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Indonesian Journal of
Tropical and Infectious Disease

Vol. 10 No. 1 January–April 2022

Review Article

Human Norovirus Molecular Analysis and Development of Norovirus Vaccine

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Received: 5th December 2021; Revised: 16th December 2021; Accepted: 4th January 2022

ABSTRACT

The most common organism of acute viral gastroenteritis is norovirus, which accounts for roughly 20% of all occurrences of acute gastroenteritis globally. The virus kills over 200,000 children each year and is the leading cause of childhood diarrhea in the rotavirus-vaccinated population. This study aims to review available studies regarding the information on the genogroup norovirus in humans, development of norovirus vaccines, and effectiveness of norovirus vaccines. A systematic review using Science Direct, PubMed, and Scopus databases to identify eligible case studies. The search was conducted in September-October 2021. The quality of the included literature used checklists from the Critical Appraisal Skills Program (CASP). All of the six selected studies with populations given RT-PCR intervention showed positive for norovirus infection. The most predominant genogroups in humans are GI and GII. As for the research results of the two selected studies on norovirus vaccine, namely the human phase 2 trial containing two Virus-Like Particles (VLP) genotypes, one study showed efficacy at 18-49 one study at ≥ 60 years of age. This study analysis uses Takeda bivalent vaccine. The vaccine includes norovirus antigens of the GI and GII genogroups, intending to expand its protective immune potential. GI, GII, and GIV genogroups are prevalent in humans. VLP that contains GI.I and consensus GII.4c have been created as the NoV vaccine, providing significant efficacy. Very likely because they contain GI dan GII antigens, which are the genogroups that infect humans the most. Patients given a placebo developed acute gastroenteritis due to norovirus GII.2, indicating a genotype cross-reactivity.

Keywords: *norovirus, genogroups, vaccine, human, systematic*

ABSTRAK

Norovirus adalah agen etiologi paling umum dari gastroenteritis akut yang menyebabkan sekitar 20% dari seluruh kasus gastroenteritis akut yang terjadi secara global. Virus ini menyebabkan sekitar 200.000 kematian anak setiap tahun, dan sekarang menjadi penyebab paling umum dari diare anak pada populasi yang divaksinasi rotavirus. Tujuan penelitian ini adalah untuk meninjau studi yang tersedia mengenai informasi tentang genogroup norovirus pada manusia, pengembangan vaksin norovirus, dan efektivitas vaksin norovirus. Systematic review menggunakan database Science Direct, PubmMd dan Scopus untuk mengidentifikasi studi kasus yang memenuhi kriteria. Pencarian dilakukan pada bulan September-Oktober 2021. Kualitas literatur yang disertakan dinilai menggunakan checklist dari Critical Appraisal Skills Program (CASP). Keenam studi terpilih dengan populasi yang diberikan intervensi RT-PCR menunjukkan positif terinfeksi norovirus. Genogroup yang paling dominan pada manusia adalah GI dan GII. Adapun hasil penelitian dari dua studi terpilih pada vaksin norovirus, yaitu uji coba fase 2 pada manusia yang mengandung dua genotipe Virus-Like Particles (VLP), satu studi menunjukkan efikasi pada usia 18-49 tahun dan satu studi pada usia ≥ 60 tahun. Analisis studi ini menggunakan Takeda bivalent vaccine. Vaksin ini mengandung antigen

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norovirus genogroup GI dan GII, yang bertujuan untuk memperluas potensi imun protektifnya. Genogroup GI, GII, dan GIV banyak terdapat pada manusia. VLP yang mengandung GI.I dan konsensus GII.4c telah dibuat sebagai vaksin NoV dan memberikan efikasi yang signifikan. Hal ini sangat memungkinkan karena mengandung antigen GI dan GII yang merupakan genogroup yang paling banyak menginfeksi manusia. Pasien yang diberi plasebo mengalami gastroenteritis akut akibat norovirus GII.2, yang menunjukkan adanya reaktivitas silang antar genotype.

