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EPIDEMIOLOGIA MOLECULAR DE GASTROENTERITE AGUDA CAUSADA POR NOROVIRUS EM CRIANÇAS MENORES DE 5 ANOS A NÍVEL MUNDIAL: REVISÃO SISTEMÁTICA E META-ANÁLISE

HIRAM MENEZES NASCIMENTO FILHO

Aracaju-SE

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Monografia apresentada ao Colegiado do Curso de Medicina da Universidade Federal de Sergipe como requisito parcial para conclusão da graduação em Medicina.

Acadêmico: Hiram Menezes Nascimento Filho

Orientador: Prof. Dr. Ricardo Queiroz Gurgel

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"A esperança tem duas filhas lindas, a indignação e a coragem: a indignação nos ensina a não aceitar as coisas como estão; a coragem a mudá-las".

(Santo Agostinho)

LISTA DE ABREVIATURAS E SIGLAS

ADN	Adenovírus
AGVI	Aliança Global para Vacinações e Imunizações
EIA	Ensaio Imunoenzimático
ELISA	Ensaio Imunoabsorvente mediado por Enzimas
GEA	Gastroenterite Aguda
IgA	Imunoglobulina A
IgG	Imunoglobulina G
MS	Ministério da Saúde
ODM	Objetivo de Desenvolvimento do Milênio
OMS	Organização Mundial da Saúde
PCR	Reação em Cadeia da Polimerase
ROV	Rotavírus
SBP	Sociedade Brasileira de Pediatria
SF 0,9%	Soro Fisiológico concentrado a 0,9%
SRO	Soro de Reidratação Oral
VLP	Partícula semelhante a Vírus

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1.1. GASTROENTERITE AGUDA

1.1.1 Impacto em Saúde

A gastroenterite aguda (GEA) revela-se importante causa de morbidade e mortalidade em crianças no mundo. Estima-se que essa patologia cause 526.000 mortes em menores de 5 anos anualmente, sendo a 4ª principal causa de mortalidade (Liu *et al.*, 2016). O combate à GEA compreende, portanto, parte fundamental do Objetivo de Desenvolvimento do Milênio (ODM) de redução da mortalidade infantil, afirmado pela Declaração do Milênio das Nações Unidas (United Nations, 2000).

Anualmente os episódios ambulatoriais de GEA respondem por aproximadamente U$325 milhões em custos médicos diretos e U$423 milhões em custos à sociedade. Observam-se, entretanto, dois cenários distintos entre os países desenvolvidos e os países em desenvolvimento. Aqueles enfrentam as consequências decorrentes de hospitalizações, dias perdidos de produtividade e afastamento dos responsáveis das atividades laborais. Enquanto isso os últimos concentram alta carga da doença, lutando contra a mortalidade provocada pela mesma (Rheingans *et al.*, 2009).

Em virtude do conhecimento de que o Rotavírus (ROV) era o principal agente etiológico responsável por morbidade e mortalidade por GEA em crianças menores de 5 anos, em 2009 a Organização Mundial de Saúde (OMS) recomendou a inclusão da vacina contra ROV nos programas nacionais de imunização dos países onde a mortalidade por GEA representava valores maiores ou iguais a 10% nessa faixa etária mesmo se a eficácia avaliada não fosse elevada (WHO, 2009).

O Brasil tornou-se pioneiro na vacinação contra ROV, introduzindo a vacina monovalente Rotarix® no seu Programa Nacional de Imunização em 2006. O país alcançou elevados índices de vacinação na população infantil (85%), e assim como Estados Unidos da América, Finlândia, Bélgica, El Salvador, México, Panamá e Nicarágua atingiu redução na incidência de GEA por RoV, bem como hospitalizações e mortalidade por gastroenterite de todas as causas (Gurgel *et al.*, 2009; Orozco *et al.*, 2009; Richardson *et al.*, 2010; Sáfadi *et al.*, 2010).

