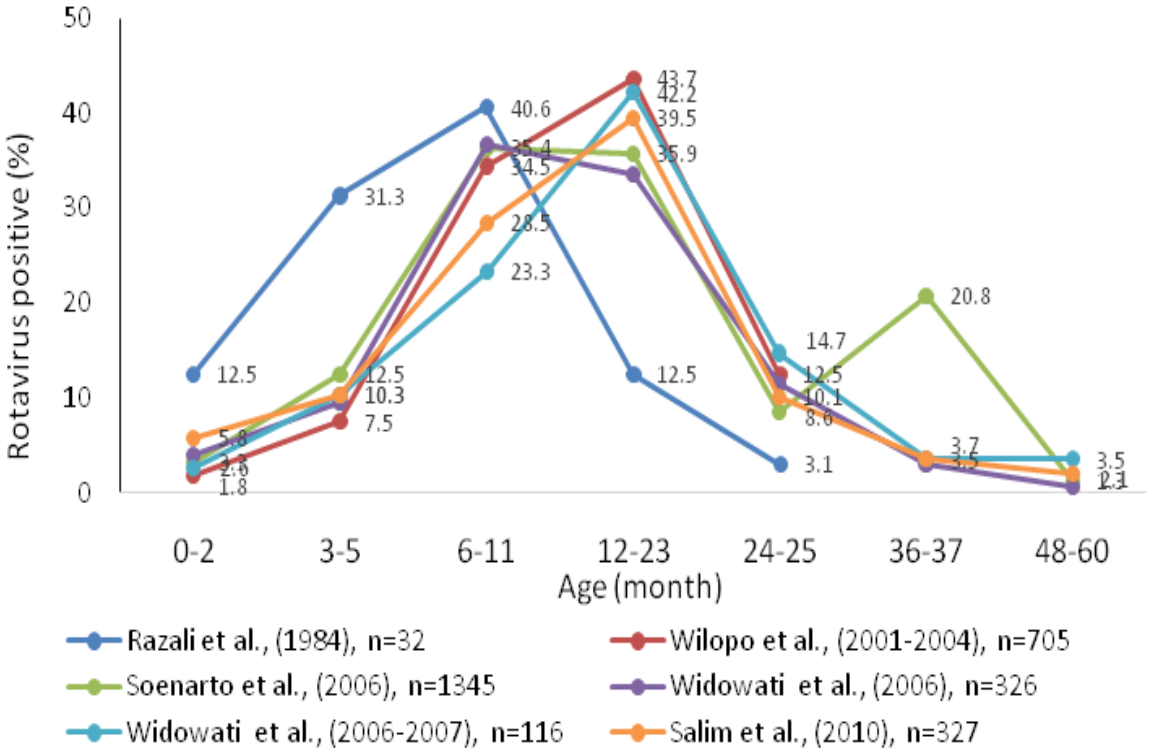

FIGURE 2. Pattern of symptomatic rotavirus infection in children younger than 5 years old(The year of study conducted is indicated in the brackets). The peak of infection occurred between 6 to 23 months. [8,14,16,17,18,23]

Clinical features and severity of rotavirus infection

The major clinical features reported in various studies were diarrhoea, vomiting, and fever (FIGURE 3). Diarrhea was the major sign of rotavirus infection, with almost all children (99.6%-100%) with confirmed rotavirus in their feces were surviving diarrhea. Vomiting is the second most reported clinical manifestation, although its occurence was variable, about 52.3%-93.7% rotavirus positive children complain of vomiting during their illness. The third frequently reported clinical feature was fever. It is interesting that the difference in the percentage of subjects with fever was large. The lowest (12.1%) was found by Kadim *et al.*[20] in the hospital- based study in an urban area (Ciptomangun Kusumo Hospital), while the highest fever rate reported by Tjitrasari *et al.*[13] (85.7%, 2011) was conducted at the same hospital, however with different time. The different in the time of study produce quite different clinical manifestations (i.e. fever). Whether the difference in the clinical manifestations suggested difference in the virulence of the infecting rotaviruses, remain to be studied. Other clinical features also presented although less frequent, such as bloody stool, and stool mucous that appeared in 0.3%-11.4%, and 10.5%-44.8% of rotavirus cases respectively (FIGURE 4).

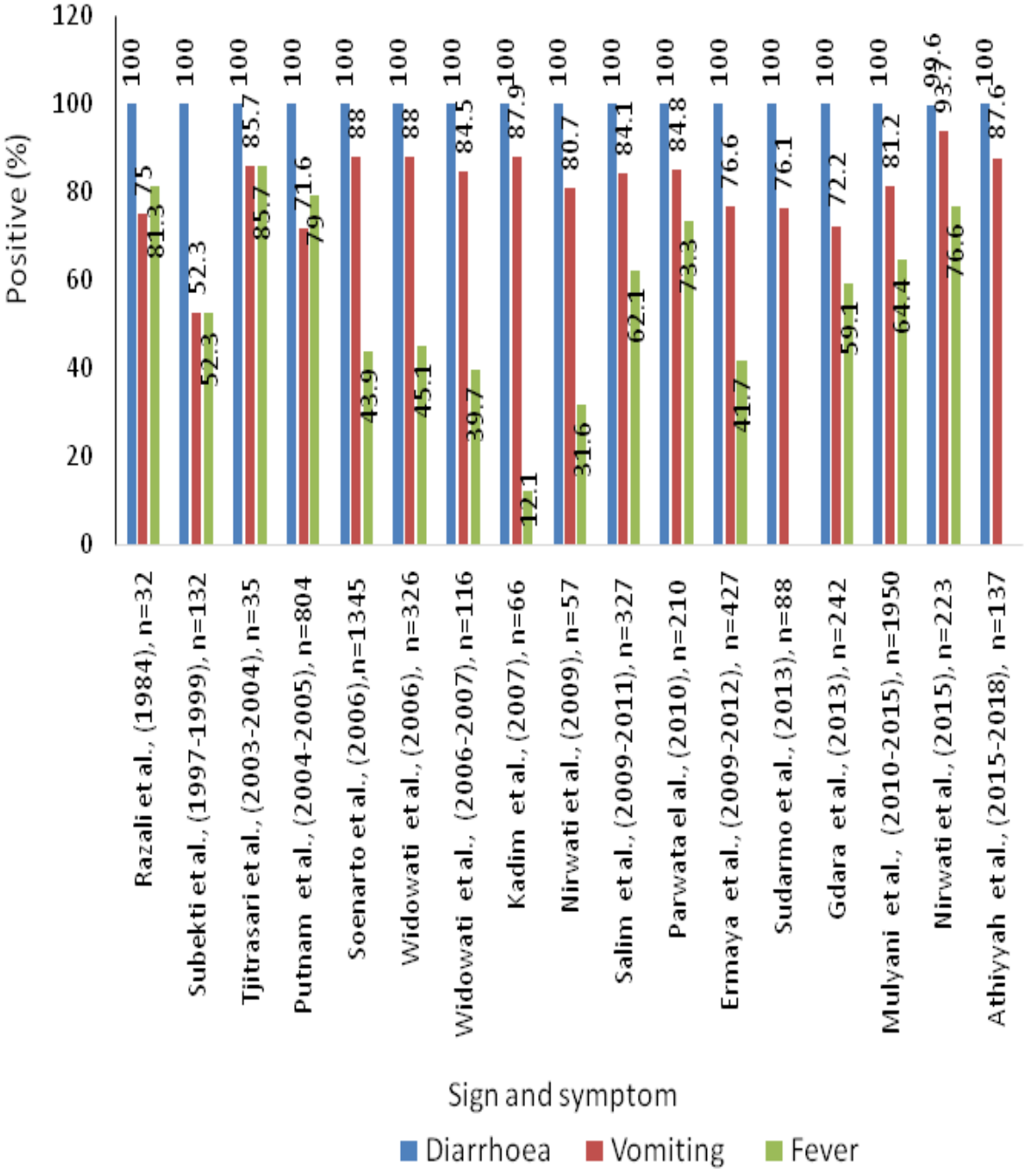

FIGURE 3. The frequent clinical features (diarrhoea, vomiting and fever) observed in rotavirus patient in Indonesia from various studies conducted during 1984-2018. Each study indicates percentage of clinical features among rotavirus patients and the year of study period(The year of study conducted is indicated in the brackets).[8,10,13,15,16,17,18,20,21,23,25,28,29,30,32,33,35]