***Kata kunci**: norovirus, genogroup, vaksin, manusia, systematic*

How to Cite: Elizafanti, A. J. S., Lusida, M. I., Miftahussurur, M., Athiyyah, A. F. Human Norovirus Molecular Analysis and Development of Norovirus Vaccine. Indonesian Journal of Tropical and Infectious Disease, 10(1), p. 8–17, Apr. 2022.

INTRODUCTION

Norovirus is a ribonucleic acid virus (RNA) discovered in 1970 with 27 nm diameter, single-strand, and no veil. They belong to the family Caliciviridae.[1] Norovirus is a virus that may cause outbreaks of severe gastroenteritis with the main symptom of diarrhea, which appeared after the Rotavirus vaccine was discovered. Norovirus was found positive in 64 (19%) samples of 340 stools of children with a mean age of 11–12 months (11.75 months). It was generally found in patients suffering from diarrhea under 24 months (95%), with 64% of sufferers male in a study in Indonesia. Infection from norovirus is most common in November, followed by May and April in 2020 because, in that month, it is a rainy season in Indonesia. Important factors that play a role in transmitting norovirus are raining. Rainwater changes the norovirus viral load, and thus, norovirus transmission is easier.[2] Clinical attributes of norovirus infection consist of asymptomatic and symptomatic infections.[3] Clinical symptoms of infection are fever (72%), bloating (59%), vomiting (66%), abdominal colic (34%), anal fistula (27%), seizures (8%), and abdominal distension (16%).[2] Natural infection increases in children during the first two years of life.[4]

Noroviruses are varied in genetic and antigenic properties.[5] One of the epidemics caused by norovirus was the outbreak in Korea in 2013.[6] Kim[6] performed a study and found that of the 230 genotyped norovirus strains, GII.4 (77.3%) was the most prevalent capsid genotypes, followed by GII.3 (6.1%) and GII.13 (3.9%). According to a meta-analysis study, the global prevalence of asymptomatic norovirus is estimated to be 7%, with Africa, Mesoamerica, and South America having a high incidence (11-15%). However, Europe and North America are still having a low prevalence.[7]

People of all ages can be infected with norovirus, with the elderly and youngsters being most vulnerable.[8] Norovirus is the second most frequent source of death by diarrhea for children under the age of five across the region of the World Health Organization.[9] Norovirus outbreaks are prevalent in nursing homes, daycare facilities, and hospitals.[10] Norovirus is highly contagious and pervasive.[11] Various factors that could affect the increase of norovirus transmission are the minimal amount of inoculum required to cause infection (100 particles of the viral agents), prolonged discharge of the viral agent, and its survivability in the environment.[12] This virus plays a significant role in the food-borne epidemic.[13] Efforts are currently underway to develop an effective norovirus vaccine using virus-like particles (VLP), which is regarded as a promising approach to administering cases of norovirus infection.[10] Identification from the study of VLP bivalent vaccine usage on animals and human suggest that multivalent vaccination may be an effective strategy for inducing a broadly neutralizing antibody protective against challenge with the latest and heterologous norovirus strain.[14]

An efficient norovirus vaccine can lower direct influence on gastroenteritis and have indirect socioeconomic costs. The relationship between protective immunity and norovirus infection must be further explored to permit more acceptability and efficacy of norovirus vaccine candidates in humans.[8] Therefore, this study was

conducted to obtain information related to the molecular analysis of norovirus in humans and the development of the norovirus vaccine.

METHODS

The method used in this study is a systematic review, which focuses on searching comprehensive and detailed data on several relevant works of literature. It aims to reduce biased information by identifying, assessing, and synthesizing all studies relevant to related topics.[15]

The following criteria are used to consider the study for this review: literature that discusses genogroup of norovirus and that of norovirus vaccine, published in 2017-2021, types of literature research articles, and Randomized Controlled Trial (RCT) with full text in English. While the exclusion criteria in this review are works of literature on norovirus genogroup other than in humans and those on norovirus vaccines tested besides humans.