Mesmo com o incentivo proporcionado pela Aliança em Vacina (GAVI Global Alliance for Vaccines and Immunization), a vacinação contra ROV é dispendiosa para o sistema de saúde, especialmente para países de média e baixa renda. Somado a isso, sabe-se que os indicadores de redução na mortalidade infantil exigem medidas mais amplas, saneamento, tratamento de água, oferta de atenção básica à saúde (Loganathan *et al.*, 2016).

1.1.2 Definição e Etiopatogenia

Define-se GEA a diminuição da consistência das fezes (amolecidas ou líquidas) e/ou frequência maior ou igual a três vezes por dia, com ou sem vômitos, de duração inferior a 14 dias (Guarino *et al.*, 2014).

Essencialmente a GEA é estabelecida por 5 mecanismos etiopatogênicos: osmótico, secretor, invasivo, por redução da motilidade, por redução da área de superfície intestinal. A desidratação é a principal complicação da GEA, sendo a faixa etária menor de 5 anos o grupo mais vulnerável aos distúrbios hidroeletrolíticos e acidobásicos provocados pela doença (Pediatria, 2014).

Entre os casos de gastroenterite em crianças menores de 5 anos, identificam-se patógenos entéricos na maioria das amostras de fezes. Os vírus são os principais agentes implicados na etiopatogenia da doença (70%), liderados por ROV e NOV, enquanto as bactérias *Escherichia coli*, *Campylobacter jejuni*, *Yersinia* spp, *Shigella* spp, *Salmonella* spp, *Clostridium difficille*, e protozoários, *Crypstosporidium parvum*, *Giardia intestinalis*, *Entamoeba histolytica* contam com papel de significância no diagnóstico diferencial (Elliott, 2007).

O ROV, que por muitos anos foi alvo de estudos na temática da GEA, é responsável pelos quadros mais severos. Atua por mecanismos osmótico e secretor através da toxina NSP4 (Halaihel *et al.*, 2000). O NOV, também conhecido como Vírus de Norwalk, ainda não possui mecanismo bem estabelecido. Aceita-se o postulado de apoptose de enterócitos do intestino proximal, entretanto não se sabe se por efeito viral direto ou toxina (Troeger *et al.*, 2008).

Desde o licenciamento das vacinas contra ROV, o NOV emergiu como principal agente etiológico de GEA em crianças menores de 5 anos em países que atingiram altos índices de cobertura vacinal. Embora se trate de agente responsável por doença de alto impacto em saúde, provoca quadro clínico mais brando que o ROV (Bartsch *et al.*, 2016; Hemming *et al.*, 2013; Lanata *et al.*, 2013; Lopman *et al.*, 2016; Orozco *et al.*, 2009; Riera-Montes, O'Ryan e Verstraeten, 2017).

1.1.3 Fatores de Risco

Enquanto o agente etiológico tem papel significante na evolução da GEA, existem fatores de risco inerentes ao hospedeiro associados à severidade e persistência da doença: (1) Idade - Lactentes menores de 6 meses são mais suscetíveis a episódios diarreicos persistentes e severos (Strand *et al.*, 2012). (2) Alimentação - Crianças alimentadas com amamentação exclusiva durantes os primeiros seis meses de vida e que são amamentadas até os dois anos apresentam menos infecções e quadros patológicos menos graves (Victora e Barros, 2000). (3) Status imunológico - Imunodeficiência e doenças crônicas são fatores de risco para diarreia por agentes oportunistas como *Clostridium difficille* e *Cryptosporidium* (Vecchio, Lo e Zacur, 2012). (4) Condições Socioeconômicas – Baixa cobertura sanitária e acesso limitado ao sistema de saúde estão associados a maior mortalidade por GEA (Kotloff *et al.*, 2013). Figura 1.