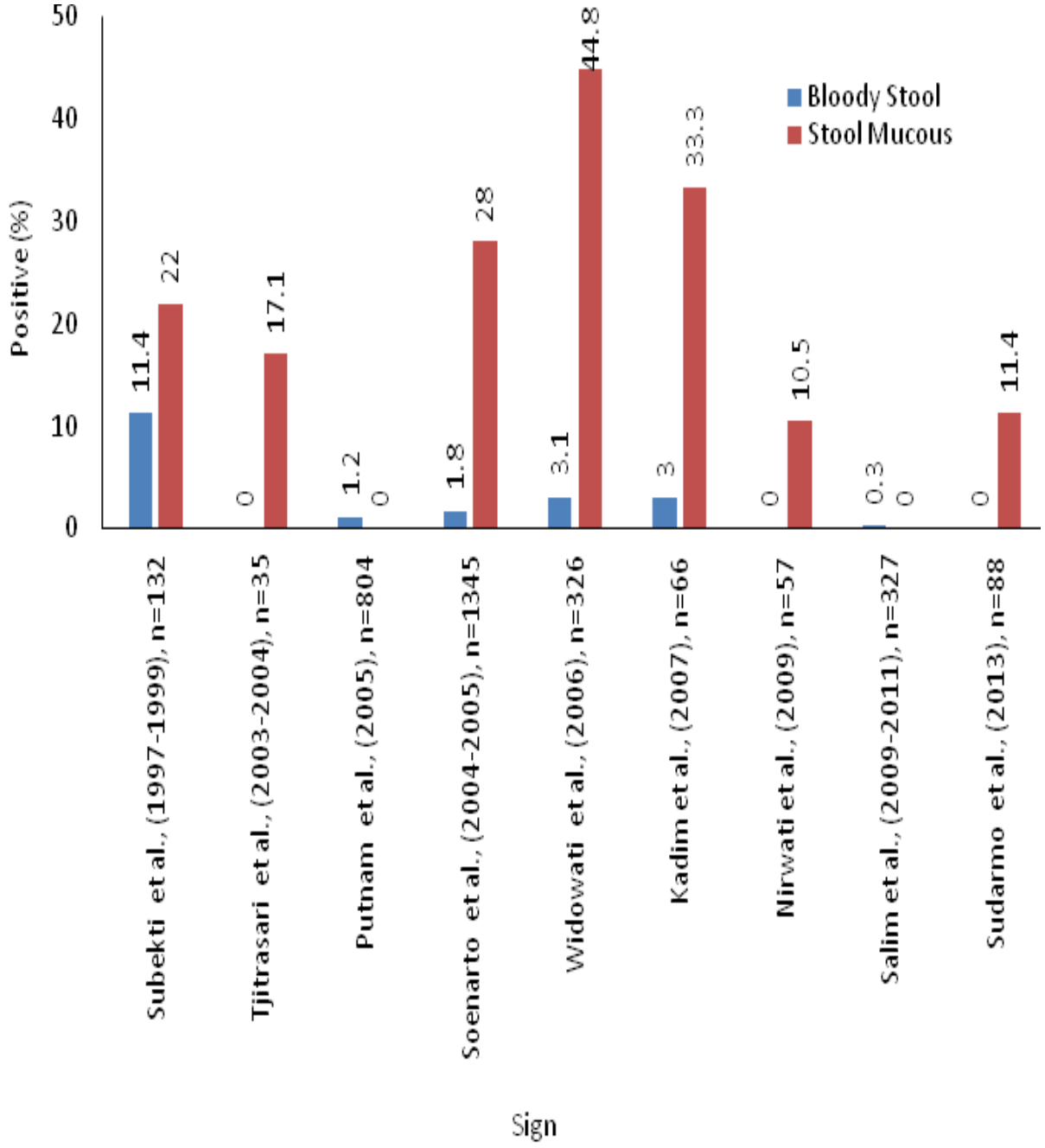

FIGURE 4. Percentage of bloody stool and stool mucous among rotavirus patient. Each study indicates the study period (The year of study conducted is indicated in the brackets).[10,13,15,16,17,20,21,23,29]

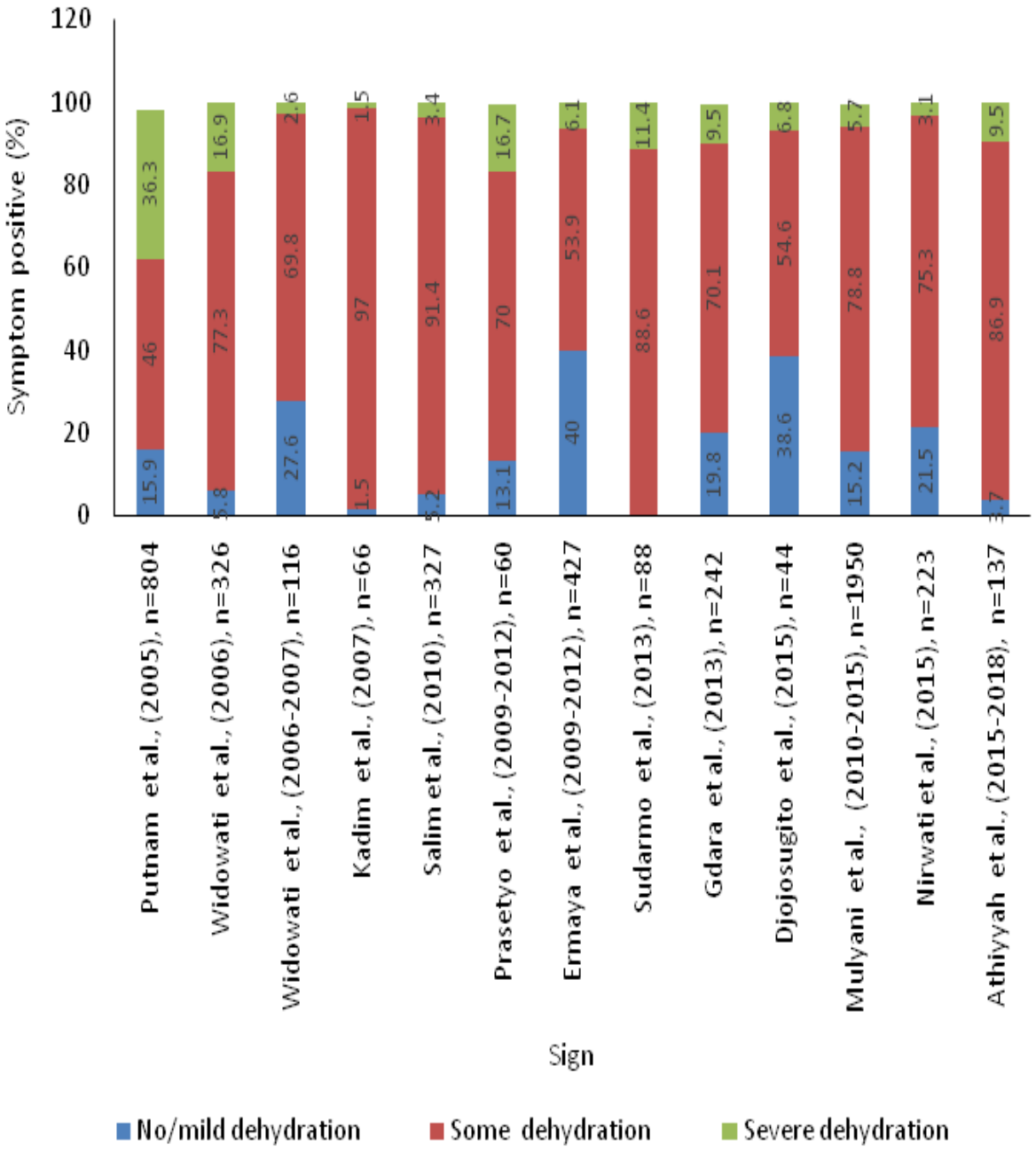

FIGURE 5. Percentage of dehydration (mild, some, severe) among rotavirus diarrhoea patients in children under 5 years old.Each study indicates the study period.[15,17,18,20,23,26,28,29,30,31,32,33,35]