Finding Strategy

Literature was carried out using the Boolean Operator in OR for literature search with alternative keywords. Thus, broader literature coverage and AND for a complete literature search keyword. The keywords used are entered together in the database using the advanced search. The literature search strategy is carried out with the following two keywords of (Norovirus OR NoV OR Norwalk like viruses) AND Gastroenteritis AND Human AND (Molecular OR RT-PCR) and (Norovirus OR NoV OR Norwalk like viruses) AND Gastroenteritis AND Vaccine AND(Efficacy OR immunogenicity).

Study Selection

Articles considered potentially eligible for inclusion criteria are selected based on the abstract with PICO criteria. It consists of norovirus patients as a population, molecular development in detection with RT-PCR and the provision of norovirus vaccines as interventions, norovirus identification with analysis (sequencing, phylogenetic analysis, RNA extraction) and placebo administration as a comparison, norovirus genogroup and vaccine effectiveness norovirus as an outcome. Then assessed for quality, literature quality was assessed using the Critical Appraisal Skills Program (CASP). The collected data is then managed by applying the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Fundamental literature research obtained will be carried out for Identification, Screening, Eligibility, and Include.

Data Extraction

This data extraction is done by transferring important information from the literature figures selected into the data collection form. The data are modified from Cochrane (The Cochrane Library). The Cochrane data collection form contains the identity, characteristics, methods, and research results to make it easier for researchers to analyze the writing reviewed for further presentation in a summary table, thereby making it easier for writers and readers to understand the results.

RESULTS AND DISCUSSION

Norovirus in Humans

The search results acquired 3,114 articles from Science Direct, 662 from PubMed, and 3,237 from Scopus. The strategy used to filter research articles is with Boolean Logic with the keyword. Furthermore, it was screened using an advanced filter, and the results of the obtained screening of 1,256 works of literature with 17 duplicated literature excluded so that 1,239 works of literature are obtained. The literature was screened by reading titles and abstracts to find 1,228 pieces of literature that do not meet the PICO and sample criteria. After screening, 11 appropriate pieces of literature were obtained to be studied in this systematic review. After further study throughout the literature, five studies were excluded because: Not only focusing on norovirus and discussing other enteric viruses (n=3), discussing other norovirus strains besides GI, GII, and GIV (n=2). So that the results of the literature screening are six pieces of literature that meet the criteria to be studied in this systematic review (Figure 1).