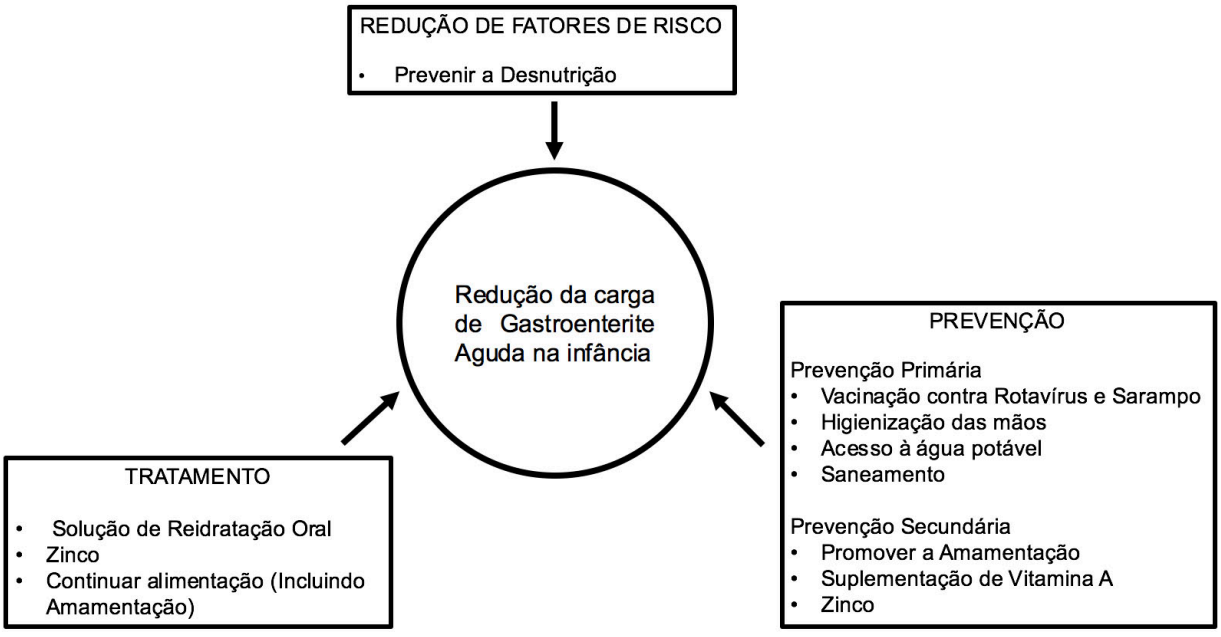

Figura 1. Adaptado de Grupo de Referência Saúde Epidemiológica da Criança, 2009
Nutrição, saúde e ambiente têm grande importância na prevenção e tratamento da Gastroenterite Aguda infantil

1.1.4 Determinação da Severidade da Doença

As estratégias de tratamento da GEA baseiam-se essencialmente na determinação do grau de desidratação da criança. Durante os ensaios clínicos das vacinas contra ROV foram desenvolvidas as escalas de Vesikari e Clark. Amplamente difundidas no meio científico, avaliam número de episódios e duração de diarreia e vômitos, bem como a temperatura do paciente. Embora forneçam subsídio para as decisões clínicas, não atestam o estado nutricional, estado de alerta, diurese e capacidade de ingerir líquidos (Fired Clark *et al.*, 1988; Ruuska e Vesikari, 1990)

O Ministério da Saúde (MS) e a Sociedade Brasileira de Pediatria (SBP) endossam a orientação da OMS na avaliação da criança com GEA. O estado de hidratação do paciente com diarreia deve ser criteriosamente avaliado por meio de exame do estado geral, dos olhos, quanto a presença de lágrimas, se o paciente tem sede, nível de consciência, sinal da prega cutânea, pulso e tempo de enchimento capilar (Ministério da Saúde, 2012; WHO, 2005; Rodrigues, 2017).

1.1.5 Conduta Terapêutica

Embora não exista evidência científica de forte impacto, recomenda-se fortemente a internação hospitalar de crianças que se apresentam com choque, desidratação severa, alteração neurológica, vômitos incoercíveis, falha na reidratação oral, suspeita de patologia cirúrgica ou quaisquer outras condições cujo manejo ambulatorial não é seguro (Guarino *et al.*, 2014).