Rotavirus causes diarrhoea with variety degree of severity, from no or mild dehydration, to some, and severe dehydration. Severe dehydrations recognized in majority (60-100%) of patients sought care from hospitals (FIGURE 5). Some dehydration occurred in 46 to 91.4% of rotavirus positive children, where as the severe dehydration presented in 1.5 - 36.3% of the cases, and only relatively small portion of the rest were show no or or mild dehydration. It has to be noted that 13 hospital-based studies were reported that only some degree of dehydration attributed to the majority of subjects.

Genotypes of circulating rotavirus in Indonesia

The genotypes of rotavirus were presented as the percentage of G, and P genotypes among sample of rotavirus tested with RT-PCR, except one study which used neutralization reaction to determine serotyping.[9] The first genotyping study conducted by Bishop *et al.*[7] in 1978-1979 recorded only four G genotypes identified (G1, G2, G3, and G4). Recently, the genotype G1, G2, G3, G4, G9 were the common rotavirures strain circulating in Indonesia (FIGURE 6). This review also found that the common P genotypes of rotaviruses were P[4], P[6], and P[8] with less frequent genotypes of P[10], and P[11] (FIGURE 7).

During 2003-2015, the G genotypes distribution was dominated with G1(8.5- 86%), followed by considerable amount of G2(5-31.8%) and G9 (3.1-62.5%) with 2- 38.8% rotaviruses were showed mixed G genotypes, and 4- 45% of rotaviruses were G untypable. Small fractions of G2 and G4 were observed during 2003-2015. G2 was identified in 0.4-3.6% during 2003-2013, and rose after 2013. Meanwhile, G4 was observed in 0.4 -4.5% of identified rotaviruses during 2003-2013. In 2015, Djojosugito *et al.*[31] conducted a study in Riau which revealed a shift of proportion of G genotypes among identified rotaviruses compared to other preceding studies; G1 was still predominating (57.4%), but G3 proportion increased to 26%, compared to relativelly small proportion of G2 (9.5%), G9 (0.1%), and G12 (1%). In 2015-2018, the G3 genotype rotavirures were predominantly circulating in Indonesia, as shown by several studies that recorded 85.7-100% G3 genotypes identified in their studies. Although an outbreak investigation in Belu, East Nusa Tenggara (2018) revealed that G2 was the solely genotype of rotavirus which responsible for the outbreak, however, only five samples were available representing the outbreak. The prior outbreak in 2008, in different island (Bintuni, Papua) documented G1 (75%) and G2 (25%) were the genotypes of identified rotaviruses from 12 samples. However, in hospital based studies, aminor portion of G1 (9.5%), G2(2.9-9.5%), G9 (0.1-2.9%), and mixed genotypes were observed during 2015-2018.

The P genotypes distribution of rotavirusesin Indonesia during 2003-2018 were also described (FIGURE 7). The P[4], P[6], and P[8] were relatively constant identified throughout the years. P[4] was found in 5 to100% of stool specimens of under 5-years old children with gastroenteritis. P[6] and P[8] were also relatively frequently identified in these population that accounted for 2.8-72.5%, and 15-92.3% respectively. Other P genotypes of P[9], P[10], and P[11] were less frequently identified compared to the previous P genotypes. P[9] was only identified in 0.1-11.4% in five studies conducted during these period. Only 3 studies identified P[10] in the subjects' stool, P[10] was identified as 1, 2.3, and 9.1% in the studies conducted by Putnam *et al.*[15] Sudarmo *et al.*[29] and Djojosugito *et al.*[31] respectively. Likewise, P[11] was only identified in 3 studies with positivity range from 0.2 to 2.3%. Notable percentages of mixed P genotypes and untyped P genotypes were observed throughout 2003-2018. Mixed P genotypes was identified in 2.6-14% of stool samples. Nine studies revealed wide variety of untyped P genotypes proportion, that range from 1.5 to 52.5%.

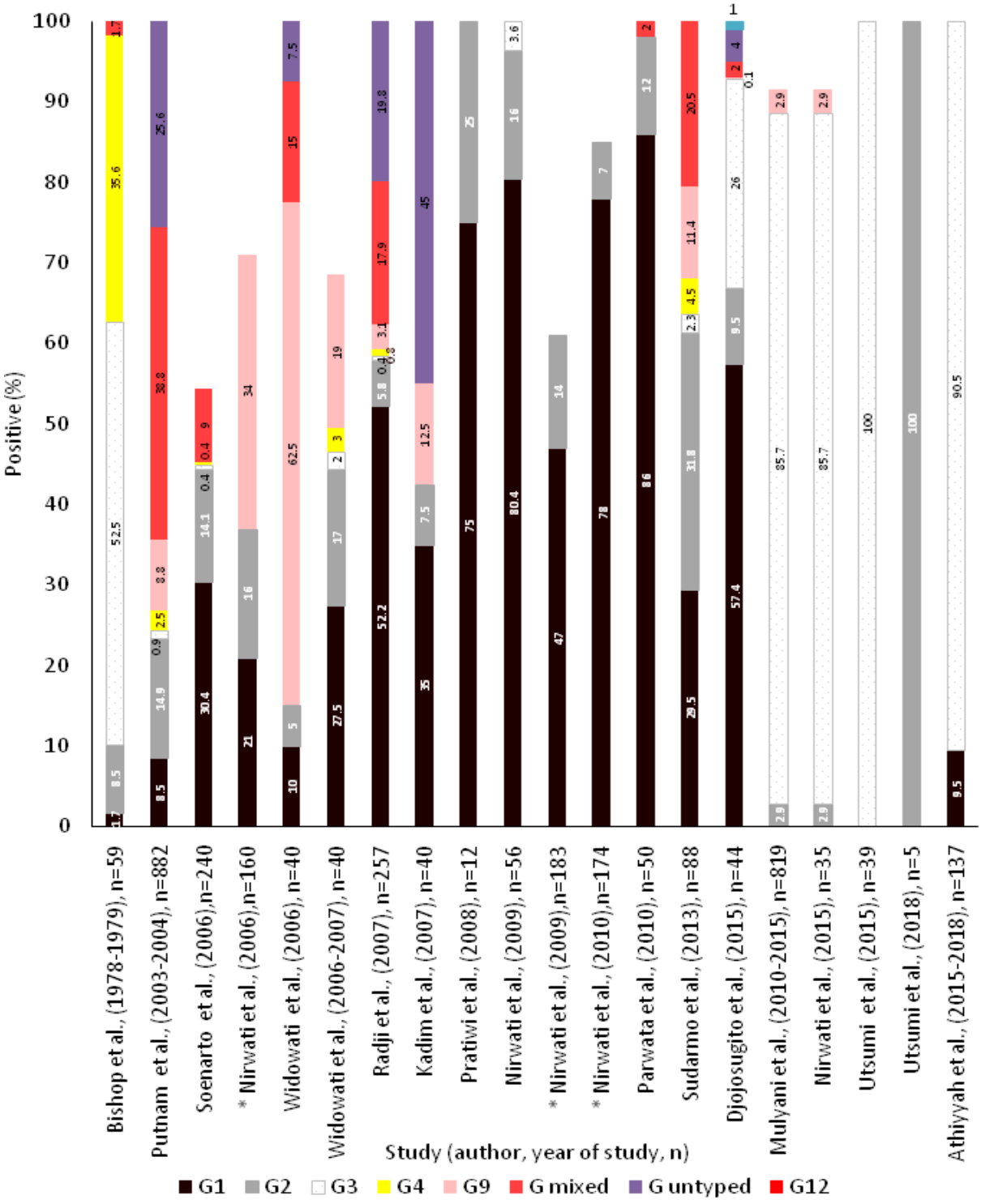

FIGURE 6. The G genotypes of rotavirus found among children with rotavirus diarrhoea and their percentage in Indonesia during 2003-2018. Data generated from 18 studies, *: denotes the same origin of study (3 separated data from one study conducted by Nirwati *et al.*, in the year of 2006, 2009, and 2010).[3,7,15,16,17,18,19,20,21,22,24,25,29,31,32,33,34,35]