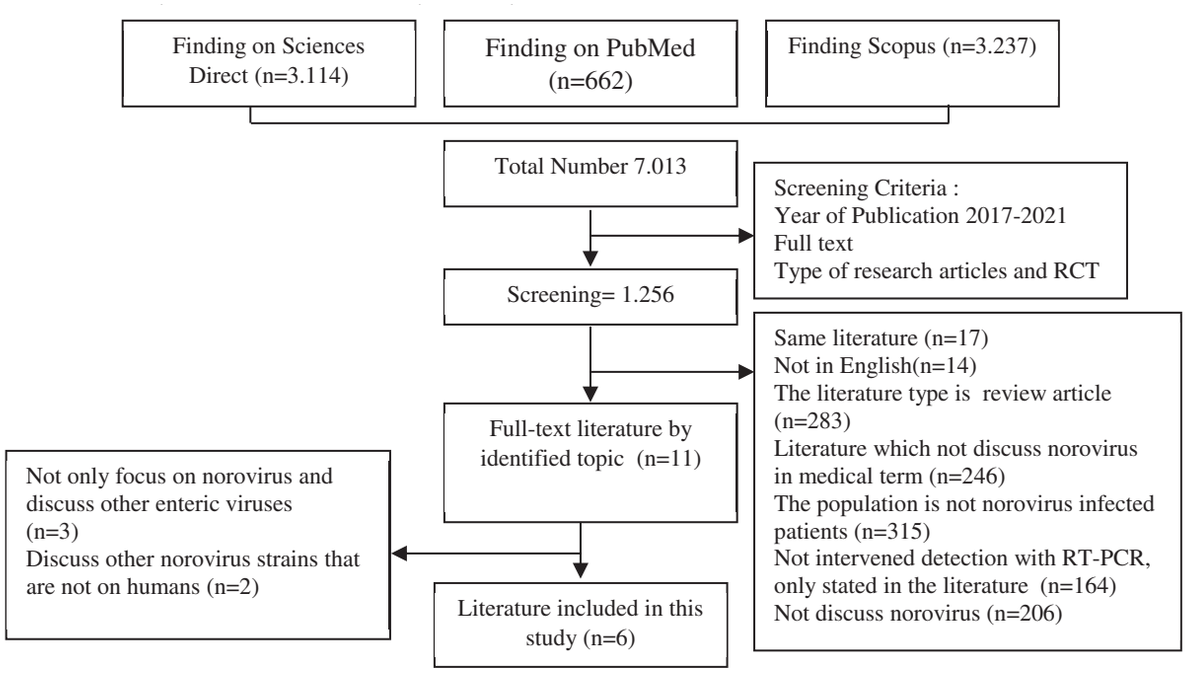

Figure 1. Diagram of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Molecular Norovirus

Table 1. Analysis of Molecular Norovirus

No.	Author	Title	Background	Methods	Time	Participants	Inclusion Criteria	Exclusion Criteria	Variables	Variables Bound	Research Findings
1	Toren et al., 2021[16]	Risk factors for norovirus infection in healthcare workers during nosocomial outbreaks: a cross-sectional study,	Gothenburg, Sweden	Norovirus detection by GII specific RT-PCR with a cross-sectional study	January-April 2012	308 participants	Health workers in the ward infected with norovirus at Sahlgrenska University Hospital	Cleaners are not employed by the hospital	Fecal samples	Strains of norovirus	A total of 26 out of 129 patients were positive for GII norovirus
2	John et al., 2021[17]	High proportion of norovirus infection and predominance of GII.3[P12] genotype among the children younger than 5 in Sabah, Malaysian Borneo	Sabah, Malaysia	RT-PCR assay with amplification of C of the capsid region	January 2018–March 2019	299 participants	Pediatric patient under 5 years old with acute gastroenteritis admitted to hospital Sabah, Malaysia	Children Aged >5 years old, not suffered diarrhea or fever	Fecal samples	Strains of norovirus	A total of 17.7% of patients were positive for norovirus infection, the majority were caused by the genotypes GII (71,7%), then GI (24,5%), and the combination of GII and GI (3,8%)
3	Cao et al., 2021[18]	Epidemiology of norovirus gastroenteritis in hospitalized children under five years old in western China, 2015-2019	Chengdu, China	RT-PCR assay with nucleic acid norovirus kit using Applied Biosystems 7500	2015-2019	1181 Participants	Pediatric patients under 5 years old with acute gastroenteritis who are hospitalized at Chengdu Hospital, China	Children Aged >5 years old, did not experience Acute gastroenteritis	Fecal samples	Strains of norovirus	20% of patients were infected with norovirus. Most of the samples came from genotypes GII, id est GII.4 Sydney 2012 and GII.3