A hidratação é o padrão-ouro para o tratamento da GEA, contando com o Soro de Reidratação Oral (SRO) como grande pilar da terapêutica (Hartling *et al.*, 2006). O MS define três planos terapêuticos que guiam a via de administração e volume de reposição volêmica de acordo com o grau de desidratação do paciente. O Plano A, aplicado em pacientes hidratados, orienta o aumento da ingesta hídrica de modo a prevenir desidratação. Mantém-se a alimentação habitual e instrui-se quanto aos sinais de alarme. O Plano B, aplicado em pacientes desidratados, consiste na administração do SRO. O paciente segue sob observação e avaliação do estado de hidratação. O Plano C, aplicado em pacientes francamente desidratados e desidratados refratários ao uso de SRO, consiste na administração de salina isotônica via parenteral em uma fase rápida e uma fase de manutenção. Uma vez capaz de ingerir líquido pela via oral, será iniciado SRO concomitante à reposição intravenosa (Ministério da Saúde, 2012).

Os pacientes submetidos ao Plano B, quando refratários à desidratação, podem se beneficiar de reposição volêmica por via nasogástrica. Sabe-se que a gastróclise está associada a mínimos

eventos adversos e permanência hospitalar mais breve que a via parenteral, entretanto não é comumente indicada pelos profissionais de saúde no manejo da GEA (Freedman *et al.*, 2011).

Uma vez iniciado o Plano C, a fase de expansão deverá ser executada com Salina Isotônica (SF 0,9%). Esta constituição diminui o risco de hiponatremia e suas graves consequências (Neville *et al.*, 2006). Reestabelecida a volemia, segue-se com a administração de solução acrescida de glicose e cloreto de potássio para a manutenção da necessidade basal do paciente.

No caso de pacientes que se apresentam com sangue nas fezes e queda do estado geral deve ser iniciada antibioticoterapia empírica com uso de Quinolona ou Betalactâmico com cobertura para bactérias Gram negativas (Ministério da Saúde, 2012).

No tocante às medidas adjuvantes no tratamento da GEA, investe-se na administração de zinco suplementar, alimentação livre de lactose e uso de probióticos.

Revisão de literatura conduzida em 2013 identificou importante efeito da suplementação com zinco na redução da duração de diarreia em crianças entre 6 meses e 5 anos. Os principais beneficiados com as medidas foram crianças residentes em países em desenvolvimento, onde ainda se registra significante deficiência do nutriente (Lazzerini e Ronfani, 2013).

Embora registre importância no manejo de uma consequência patológica, o consumo de produtos livres de lactose está associado à redução na duração da diarreia em crianças hospitalizadas. A agressão à mucosa intestinal pelos agentes causadores da doença reduz a expressão de enzimas responsáveis pela degradação do carboidrato, contribuindo com a manutenção das perdas digestivas (MacGillivray, Fahey e McGuire, 2013).

Muito se discute quanto ao uso de moduladores da microbiota intestinal no tratamento da gastroenterite aguda. Cepas de *Lactobacillus rhamnosus* e *Saccharomyces boulardii* podem ser consideradas no manejo da doença associadas ao SRO. Considerando-se a pequena força de evidência dessa medida e o alto custo inerente, recomenda-se avaliar a relação custo/benefício (Vandenplas *et al.*, 2012).

1.2. NOROVÍRUS

1.2.1. Histórico

Data de 1929, por Zahorsky, a primeira descrição de uma gastroenterite epidêmica não causada por bactérias. Foi denominada naquela oportunidade "Winter Vomiting Disease" e caracterizada por início súbito de náusea, vômitos, diarreia e febre baixa, envolvendo estudantes e indivíduos institucionalizados, com disseminação secundária para familiares. Em 1969, na cidade de Norwalk, Ohio, 50% dos estudantes e professores de uma escola de ensino fundamental desenvolveram quadro clínico semelhante ao descrito por Zahorksy em intervalo de 24 horas. Nas 48 horas seguintes identificou-se taxa de ataque secundário de 33%, e ao longo das semanas seguintes novos casos foram notificados, mantendo os potenciais padrões de transmissão pessoa-pessoa e fonte comum. No decorrer da investigação amostras de fezes de 39 indivíduos foram avaliadas para a presença de *Salmonella sp.*, *Shigella sp.*, *Escherichia coli* enteropatogênica, *Staphylococcus aureus* e vibriões não coléricos, sem sucesso. Propusera-se a hipótese de que um agente viral era responsável pela gênese da doença (Adler e Zickl, 1969).