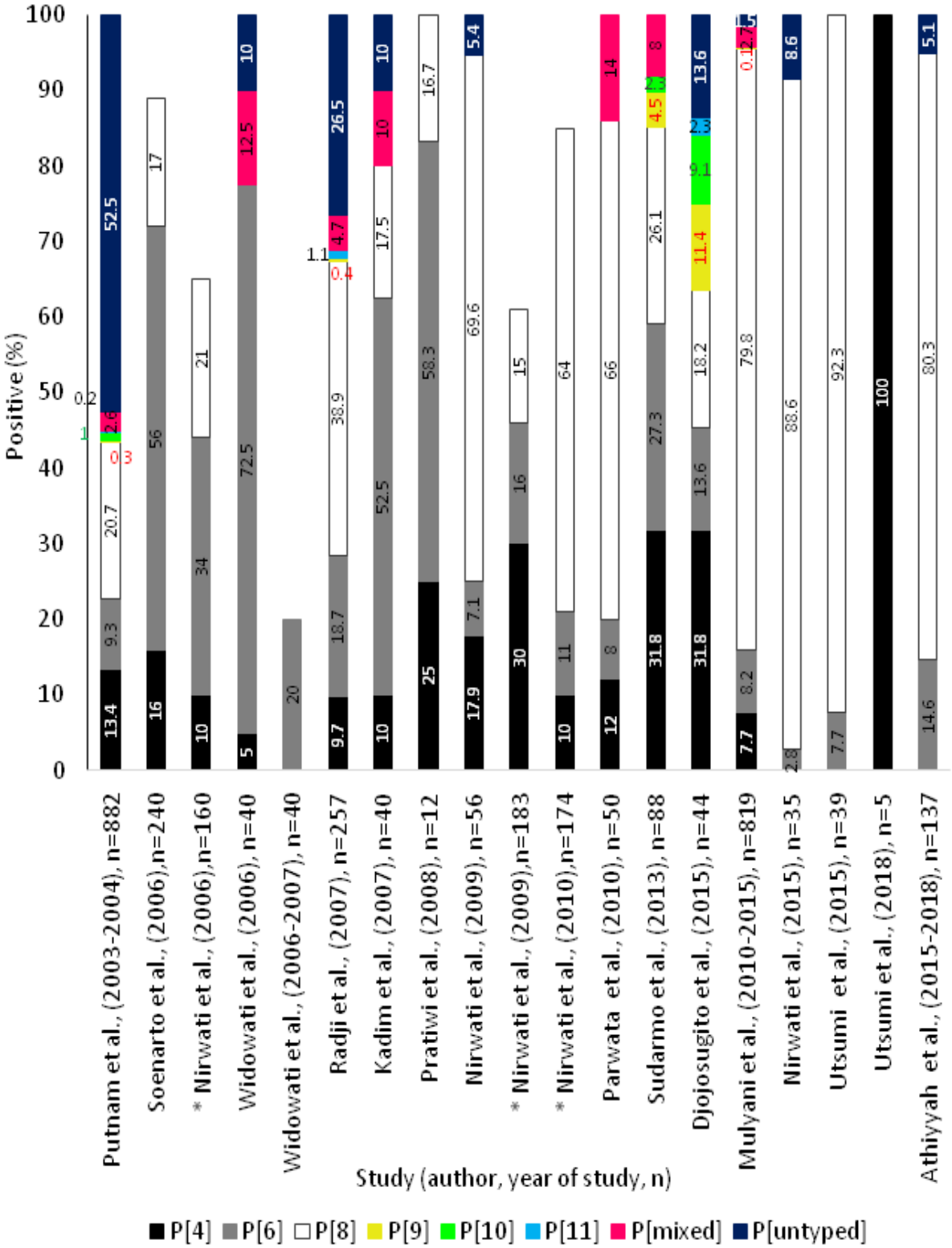

FIGURE 7. Percentage of P genotype of rotavirus isolated from children with rotavirus gastroenteritis in Indonesia. Data were generated from 17 studies conducted during 2003-2018. * : denotes the same origin of data (3 separated data from one study conducted by Nirwati *et al.*, in the year of 2006, 2009, and 2010).[15,16,17,18,19,20,21,22,24,25,29,31,32,33,34,35]

DISCUSSION

The detection rate of rotavirus infection in Indonesia

In four decades, numerous studies illucidated the high burden of rotavirus infection in Indonesian children with acute gastroenteritis. In 1981, two hospital-based surveillances revealed rotavirus as the etiology pathogens of acute gastroenteritis in several places of Indonesia.[5,6] Soenarto *et al.*[6] conducted study using electron microscope with staining to identify rotavirus from feces of under 2-years old children with diarrhea that had been stored in -70^{o}C since 1978, and reported positive rate of 39.7%in Yogyakarta. This number could be larger, since electron microscopy methods possess detection character of high specificity but less sensitivity compared to other methods.[36,37] At the same time, another study using ELISA reported detection rate of 46.4% from 91 feces samples of under-5 years old children collected in Jakarta and Medan during 1972-1975.[5] With similar methods (ELISA), Razali *et al.*[8] reported higher detection rate (54.2%) from 59 samples collected in Medan. A decade later, Wasito *et al.*[9] using a less sensitive and less specific methods (antibody sensitized methods) to detect rotavirus in 1184 stool samples from under 2-years old diarrheal children, and yet yielded positive rate of 34.5% in Surabaya. In Jakarta (1997-1999), rotavirus detection rate was 47.2% with EIA.[10] Asian Rotavirus Surveillance Network (ARSN) also implemented EIA, and somehow reported higher detection rate of 52.4% from 577 stool sampels obtained in Yogyakarta and Purworejo.[11] Tjitrasari *et al.*[13] using ELISA detected rotavirus in 35.7% of 98 sample tested. Other studies using EIA only revealed positive rate range of 44.8-49.8%.[23,26-28]

In the following dacade, the use of reverse-transcriptase (RT)-PCR to determine their genotypes geting more widespread. The use of EIA or other laboratory methods for rotavirus detection was combine with other laboratory methods in some studies, in addition for using RT-PCR for genotypes determinations. A multisites research conducted in Palembang, Jakarta, Bandung, Yogyakarta, Denpasar, and Mataram confirmed rotavirus in 1418 out of 2440 samples (58.1%) in 2006,[16] while other studies conducted as part of ARSN yielded detection rate of 52% and 53.4%.[12,14] Later, several studies reported higher detection rates of rotavirus, Widowati *et al.*[17] reported 64% of rotavirus positive rate in Palembang (2006), while multi-sites study conducted in Jakarta, Yogyakarta, Denpasar, Makasar, and Mataram yielded 257 positive rotavirus of 421 stool samples (61%) in 2007.[17,19] In Jakarta (2007) the detection rate was 67%.[20] A hospital based surveillance in Mataram (2010) revealed positive rate of 63.8%.[25] Similarly, a hospital based study in Riau (2015) reported detection rate of 62%.[31] During outbreak period in Lampung (2016 and 2018), positive rate of 74 samples collected from hospital and community was 74.3%.[2] These relatively high detection rates may also attributable to the study design and sampling methods. Other studies reported rotavirus detection rates were similar or no higher than when RT-PCR unimplemented. A study in Yogyakarta (2006-2007) reported positivity of 32.7% by implementing EIA and RT-PCR.[18] Nirwati *et al*,[22] conducted rotavirus study in 2009, showed a positive detection rate of 54.8%, and their larger sample size study reported 2220 positive rotavirus among 4235 samples (52.4%) from stool samples collected in Bandung, Yogyakarta, Denpasar, and Mataram (2009, 2009-2010). The recent study reported detection rotavirus of 54.9% among 406 tested samples collected from Yogyakarta and Mataramin 2015.[33]