No.	Author	Title	Background	Methods	Time	Participants	Inclusion Criteria	Exclusion Criteria	Variables	Variables Bound	Research Findings
4	Utsumi et al., 2021[20]	Molecular epidemiology and genetic diversity of norovirus infection in children hospitalized with acute gastroenteritis in East Java, Indonesia in 2015-2019	East Java, Indonesia	Conventional TaqMan RT-PCR based uses Applied Biosystems 7300	June 2015-July 2019	966 participants	Pediatric patients aged 1-191 months with acute gastroenteritis that hospitalized in the East Java hospital region, Indonesia	Children aged>191 months, No AGE	Fecal samples	Strains of norovirus	A total of 12.3% of samples were detected as positive for norovirus. The predominant genotypes in each year were GII.13 in 2015, GII.4 Sydney in 2016, GII.3 in 2017, and GII.4 Sydney in 2018
5	Shen et al., 2020[21]	Molecular epidemiology of norovirus associated with acute gastroenteritis in Taizhou, China: A retrospective study	Taizhou, China	Multiplex RT-PCR with the Applied Biosystems 7500 using AgPath-ID One step RT-PCR kit	January 2016-December 2017	1464 participants	Patient of acute gastroenteric, episodic diarrhea and vomiting is in emergency hospital that handle diarrhea	No AGE	Fecal samples	Strains of norovirus	9.49% of samples of patients with acute gastroenteritis were positive for norovirus. GII was the main genotype. A total of 12 genotypes and seven recombinant strains were found in the study.
6	Bonura et al., 2021[19]	Recombinant GII.P16 genotype challenges RT-PCR based typing in region A of norovirus genome	Palermo, Italy	QIAamp Viral RNA extraction kit and RT-PCR assay using two sets of modified GII primers (deg 1 and deg 2)	January 2016–December 2019	2194 participants	Children under 5 years old being treated for acute gastroenteritis at the children hospital in Palermo, Italy	No AGE Children aged>5 years old	RNA extracted from fecal samples	Strains of norovirus	Norovirus GII identified the most between 2016-2019 were GII.2 and GII.4 Sydney

The Study Characteristics of Molecular Norovirus

Studies used in this literature review came from five different regions, each from Sweden, Malaysia, China, Indonesia, and Italy. As shown in Table 1, the population used in the study involved health workers in hospitals in one study[16], pediatric patients aged under five years with acute gastroenteritis in three studies[17–19], children were suffering from severe gastroenteritis in private and government hospitals in Surabaya, East Java in one study[20], acute gastroenteritis patients in southeast China in one study.[21] The intervention used in six references is rectal samples detected for norovirus by specific RT-PCR[16], RT-PCR assay with amplification of region C[17], RT-PCR assay with norovirus nucleic acid kit using Applied Biosystems 7500[18], RT-PCR assay with QIAamp Viral RNA kit[19], Taqman test based on conventional RT-PCR using the Applied Biosystems 7300 system[20], Multiplex RT-PCR assay with Applied Biosystems 7500 using AgPath-ID One step kit.[21] Two studies stated that norovirus-positive patients had GII norovirus, two studies with GII and GI genotypes, and two studies with GII, GI, combination GII, and GI genotypes as shown in Table 1.

Individual contact is strongly associated with norovirus infection. Health workers in large hospitals, especially psychiatric wards, are highly susceptible to norovirus infection. The main symptom of health workers infected with norovirus is experiencing acute gastroenteritis, and the most common norovirus strain is GII.4.[16] The risk of norovirus is higher in children under five years old. It is primarily due to the

strain when the capsid and RdRp genotypes are combined. The highest prevalence of the NoV strain was GII.3[P12], followed by GII.6[P7] and GII.17[P17] in Sabah, Malaysia, from 2018 to 2019.[17] Norovirus of strains GII.17 and GII.2, is one of the most prevalent causes of viral gastroenteritis in children under five in China.[18] Children under two years of age tend to be more susceptible to norovirus infection. In Indonesia, GII norovirus is more connected with disorders that require medical care, whereas GI norovirus causes moderate symptoms and does not necessitate hospitalization. Indonesia's norovirus genotypes are genetically varied and similar to those seen in Asia and Europe.[19]

The norovirus genotypes were dominated by GII, and a small proportion is GI and the combination of GI and GII. The most common strains found in Taizhou, China, are GII.P17/GII.17, GII.Pe/GII.4, and GII.P16/GII.2. The percentage of norovirus infection was 9.49% among all acute gastroenteritis patients of all age groups in Taizhou. The incidence of norovirus infection in various age groups is connected to population immunity, public health, and the usage of over-the-counter medications.[20] Norovirus GII was the most dominant genotype infecting acute gastroenteritis patients in Taizhou. The three main norovirus strains that infect patients in the region are GII.P17/GII.17, GII.Pe/GII.4 and GII.P16/GII.2.[20] The molecular examination is quintessential because the identification of norovirus is generally made by identifying the RNA. Most norovirus outbreaks globally are caused by strains GII.4, including a new variety of GII.4 that appears every 2 to 3 years. The plasticity of the norovirus genome requires periodic renewal of the primers used for RT-PCR amplification[21] (Table 1).