1.2.2. Características e Evolução

O NOV é conhecido na literatura por seu formato pequeno e circular, bem como sua similaridade com o agente de Norwalk. Trata-se de um vírus de estrutura icosaédrica, cujo genoma é formado por fita única de RNA, de tamanho de 7.7kb, envolvido por um capsídeo proteico (Proteína VP1) sem envelope e com depressões características na superfície. Visualmente lembra um cálice, sendo classificado por taxonomia na família *Caliciviridae* (Glass, Parashar e Estes, 2009).

O NOV registra grande diversidade (Figura 2). Dentre os 6 genogrupos existentes, 3 (GI, GII e GIV) estão implicados nas infecções em seres humanos. As cepas virais são classificadas de acordo com o genótipo, determinado pela sequência genética codificadora da proteína VP1 (Zheng *et al.*, 2006).

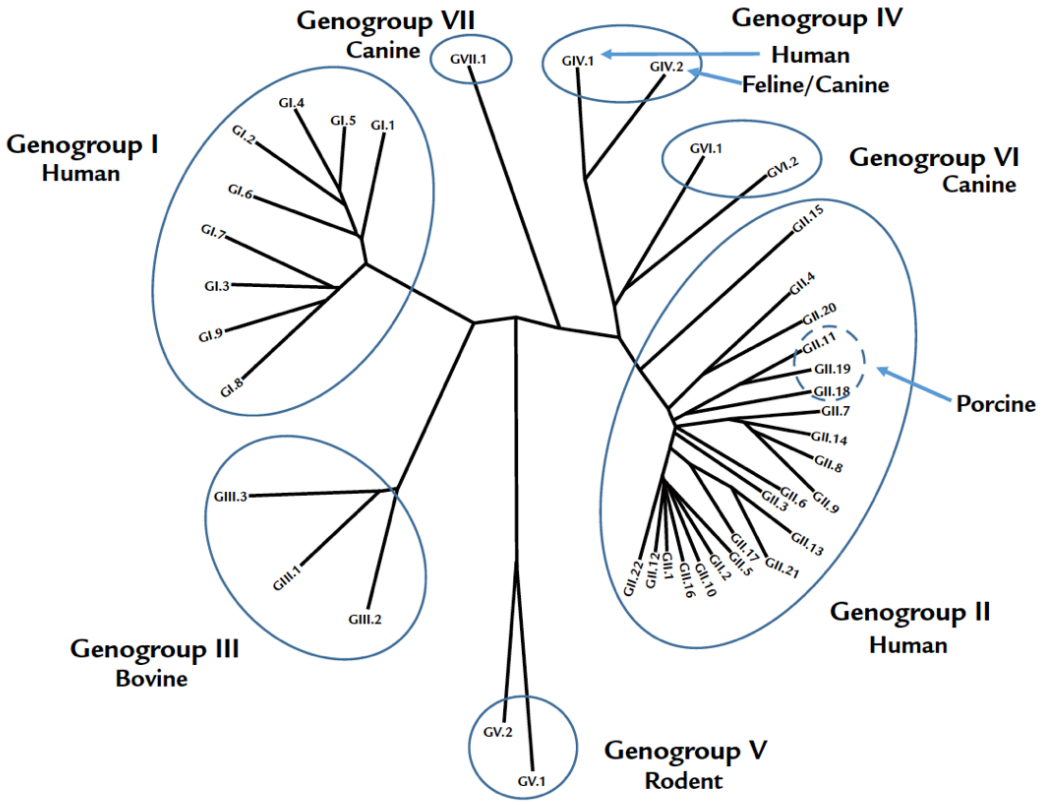

Figura 2. Adaptado de N.W. Cortes-Penfield et al.