However, some studies also reported various lower detection rate of rotavirus which range from 31.3-48.6%.[3,15,29,30,32,35]

Rotavirus is known for its efficient transmission and could invoke outbreak. Threeprobable rotavirus outbreaks were documented in Indonesia. The first outbreak documented was in September-October 2008 in West Papua.[24] The outbreak affected five villages, in Bintuni Bay district, then field investigation collected stool samples from 15 children of 6-41 months with diarrhea that revealed rotavirus positive rate of 67%.[24] However the local terrain of Bintuni Bay was challenging, so a systematically sampling might be difficult, and that study was inconclusive in establishing rotavirus as pathogen causedthe outbreak. The second outbreak investigation was conducted recently in September 2018, that affected 631 individuals in 17 primary health care facilities in Belu, East Nusa Tenggara.[3] The region was primarily mountainous, and only 11 rectal swabs samples were collected although 435 children of under 5 of age were affected.[3] The result was a extraordinary high detection rate, 10 of 11 (90.9%) samples were rotavirus positive.[3] Another outbreak investigation yielded rotavirus positive rate of 74.3% from 74 specimens of 2016 and 2018 diarrheal outbreak.[2]

Some studies provided slightly different clustered period of rotavirus infection. African Rotavirus Network reported that cummulative percentage of rotavirus infection had achieved > 90% within the first two years of life and almost reached 100% when the age was 35 months.[38] A study in India revealed similar pattern that distribution of rotavirus positive children were clustered in the first two years of life and almost all rotavirus infection occurred within the first 35 months of life.[39] Study in the developed countries, described similar pattern. In the USA > 90% of cummulative rotavirus infection occurred within the first 35 months.[40] In Taiwan, cummulative incidence of rotavirus positive gastroenteritis reached 80% in the first 35 months of age.[41] Rotavirus may infect on first days of life, 60% infection occurred by the fourth day but they were asymptomatic.[42] This first neonatal infection gave 46% protection from the subsequent rotavirus infection.[42] Furthermore, another study found that both symptomatic and asymptomatic rotavirus primary infection provided protection from secondary rotavirus infection, that explained the decline of rotavirus infection by time, after two years of age.[43] Rotavirus infection incidence was obviously declined after the 3rd infections, with incidence of 11.3 infections/100 child months among children without previous infection, and decreased to 4.2/100 child-months among children with three previous infectons.[44]

Clinical features and severity of rotavirus infection

Rotavirus infection in young children could causesevere inflammation of upper small intestine, with villous athrophy.[45] Although rotavirus infection can be a symptomatic, or mild, some infected children could suffer from severe clinical manifestation.[46] Diarrhea, vomiting, and fever are the cardinal signs of rotavirus gastroenteritis. All studies in Indonesia reported diarrhea in almost all the cases during enrollmen (99.6-100%). Other frequently reported symptoms were vomiting (52.3-93.7%), and fever (12.1-85.7%). Rotavirus diarrhea commonly is osmotic or secretory type-watery diarrhea as the consequence of enterocyte damage and death causing shorthening and atrophy of microvilli, mononuclear cell infiltration, as well as enterocyte vacuolization, damage and death.[47] However bloody stool and stool mucous can sometimes occurred in

rotavirus acute gastroenteritis, requiring the evaluation of any concomitant bacterial infection.[48] Subekti *et al.*[10] reported bloody stool occurred in 11.4% rotavirus positive diarrhea, while other studies reported less (0.3-3.1%).[10,15-17,20] Stool mucous appeared in some rotavirus diarrhea, Widowati *et al.*[17] reported this sign in 44.8% of 326 rotavirus cases, while other studies recorded less frequent of stool mucous (10.5-33.3%).[13,16,17,20,21,29] Rotavirus infection can activate vagal nerves which associated with nausea and vomiting.[47] Subekti *et al.*[10] and Putnam *et al.*[15] reported nausea in rotavirus gastroenteritis were 9 and 44.2% respectively. Intestine hypermotality in rotavirus infection could lead to abdominal pain or cramp,[47,49] which observed in 40-52.3% of cases.[10,15]

Rotavirus infection can cause fever, and commonly associated with malaise or fatique, and chills which usually occurred in severe cases.[47,50] Putnam *et al.*[15] reported fatique and chills in 64and 4.9% of children with rotavirus infection respectively. Rotavirus infection also associated with malabsorbtion secondary to enterocyte damage or death.[47] Kadim *et al.*[20] observed that bloating occurred in 62.1% of cases, while other study reported lactose, and fat malabsorption in 20 and 31.4% of rotavirus infections.[13,20]

After ingestion, rotavirus known for the ability to attach to upper epithelial intestinal cells, lead to the clinical symptomps in gastrointestinal tract, however some studies have demonstrated detection of viral RNA in blood, organs and cerebrospinal fluids, although the implications was unclear.[51] In Indonesia, two studies reported seizure during rotavirus infection. Razali *et al*,[8] reported 1(3.1%), while Salim *et al*,[23] reported 23(7%) convulsion as additional sign of rotavirus infections. Nervous system activation can be secondary to rotavirus infection,[47] however CNS complications can be primarily caused by the presence of rotavirus in CNS.[52] There is increasing evidence that alternate mechanism of encephalophaty following rotavirus diarrhea was the rotavirus infiltration into CNS. A case report described the presence of rotavirus RNA in cerebrospinal fluids from two children with encephalopathy that following rotavirus gastroenteritis, on one of the case, rotavirus was detected in two ocassion of three week apart.[52] However whether Indonesian studies tested the CSF of those children with CNS symptoms were unknown.

Other uncommon symptoms reported in rotavirus infections were respiratory symptoms. Razali *et al.*[8] reported that children with rotavirus infection also experienced rhinorhea, and hyperemic throat that accounted for 12.5 of and 18.8% respectively. While other study (2003-2004) reported rhinitis occurred in 65.7% of rotavirus gastroenteritis.[13] Other respiratory symptoms in rotavirus gastroenteritis was cough which reported in 3 studies. Tjitrasari *et al.*[13] reported cough in 77.1% of rotavirus infections, while other studies recorded cough in 40.6 and 28.4% of the cases.[8,13,29]

Rotavirus infections remains the major causative agent of serious diarrhea in children of under 5 years of age. The majority of Indonesian children with rotavirus infection were enduring severe clinical manifestation. Previous studies showed that 60-100% rotavirus infected children were experienced some, and severe diarrhea in Indonesia. However most of rotavirus infections were detected in hospital settings, and less about the real burden of rotavirus infections in community, although two outbreak investigations in West Papua, and East Nusa Tenggara stated its magnitude in remote area of Indonesia. In 2008, the global mortality estimate of children younger than 5-years old was 453,000 (420,000-494,000) associated

with rotavirus infection, or equivalent to 37% of death due to diarrhea disease, that represented 5% of all cause death of children less than 5-years old.[53] In Asia, 145,000 deaths were associated with rotavirus infection, with greatest deaths from rotavirus occurred in India, Pakistan, and Indonesia.[54] While in Indonesia, the rotavirus associated mortality of children under 5-years old was 50-100 deaths/100,000 children.[53] Salim *et al.*[23] reported 8 (2.5%) deaths among 327 rotavirus infected children of under 5-yearsold during 2009-2011 in Denpasar.