Norovirus Vaccines

Based on the search results, there are 2,717 articles with potential from Science Direct, 662 from PubMed, and 3,237 from Scopus. Furthermore, it was screened using an advanced. The results from 135 works of literature were obtained. Then, the researchers excluded six duplications of them to obtain 129 works of literature. The literature was re-screened through reading the title and abstract so that two works of literature were obtained that met the criteria to be studied in this systematic review (Figure 2).

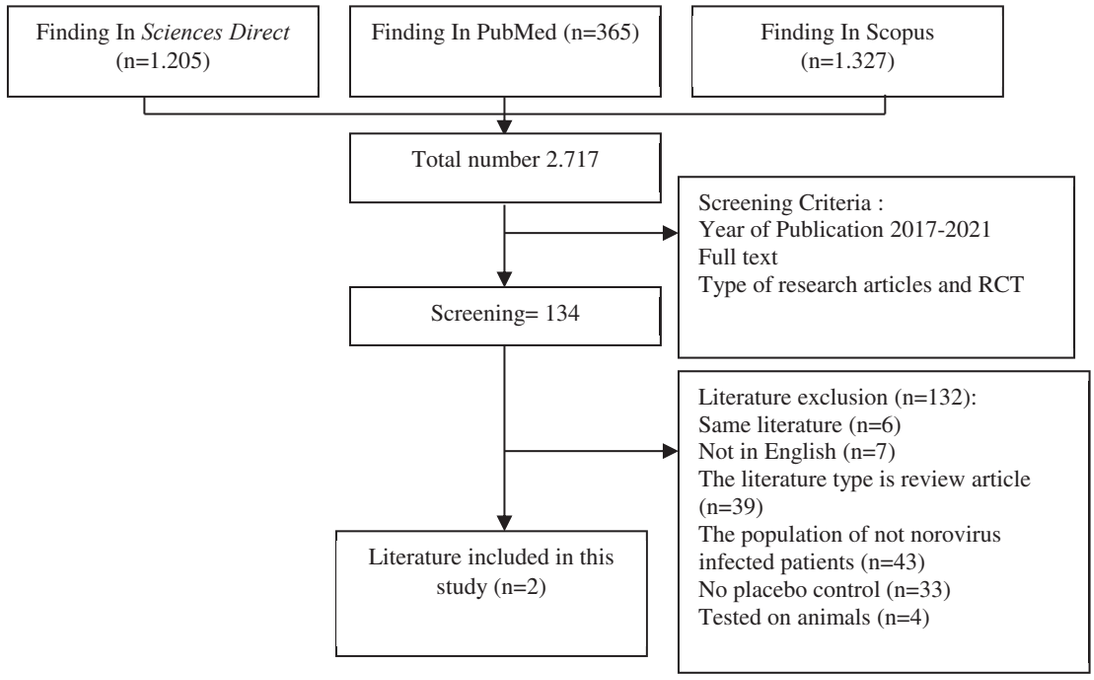

Figure 2. Diagram of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Norovirus

Study Characteristics of Norovirus Vaccines

The studies used in these two literature reviews are from the United States. The populations used in the literature review are one study using a population of naval soldiers aged 18-49 years[22], and a study using a population of adult subjects aged ≥ 60 years.[23] The two norovirus Takeda vaccine (TAK-214) studies contained 15 µg GI.1 and 50 µg GII.4c VLPs, 0.5 mg Al(OH)3].[22,23] One study showed vaccine effectiveness, indicated by antibodies that can block genotype-specific histo-blood group antigen (HBGA), 80% for GI.I/GII.4 homogenotypes, and 61.8% for any genotypes.[22] There was no safety concern and similar effectiveness of vaccinees over 60 years of age as those of 18-48 years of age[23] (Table 2).