Filogenia de Norovírus, baseado no sequenciamento dos aminoácidos da proteína VP1

Pelo menos 40 genótipos já foram isolados de amostras de fezes de indivíduos com GEA. Destaque para a cepa designada GII.4 (Genogrupo II, genótipo 4), responsável por aproximadamente 80% das infecções por NOV (Siebenga, J. Joukje *et al.*, 2009).

Desde a década de 1990 observa-se que algum genótipo predomina mundialmente nos eventos infecciosos por NOV. Estima-se que a cada 2-3 anos uma nova variante assuma o protagonismo. GII.4 US95/96 (1996), seguido de GII.4 Farmington Hills (2002), GII.4 Hunter (2004), GII.4 Den Haag (2006b), GII.4 New Orleans (2009), GII.4 Sydney (2012), foram identificadas como as variantes predominantes nos respectivos anos com quebra desse domínio pelo GII.4 em 2015 em Houzhou, China, quando foi identificado o GII.17 como grande responsável por surtos de GEA locais, depois de registro do mesmo genótipo na Austrália (Beek, van *et al.*, 2013; Bull *et al.*, 2006; Eden *et al.*, 2010; Fankhauser *et al.*, 1998; Han *et al.*, 2015; Lopman *et al.*, 2004; Yen *et al.*, 2011).

Acredita-se que o comportamento evolutivo do NOV se assemelha ao Vírus Influenza. Esse comportamento pode explicar a contínua evasão aos mecanismos de defesa dos hospedeiros (Bull e White, 2011). Análise Bayesiana usando somente dados de NOV isolados no território da China propuseram uma taxa de 4.74 a 7.68 $x10^{-3}$ substituições de nucleotídeos por território e por ano entre 1978 e 2000 (Qiao, Wang e Liu, 2016).

1.2.3. Diagnóstico Laboratorial

Em um passado recente, as técnicas de Microscopia Eletrônica direta e imune eram aplicadas em amostras de fezes para o diagnóstico de NOV. Apesar de especificidade considerável, a sensibilidade do teste era dependente da coleta de amostras por até 3 dias após o início do quadro clínico, bem como do treinamento do operador da técnica (Schmid *et al.*, 2004).

Atualmente identifica-se crescente implementação de métodos moleculares na rotina diagnóstica dos laboratórios. As técnicas de inoculação viral em culturas de tecidos, incentivadas pelo Programa Global de Erradicação de Poliovírus, vêm sendo substituídas pelo sequenciamento do gene codificador da proteína VP1(She *et al.*, 2010). Contando com elevadas taxas de sensibilidade e especificidade, os métodos diagnósticos derivados da Reação em Cadeia da Enzima Polimerase (PCR) mantêm-se como padrão-ouro para diagnóstico de GEA por NOV em amostras de fezes. Mesmo com baixa disponibilidade de carga viral nas amostras de fezes a detecção do agente costuma ser bem-sucedida (Schmid *et al.*, 2004).

Kroneman e colaboradores (2011) propuseram uma ferramenta para sequenciamento/definição de genótipo automatizada de NOV e Enterovírus pertencentes às famílias *Picornaviridae* e *Caliciviridae*. Essa ferramenta amplamente difundida pretere valores de corte para sequências de aminoácidos em prol de similaridades filogenéticas entre as cepas virais. Tal abordagem revela-se mais robusta, permitindo maior sensibilidade na identificação viral, muitas vezes dificultada pelo acúmulo de mutações ao longo do tempo (Kroneman *et al.*, 2011).