The G and P genotypes circulating in Indonesia, 2004-2018

The first genotyping of rotavirus from Indonesia was conducted by Bishop *et al.*[7] from 111 specimen collected in 1978–1979. During that period, 59(53%) were successfully identified with monoclonal antibodies, yielded four genotypes comprised G1, G2, G3, G4 and mixed G infection, that accounted for 1(1.7%), 5(8.5%), 31(52.5%), 21(35.6%) and 1(1.7%), respectively.[7] More than a decade later, Putnam *et al.*[10] (2004) conducted a study infour referral hospitals, and carried out genotyping using RT-PCR, and reported the first time rotavirus genotipe G9(8.8%).[15] Since then, G9 was reported elsewhere, including by a multi-sites study (2006) conducted in Yogyakarta, Bandung, Denpasar and Mataram that identified G9 (34%) from 160 samples.[22]

Some centres in Indonesia conducted genotyping with various results of G and P proportion. Studies in Indonesia revealed G genotypes were identified in 55-100 % rotavirus strains, and 4-45% of untyped rotavirus strains circulated in Indonesia. The G genotypes commonly identified were G1, G2, G3, and G9, however a little (0.4- 4.5%) proportion of G4 was also identified. It is interesting that G4 which commonly distributed in the early 1980s, then almost undetectable two decades later. In the contrary, G1, and G2 were in the raise in the next decade, while G9 was detected until 2007, and re-appear again in 2013. The percentage of G1 had been increasing again since 2003, and predominantly circulated in Indonesia during 2003-2015. In Addition, G2 continuously moderately identified during 2003-2018, with substantial decreased when G3 overtook G1 and G2 in 2015. The studies recorded trivial number of G3 genotype identified which accounted for 0.4-3.4% before 2015, but abrupt increase of G3 genotype occurred in 2015, with steady high number until the last recorded data in 2018. However an outbreak in East Tenggara was associated with G2 as the solely strain identified genotypes indicating that genotypes differ by region in Indonesia.[3] Although in 2003, G9 was identified in 8.8% of 882 rotavirus cases, it was unidentified in a multicenter study in 6 cities of populous island of Indonesia conducted in 2006.[15,16] Another data generated from multicenter study revealed 34% G9 genotype in 2006.[22] G9 was identified in 62.5% of 40 rotavirus isolated from Palembang in 2006,[17] and soon decreasing and became unidentified in 2008. G9 was re-appeared in small proportion (2.9-11.4%) in 2013 and 2015. Once, insignificant number (1%) of G12 was identified in one study in Riau in 2015, and never identified in other studies.[29] G9 was initially identified since 1997 and became the emerging G type which become secondly important after another globally common G type in numerous countries such as Australia (2000-2001), Ireland (2001-2005), India (2006), Turkey (2014), and Tunisia (2015-2017).[55-59]

Untyped, and mixed G genotypes also identified in 4-45%, and 2-38.8% respectively. The untyped and mixed G gen otypes may indicated reassorment and genome mobility phenomenon.[7,60]

It may also implied the magnitude of diversity of rotavirus genome, a short electrophore type genome which relatively unstable to gut enzyme during storage, antigenic variation of VP7 epitope, or intratypic variation.[7,61] Technical factors can also associated with untyped genotypes, i.e. loss of outer capsid during transport or storage of specimens.[7]

Indonesian studies revealed predominant P genotypes were P[4], P[6], and P[8], with the minor P[9], P[10], and P[11] were circulating in Indonesia. P[8] was the most prevalent P genotype which constantly found since genotyping was conducted in Indonesia, until the recent data shown in 2018. P[4] and P[6] were the second important P genotypes that detected throughout period of 2003-2018 in Indonesia. An outbreak in Papua was associated with P[4], P[6], and P[8], while a recent outbreak in East Nusa Tenggara was associated with P[4]. The extanct of unusual P genotypes (P[9], P[10], and P[11]), untyped, and mixed P genotypes were indicated potential source of reassortment and emergence of new rotavirus strain. Other uncommon G and P types (e.g. G5, G6, G8, G10, G12, P[9], P[11], and P[14]) have been reported in a variety locations worldwide and are the important causes of diarrhea in countries where they are found.[62]

In Indonesia predominant G and P genotypes were also found, along with unusual, mixed, and untyped G or P genotypes. They occurred vary in number, differ in each study, and also vary among regions or islands in Indonesia. Although rotavirus is a vaccine-preventable disease,[62] the great rotavirus genotypes diversity circulating in Indonesia implicated that implementation of rotavirus vaccination program required continuous surveillance of circulating rotavirus genotypes.

CONCLUSION

Rotavirus was a major causative agent of diarrhea in children younger than 5-years old, and can cause severe manifestations, including fever, vomiting and watery diarrhea. Those usually lead to some-severe dehydration requiring hospitalization. The predominant rotavirus genotype circulating in Indonesia showed shifting continuously, and some new strains emerge in some region of Indonesia. In addition, homotypic response somewhat better compare to heterotypic responses, therefore, continuous surveillance should be conducted to monitor the dynamic rotavirus genotypes circulating in Indonesia.

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For every child in the world whose healthy life is their very rights

REFERENCES

1. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD, World Health Organization-Coordinated Global Rotavirus Surveillance N. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013. Clin Infect Dis 2016; 62 Suppl 2: S96-S105. https://doi.org/10.1093/cid/civ1013
2. Ana EF, Wahyuni RM, Yamani LV, Dinana Z, Ani DO, Megasari NLA, *et al.* Identification of rotavirus infection during diarrhoea outbreaks among children under five years of age in Lampung, Indonesia. Paediatr Croat 2019; (63):100-4. http://dx.doi.org/10.13112/PC.2019.24
3. Utsumi T, Wahyuni RM, Dinana Z, Gunawan E, Putra ASD, Mubawadi T, *et al.* G2P[4] rotavirus outbreak in Belu, East Nusa Tenggara Province,