Levels of antibodies that block GI.1 and GII.4c increased in the vaccinated population aged 18-49 years. At the same time, some given a placebo developed acute gastroenteritis due to the GII.2, which means cross-reactivity among genotypes.[22] The adult population over 60 years also showed no worrying conditions when given the vaccine, and the response was similar to the vaccine given to the younger population[23] (Table 2).

Table 2. Analysis of the Norovirus Vaccine Study

No	Author	Title	Backg round	Methods	Time	Participants	Inclusion Criteria	Exclusion Criteria	Variables	Variables Bound	Research Findings
1	Sherwo od et al., 2020[22]	Efficacy of an intramuscular bivalent norovirus GI.1/GII.4 virus-like particle vaccine candidate in the healthy US adults	Illinois, United States	Randomized controlled phase 2b trial	June 2016 – June 2018	4,712 participants: 2,355 vaccinated and 2,357 saline placebo	Soldier Navy United States in Illinois aged 18-49 years, healthy	Have comorbid disease	Causative genotypes	Effectiveness and Immunoge nicity to vaccine	Level of GI.1 and GII.4c HBGA-blocking antibodies increased on vaccines and in some placebo AGE cases infected with GII.2. It shows that there is a genotype cross-reactivity
2	Treanor et al., 2020[23]	A phase 2 study of the bivalent VLP norovirus vaccine candidate in older adults; impact of MPL adjuvant or a second dose	10 trial centers in the United States	Randomized controlled phase 2 trial	February 2016 – October 2017	294 participants	Adult subject healthy one same age as or older than 60 years with BMI <35 kg/m2	Hypersensitivity to vaccine, showing the presence of fever or infection, clinical and mental disorders in immunosup pressive condition	Age strata 60-74, 75-84, ≥ 85 years of age; second vaccination; MPL (monophos phoryl lipid A, an adjuvant)	Immunoge nicity to vaccine	Adults over 60 years old do not present worrisome conditions when vaccinated and respond similarly to that of younger vaccine, and not affected by second vaccination and MPL

Discussion

Molecular Norovirus in Humans

Norovirus is a positive-sense, single-stranded, non-enveloped RNA virus. The norovirus genomes evolve rapidly, resulting in a wide range of genotypes. Noroviruses are now divided into ten genogroups (GI-GX) based on the variations in ORF2, which encodes the VP1 protein. Human infections are caused by the genogroups GI, GII, and GIV. This genogroup was further subdivided into nine GI, 27 GII, and two GIV genotypes. Since recombination in the norovirus genome frequently occurs at the ORF1-ORF2 junction, each genotype consists of those of capsid and polymerase gene, h currently of a polymerase (RdRp) and a capsid (VP1). Based on the RdRp

gene sequence, GI and GII viruses are presently divided into 14 and 37 P-genotypes, respectively. The norovirus capsid consists of 90 capsid protein dimers, forming a shell of 90 protruding arch-like dimers.[19]

Different types of cells in the human gut are involved in norovirus infection. The human gut's predominant cell is a single layer of intestinal epithelial cells (enterocytes), including many immune cells. According to multiple studies, norovirus infects and replicates immune cells such as dendritic cells, B cells, and macrophages. The mechanism is that it enters the host through M cells, which lack microvilli and do not secrete mucous, allowing norovirus to enter the host, attack immune cells, and cause inflammation. The median duration between viral inoculation and clinical manifestations is 1-2 days, and norovirus symptoms usually clear up within 1-3 days. In some cases, symptoms may disappear, and the virus can be excreted in the stool for a prolonged period of up to 60 days.[24]

NoV, specifically genotypes GII.4, evolves quickly through the mutation and recombination events, resulting in the recurrent emergence of new antigenic variants impacted in the global outbreak of acute gastroenteritis.[16] According to Bonura et al.[19], the majority of norovirus outbreaks and sporadic cases worldwide are caused by norovirus GII.4, with new GII.4 variants appearing every 2 to 3 years. The GII.4 variant results from antigenic drift and recombination mechanisms, as evidenced by GII.4 strains epidemics in 2009 and 2012. Additional recombinant norovirus strains have emerged in recent years, particularly at the ORF1-ORF2 junction, including two different GII.4 Sydney 2012 recombination viruses, GII.4 Sydney 2012[P4 New Orleans] and GII.4 Sydney 2012[P16], as well as strains GII.2[P16], GII.3[P12], and GII.3[P16].