Finalmente, as técnicas de ensaio imunológico (EIA, ELISA) revelam papel limitado no diagnóstico de NOV. Embora facilmente conduzidas, apresentam limitações diagnósticas por conta da alta diversidade genética e antigênica do agente (Bruin, de *et al.*, 2006). Quando dois kits comerciais de ensaios imunoenzimáticos, IDEIA® e Ridascreen® foram testados frente ao padrão-ouro (PCR), identificou-se que a sensibilidade dos testes está intimamente relacionada ao padrão

de comportamento das infecções, surto de larga escala ou caso isolado. Taxas de sensibilidade mais elevadas eram alcançadas quando 6 ou mais amostras de um surto eram avaliadas. Recomenda-se, portanto, que os testes imunoenzimáticos podem servir para avaliação imediata, entretanto os resultados devem ser confirmados por PCR (Gray *et al.*, 2007).

1.2.4. Prevenção e Controle

Grande parte das medidas de prevenção e controle de infecção pelo NOV são direcionadas aos surtos de GEA provocados pelo agente. Embora se trate de uma doença benigna, crianças e idosos são suscetíveis a experimentar desfechos negativos, queda do estado geral, internação, terapêutica invasiva, decorrentes das complicações por GEA.

Em se tratando de ambiente hospitalar, recomenda-se o isolamento de contato por pelo menos 48h do início do quadro clínico. No caso de crianças < 2 anos, 5 dias de isolamento pode ser prudente. Além disso a higienização das mãos entre pacientes, acompanhantes e profissionais de saúde é fundamental para quebrar a cadeia de transmissão do agente. Devido à possibilidade do agente se depositar em superfícies, recomenda-se a limpeza e desinfecção de superfícies tocadas pelo potencial infectado. Certamente, a atitude mais importante é a comunicação do potencial surto aos órgãos competentes (Lee, Kuntz e Stevenson, 2013).

É reconhecido o potencial valor econômico na prevenção contra o NOV (Bartsch *et al.*, 2012). Somado à crescente prevalência do agente, surge o interesse na produção de uma vacina, campo em que 5 grupos distintos trabalham atualmente. Duas vacinas encontram-se em ensaio clínico: A primeira à base de Partículas semelhantes a Vírus (VLPs) e desenvolvida por Takeda vaccines; A segunda à base de Adenovírus recombinante expressando VP1 e desenvolvida por Vaxart (Cortes-Penfield *et al.*, 2017).

A vacina composta por VLPs utiliza componentes de NOV GI.3 e GII.4, variantes extremamente significantes do ponto de vista epidemiológico e molecular. Em estudo prévio de Fase II conduzido entre adultos saudáveis entre 18 e 49 anos, foram relatados mínimos eventos adversos sistêmicos entre os participantes com predomínio no grupo placebo quando comparado com outros dois grupos que receberam a vacina (23.5% x 15.2% x 21.4%). No tocante à resposta imunológica, ao final de 28 dias foi evidenciado aumento total de Imunoglobulinas e IgA nos dois grupos que receberam vacina, sendo a resposta contra VLPs de GII.4 mais intensa que contra VLPs

GI.3 (Atmar *et al.*, 2016). Entre 2012 e 2013 a mesma vacina foi testada em termos de eficácia por meio de ensaio clínico controlado e duplo-cego em busca de comparar os desfechos clínicos dos participantes. Dentre os 98 participantes (50 vacinados e 48 não vacinados) 57 investigados desenvolveram GEA por NOV quando inoculados com uma cepa desafio (54.0% dos vacinados x 62.5% dos não vacinados). Embora a incidência da doença tenha sido semelhante, ao comparar a história da doença entre os participantes a vacina mostrou-se protetora contra formas graves da doença (Bernstein *et al.*, 2015).