Indonesia, 2018. J Infect Public Health 2020; 13(10):1592-4. https://doi.org/10.1016/j.jiph.2020.05.002
4. Roczo-Farkas S, Kirkwood CD, Cowley D, Barnes GL, Bishop RF, Sakran NB, *et al.* The Impact of Rotavirus Vaccines on Genotype Diversity: A Comprehensive Analysis of 2 Decades of Australian Surveillance Data. J Infect Dis 2018; 218(4):546-54. https://doi.org/10.1093/infdis/jiy197
5. Urasawa S, Urasawa T, Djoko Y, Furuya K, Akiba S, Kanamitsu M. A survey of rotavirus infection in the topics. Jpn J Med Sci Biol 1981; 34(5):293-8. https://doi.org/10.7883/yoken1952.34.293
6. Soenarto Y, Sebodo T, Ridho R, Alrasjid H, Rohde JE, Bugg HC, *et al.* Acute diarrhea and rotavirus infection in newborn babies and children in Yogyakarta, Indonesia, from June 1978 to June 1979. J Clin Microbiol 1981; 14(2):123-9. https://doi.org/10.1128/JCM.14.2.123-129.1981
7. Bishop RF, Unicomb LE, Soenarto Y, Suwardji H, Ristanto, Barnes GL. Rotavirus serotypes causing acute diarrhoea in hospitalized children in Yogyakarta, Indonesia during 1978-1979. *Archives of virology* 1989; 107(3-4): 207-13. https://doi.org/10.1007/BF01317917
8. Razali A, Jufri A, Karo-Karo M, Sutanto AH, Siregar H. Rotavirus gastroenteritis in Medan (Part four). PaediatrIndones1984;24(7-8):145-52. https://paediatricaindonesiana.org/index.php/paediatricaindonesiana/article/view/1902/1667
9. Wasito EB, Soeparto P, Soedarmo SM, Djupri LS, Alimsardjono L, Rahardjo D, *et al.* Isolation Frequency of Enteropathogens from Pediatric Diarrheal Stool in Surabaya, Indonesia: A Five Year Hospital Based Study. Japan J Trop Med Hyg 1999; 27(3): 433-6. https://doi.org/10.2149/tmh1973.27.433
10. Subekti D, Lesmana M, Tjaniadi P, Safari N, Frazier E, Simanjuntak C, *et al.* Incidence of Norwalk-like viruses, rotavirus and adenovirus infection in patients with acute gastroenteritis in Jakarta, Indonesia. FEMS Immunol Med Microbiol 2002; 33(1):27-33. https://doi.org/10.1111/j.1574-695X.2002.tb00568.x
11. Bresee J, Fang ZY, Wang B, Nelson EA, Tam J, Soenarto Y, *et al.* First report from the Asian Rotavirus Surveillance Network. Emerging infectious diseases 2004; 10(6):988-95. https://doi.org/10.3201/eid1006.030519
12. Nelson EA, Bresee JS, Parashar UD, Widdowson MA, Glass RI, Asian Rotavirus Surveillance N. Rotavirus epidemiology: the Asian Rotavirus Surveillance Network. Vaccine 2008; 26(26):3192-6. https://doi.org/10.1016/j.vaccine.2008.03.073
13. Tjitrasari T, Firmansyah A, Chair I. Clinical manifestations of rotavirus diarrhea in the outpatient clinic of Cipto Mangunkusumo Hospital, Jakarta. Paediatrica Indonesiana 2005; 45(3-4):69-73. https://doi.org/10.14238/pi45.2.2005.69-75
14. Wilopo SA, Soenarto Y, Bresee JS, Tholib A, Aminah S, Cahyono A, *et al.* Rotavirus surveillance to determine disease burden and epidemiology in Java, Indonesia, August 2001 through April 2004. Vaccine 2009; 27 Suppl 5:F61-6. https://doi.org/10.1016/j.vaccine.2009.09.004
15. Putnam SD, Sedyaningsih ER, Listiyaningsih E, Pulungsih SP, Komalarini, Soenarto Y, *et al.* Group A rotavirus-associated diarrhea in children seeking treatment in Indonesia. J Clin Virol 2007; 40(4):289-94. https://doi.org/10.1016/j.jcv.2007.09.005
16. Soenarto Y, Aman AT, Bakri A, Waluya H, Firmansyah A, Kadim

M, *et al.* Burden of severe rotavirus diarrhea in indonesia. J Infect Dis 2009; 200 Suppl 1:S188-94. https://doi.org/10.1086/605338
17. Widowati T, Bakrie A, Nirwati H, Soenarto Y. Surveillance of rotavirus diarrhea. Paediatrica Indonesiana 2012; 52(1):22-7. https://doi.org/10.14238/pi52.1.2012.22-27
18. Widowati T, Mulyani NS, Nirwati H, Soenarto Y. Diare Rotavirus pada Anak Usia Balita. Sari Pediatri 2012; 13(5):340-5. https://dx.doi.org/10.14238/sp13.5.2012.340-5
19. Radji M, Putman SD, Malik A, Husrima R, Listyaningsih E. Molecular characterization of human group A rotavirus from stool samples in young children with diarrhea in Indonesia. Southeast Asian J Trop Med Public Health 2010; 41(2): 341-6.
20. Kadim M, Soenarto Y, Hegar B, Firmansyah A. Epidemiology of Rotavirus diarrhea in children under five: A hospital-based surveillance in Jakarta. Paediatrica Indonesiana 2011; 51(3):138-43. https://doi.org/10.14238/pi51.3.2011.138-43
21. Nirwati H, Hakim MS, Aminah S, Dwija I, Pan Q, Aman AT. Identification of Rotavirus Strains Causing Diarrhoea in Children under Five Years of Age in Yogyakarta, Indonesia. Malays J Med Sci 2017; 24(2):68-77. https://doi.org/10.21315/mjms2017.24.2.9
22. Nirwati H, Wibawa T, Aman AT, Wahab A, Soenarto Y. Detection of group A rotavirus strains circulating among children with acute diarrhea in Indonesia. Springerplus 2016; 5:97. https://doi.org/10.1186/s40064-016-1724-5
23. Salim H, Karyana IP, Sanjaya-Putra IG, Budiarsa S, Soenarto Y. Risk factors of rotavirus diarrhea in hospitalized children in Sanglah Hospital, Denpasar: a prospective cohort study. BMC Gastroenterol 2014; 14:54. https://doi.org/10.1186/1471-230X-14-54
24. Pratiwi E, Setiawaty V, Putranto RH. Molecular characteristics of rotavirus isolated from a diarrhea outbreak in october 2008 in bintuni bay, papua, indonesia. Virology (Auckl) 2014; 5:11-4. https://doi.org/10.4137/VRT.S13555
25. Parwata WSS, Sukardi W, Wahab A, Soenarto Y. Prevalence and clinical characteristics of rotavirus diarrhea in Mataram, Lombok, Indonesia. Paediatrica Indonesiana 2016; 56(2):118-23. https://doi.org/10.14238/pi56.2.2016.118-23
26. Prasetyo D, Sabaroedin IM, Ermaya YS, Soenarto Y. Association between Severe Dehydration in Rotavirus Diarrhea and Exclusive Breastfeeding among Infants at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. J Trop Med 2015; 2015: 862578. https://doi.org/10.1155/2015/862578
27. Prasetyo D, Ermaya Y, Martiza I, Yati S. Correlation between climate variations and rotavirus diarrhea in under- five children in Bandung. Asian Pac J Trop Dis 2015; 5(11):908-11. https://doi.org/10.1016/S2222-1808(15)60955-0
28. Ermaya YS, Prasetyo D, Sabaroedin IM, Soenarto Y. A Correlational study between Nutritional Status and Severity of Rotavirus Diarrhea in children under five years in Bandung, Indonesia. Journal of GHR 2017; 6(6):2490-4. https://doi.org/10.17554/j.issn2224-3992.2017.06.667
29. Sudarmo SM, Shigemura K, Athiyyah AF, Osawa K, Wardana OP, Darma A, *et al.* Genotyping and clinical factors in pediatric diarrhea caused by rotaviruses: one-year surveillance in Surabaya, Indonesia. Gut Pathog 2015; 7:3. https://doi.org/10.1186/s13099-015-0048-2
30. Gdara FO, At Thobari J, Soenarto Y.

Severity and treatment level of acute gastroenteritis with rotavirus in children under 5 years in Indonesia. J Med Sci 2018; 50(1):103-12. https://doi.org/10.19106/JMedSci005001201812