Phylogenetic analysis revealed that the Taizhou strains GII.P16/GII.2 shared an evolutionary pattern with the strains discovered in the United States and Japan in 2016.[20] The GII.P16/GII.2 recombination genotypes, previously reported infrequently in China, were first observed in Wuhan province in 2010. This uncommon variant of GII.P16/GII.2 caused a rapid increment in sporadic AGE patient populations in Europe and Asia during the winter of 2016–2017. It can emerge as a widespread strain that can trigger an epidemic or pandemic.

Norovirus Vaccine

The development of norovirus vaccines is a priority for both public health and economic benefits. However, there are difficulties in vaccine development due to the complex nature of norovirus, human immune response, viral culture, and limited animal models for vaccine testing. Several vaccines are presently in pre-clinical progress, one of which has finished phase II elderly clinical study. Because of viral evolution, research has focused on multivalent vaccines similar to influenza vaccines, namely Virus-Like Particles (VLP).[23] VLP NoV is a structure that resembles the original virus organization and conformation but lacks the viral genome, potentially resulting in safer and less expensive vaccine candidates.[25]

Takeda vaccine has developed a bivalent intramuscular norovirus vaccine candidate containing two VLP genotypes, GI.1 and consensus genotypes GII.4c synthesized from three variants, GII.4-2006a (Yerseke), 2006b (Den Haag), and 2002. (Houston), intended to provide broad cross-reactivity against various GII.4 strains. Clinical trials have shown that the TAK-214 candidate formulation is safe, well-tolerated, and immunogenic in healthy adults. The ideal adult TAK-214 regimen is a single intramuscular dosage based on the developmentof inhibitory antibodies against Histo-Blood Group Antigen (HBGA), which are expected to correlate with norovirus illness prevention.[22]

Effective norovirus vaccinations for all age ranges are required to lower the worldwide illness burden of the extremely contagious AGE norovirus. Sherwood et al.[22] found that of the 48 cases of moderate or severe AGE norovirus, 29 cases receiving placebo and 19 cases receiving the vaccine, the causative genotypes are GI.1 (n = 1), G1.7a (n = 1), GII.2 (n = 39) and GII.4 (n = 7). Due any to norovirus genotypes, 26 placebo and 10 vaccination groups showed 61.8%

(95.01 % CI, 20.8 to 81.6; p = 0.0097) vaccine effectiveness. While in vaccine genotypes AGE cases, the placebo (five cases) vs. vaccination (one case) group yielded a primary endpoint vaccine effectiveness of 80% (99.99 % CI, 1318.1 to 99.7; p = 0.142).[22] While Treanor et al.[23] showed that this vaccine, with or without MPL, with or without second dose, had similar immune responses. It is expected that the development of the norovirus vaccine will continue to reduce the rate of acute gastroenteritis that has spread throughout the world.

CONCLUSIONS

The conclusion drawn from the literature review is that the genogroups that infect humans are GI, GII, and GIV, of which GI and GII are the most. The bivalent vaccine being developed, TAK-214, showed significant efficacy to GI.I and GII.4c vaccine antigens and another genotype (GII.2) indicating a genotype cross-reactivity immunity.

Our systematic review is based on many studies and includes several countries worldwide, not only Indonesia. This study provided a more probable estimate of norovirus vaccines worldwide and methods of diagnosing norovirus infection. This study also provided the details of G.I and G.II strains infection in humans. The limitation of this study is the lack of articles about the norovirus vaccine in Indonesia. We could not assess several studies, and their exclusion may have biased our results.

ACKNOWLEDGEMENT

The authors would like to thank Sciencedirect Website, Pubmed Website, and Scopus Website, for the data and resource.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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