31. Djojosugito FA, Savira M, Anggraini D, Putra AE. Identification of the P Genotypes of rotavirus in children with acute diarrhea in Pekanbaru, Indonesia. Malaysian J Microbiology 2017; 13(1):67-72.
32. Mulyani NS, Prasetyo D, Karyana IPG, Sukardi W, Damayanti W, Anggraini D, *et al.* Diarrhea among hospitalized children under five: A call for inclusion of rotavirus vaccine to the national immunization program in Indonesia. *Vaccine* 2018; 36(51): 7826-31. https://doi.org/10.1016/j.vaccine.2018.05.031
33. Nirwati H, Donato CM, Mawarti Y, Mulyani NS, Ikram A, Aman AT, *et al.* Norovirus and rotavirus infections in children less than five years of age hospitalized with acute gastroenteritis in Indonesia. Archives of virology 2019; 164(6):1515-25. https://doi.org/10.1007/s00705-019-04215-y
34. Utsumi T, Wahyuni RM, Doan YH, Dinana Z, Soegijanto S, Fujii Y, *et al.* Equine-like G3 rotavirus strains as predominant strains among children in Indonesia in 2015-2016. Infect Genet Evol 2018; 61:224-8. https://doi.org/10.1016/j.meegid.2018.03.027
35. Athiyyah AF, Utsumi T, Wahyuni RM, Dinana Z, Yamani LN, Soetjipto, *et al.* Molecular Epidemiology and Clinical Features of Rotavirus Infection Among Pediatric Patients in East Java, Indonesia During 2015-2018: Dynamic Changes in Rotavirus Genotypes From Equine-Like G3 to Typical Human G1/G3. Front Microbiol 2019; 10:940. https://doi.org/10.3389/fmicb.2019.00940
36. Morinet F, Ferchal F, Colimon R, Perol Y. Comparison of six methods for detecting human rotavirus in stools. Eur J Clin Microbiol 1984; 3(2):136-40. https://doi.org/10.1007/BF02014331
37. Rubenstein AS, Miller MF. Comparison of an enzyme immunoassay with electron microscopic procedures for detecting rotavirus. J Clin Microbiol 1982; 15(5):938-44. https://doi.org/10.1128/JCM.15.5.938-944.1982
38. Mwenda JM, Ntoto KM, Abebe A, Enweronu-Laryea C, Amina I, McHomvu J, *et al.* Burden and epidemiology of rotavirus diarrhea in selected African countries: preliminary results from the African Rotavirus Surveillance Network. J Infect Dis 2010; 202 Suppl:S5-S11. https://doi.org/10.1086/653557
39. Kang G, Arora R, Chitambar SD, Deshpande J, Gupte MD, Kulkarni M, *et al.* Multicenter, hospital-based surveillance of rotavirus disease and strains among indian children aged <5 years. J Infect Dis 2009; 200 Suppl 1:S147-53. https://doi.org/10.1086/605031
40. Fischer TK, Viboud C, Parashar U, Malek M, Steiner C, Glass R, *et al.* Hospitalizations and deaths from diarrhea and rotavirus among children <5 years of age in the United States, 1993-2003. J Infect Dis 2007; 195(8): 1117-25. https://doi.org/10.1086/512863
41. Chen KT, Chen PY, Tang RB, Huang YF, Lee PI, Yang JY, *et al.* Sentinel hospital surveillance for rotavirus diarrhea in Taiwan, 2001-2003. J Infect Dis 2005; 192 Suppl 1:S44-8. https://doi.org/10.1086/431495
42. Bhan MK, Lew JF, Sazawal S, Das BK, Gentsch JR, Glass RI. Protection conferred by neonatal rotavirus infection against subsequent rotavirus diarrhea. J Infect Dis 1993; 168(2):282-7.

https://doi.org/10.1093/infdis/168.2.282
43. Bernstein DI, Sander DS, Smith VE, Schiff GM, Ward RL. Protection from rotavirus reinfection: 2-year prospective study. J Infectious Dis 1991; 164(2):277-83. https://doi.org/10.1093/infdis/164.2.277
44. Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, *et al.* Rotavirus infection in infants as protection against subsequent infections. N Engl J Med 1996; 335(14):1022-8. https://doi.org/10.1056/NEJM199610033351404
45. Bishop R. Discovery of rotavirus: Implications for child health. J Gastroenterol Hepatol 2009; 24 Suppl 3:S81-5. https://doi.org/10.1111/j.1440-1746.2009.06076.x
46. Bishop RF. Natural history of human rotavirus infection. Arch Virol Suppl 1996; 12:119-28. https://doi.org/10.1007/978-3-7091-6553-9_14
47. Crawford SE, Ramani S, Tate JE, Parashar UD, Svensson L, Hagbom M, *et al.* Rotavirus infection. Nat Rev Dis Primers 2017; 3: 17083. https://doi.org/10.1038/nrdp.2017.83
48. Lan WT, Lee HC, Yeung CY, Jiang CB, Kao HA, Hung HY, *et al.* Concomitant rotavirus and Salmonella infections in children with acute diarrhea. Pediatr Neonatol 2009; 50(1):8-12. https://doi.org/10.1016/S1875-9572(09)60023-1
49. Bern C, Unicomb L, Gentsch JR, Banul N, Yunus M, Sack RB, *et al.* Rotavirus diarrhea in Bangladeshi children: correlation of disease severity with serotypes. J Clin Microbiol 1992; 30(12):3234-8. https://doi.org/10.1128/JCM.30.12.3234-3238.1992
50. Scheier E, Aviner S. Septicemia following rotavirus gastroenteritis. Isr Med Assoc J 2013; 15(3):166-9. https://pubmed.ncbi.nlm.nih.gov/23662380
51. Glass RI, Parashar UD, Bresee JS, Turcios R, Fischer TK, Widdowson MA, *et al.* Rotavirus vaccines: current prospects and future challenges. Lancet 2006; 368(9532):323-32. https://doi.org/10.1016/S0140-6736(06)68815-6
52. Lynch M, Lee B, Azimi P, Gentsch J, Glaser C, Gilliam S, *et al.* Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review. Clin Infect Dis 2001; 33(7):932-8. https://doi.org/10.1086/322650
53. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD, *et al.* 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. The Lancet Infectious diseases 2012; 12(2):136-41. https://doi.org/10.1016/S1473-3099(11)70253-5
54. Kawai K, O'Brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. Vaccine 2012; 30(7):1244-54. https://doi.org/10.1016/j.vaccine.2011.12.092
55. Masendycz P, Bogdanovic-Sakran N, Kirkwood C, Bishop R, Barnes G. Report of the Australian Rotavirus Surveillance Program, 2000/2001. Commun Dis Intell Q Rep 2001; 25(3):143-6.
56. Reidy N, O'Halloran F, Fanning S, Cryan B, O'Shea H. Emergence of G3 and G9 rotavirus and increased incidence of mixed infections in the southern region of Ireland 2001-2004. J Med Virol 2005; 77(4):571-8. https://doi.org/10.1002/jmv.20494
57. Banerjee I, Ramani S, Primrose B, Moses P, Iturriza-Gomara M, Gray

JJ, *et al.* Comparative study of the epidemiology of rotavirus in children from a community-based birth cohort and a hospital in South India. J Clin Microbiol 2006; 44(7):2468-74. https://doi.org/10.1128/JCM.01882-05

58. Durmaz R, Kalaycioglu AT, Acar S, Bakkaloglu Z, Karagoz A, Korukluoglu G, *et al.* Prevalence of rotavirus genotypes in children younger than 5 years of age before the introduction of a universal rotavirus vaccination program: report of rotavirus surveillance in Turkey. PloS one 2014; 9(12):e113674. https://doi.org/10.1371/journal.pone.0113674
59. Bennour H, Bouazizi A, Fodha I, Ben Hadj Fredj M, Ben Hamida-Rebai M, Jerbi A, *et al.* Unexpected predominance of rotavirus G9P[8] strain in Tunisian adult diarrheal patients. J Med Microbiol 2020; 69(2):280-9. https://doi.org/10.1099/jmm.0.001156
60. Gentsch JR, Laird AR, Bielfelt B, Griffin DD, Banyai K, Ramachandran M, *et al.* Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine programs. J Infect Dis 2005; 192 Suppl 1:S146-59. https://doi.org/10.1086/431499
61. Albert MJ, Soenarto Y, Bishop RF. Epidemiology of rotavirus diarrhea in Yogyakarta, Indonesia, as revealed by electrophoresis of genome RNA. J Clin Microbiol 1982; 16(4):731-3.
62. Esona MD, Steele D, Kerin T, Armah G, Peenze I, Geyer A, *et al.* Determination of the G and P types of previously nontypeable rotavirus strains from the African Rotavirus Network, 1996-2004: Identification of unusual G types. J Infect Dis 2010; 202 Suppl: S49-54. https://doi.org/10.1086/653552