A vacina composta por cepa de Adenovírus (ADN) recombinante trabalha através da expressão de VP1 pertencente a variante GI.1 de NOV. Recentemente foram publicados os resultados obtidos na Fase I, que contou com 66 indivíduos alocados aleatoriamente em três grupos: Placebo, baixa dose de vacina, alta dose de vacina (20x23x23). A vacina mostrou perfil de boa tolerância e a maior parte dos eventos adversos relatados foram classificados como leves. Destaque para diarreia no grupo que recebeu alta dose de vacina, que apresentou diferença estatística confiável quando comparado ao grupo placebo (*P=0.0275*). Em relação à resposta imunológica, identificou-se elevação nos títulos de IgG e IgA contra VP1 de NoV nos grupos que receberam as vacinas, bem como persistência de resposta de IgA fecal após 6 meses da vacina (Kim *et al.*, 2018)

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4. ARTIGO ORIGINAL

GLOBAL CIRCULATION OF NOROVIRUS GENOTYPES IN YOUNG CHILDREN OVER TEN YEARS: SYSTEMATIC REVIEW AND META-ANALYSIS.

Hiram Menezes N. Filho[1], Carlos Henrique F. Oliveira[1], Paulo R. S. Martins-Filho[2], Victor S. Santos[3], Ricardo Q. Gurgel[1]*

[1]Department of Medicine. Federal University of Sergipe, Aracaju, Brazil.

[2]Investigative Pathology Laboratory. Federal University of Sergipe, Aracaju, Brazil.

[3]Centre for Epidemiology and Public Health. Federal University of Alagoas, Arapiraca, Brazil.

*Ricardo Q. Gurgel.

Email: ricardoqgurgel@gmail.com (RG)

Abstract

Introduction: Norovirus has emerged as the leading etiologic agent in acute gastroenteritis in young children since the introduction of vaccines against Rotavirus. Norovirus most predominant genotypes change every 2-3 years.

Methods: We describe the temporal dynamics involving Norovirus genotypes over ten years through a systematic review and meta-analysis of studies published between 2006 and 2015. 108 studies were included to evaluate the burden of Norovirus-associated acute gastroenteritis in children younger than 5 years of age. 51 studies provided information to estimate the proportion of Norovirus circulating genotypes into three periods 2006-2008, 2009-2011 and 2012-2015 using meta-analysis.

Results: Over the period of 10 years, 7,072 specimens of Norovirus have been genotyped from stool samples of children less than 5 years of age. Genogroup II responded to most of specimens over the three periods in America, Africa, Asia and Europe, ranging from 89.2% (95% CI, 81.8–93.4) in America 2006-2008 to 98.3% (95% CI, 96.1–99.3) in Asia 2009-2011. Genotype GII.4 presented as the most predominant genotype, accounting for the lowest proportion in Africa 2009-2011 41% (95% CI, 35.1-46.2) and the highest in America 2012-2015 80% (95% CI, 67.5-89.0).

Discussion: NoV GII.4 is the most common genotype involved in pathogenesis of NoV-associated acute gastroenteritis in children <5. Genotypes GII.3, GII.6 and GII.12 also respond to a great amount of NoV infections varying accord periods and continents.

Keywords: Epidemiology; Acute gastroenteritis; Norovirus; Genotypes.

Introduction

Despite substantial efforts in prevention and management of acute gastroenteritis (AGE), diarrheal disease remains as a leading cause of death in children less than 5 years old. Even though AGE is preventable and treatable, annually it accounts for 526.00 deaths in this age group [1].

Since the introduction of Rotavirus (RoV) vaccines in national immunization programs in developed and developing countries, overall children mortality and hospitalizations due to diarrhea as well as RoV-associated AGE have declined [2–5]. On the other hand, Norovirus (NoV), that used to be the second leading etiologic agent of AGE in children <5, has assumed a pivotal role in this pathology [6–11]. According to a recent global meta-analysis comprising studies published between January 2008 and March 2014, NoV responds to 18% of AGE cases [12]. NoV- associated AGE usually occurs in outbreaks during the year round, affecting all age groups, especially young children and the elderly. Due to fecal-oral mode of transmission, low infectious doses and extended shedding, NoV reinforces itself as a common cause of AGE [13]. Besides, NoV is genetically classified into 6 genogroups, composed by several genotypes, 9GI, 22 GII and 2 GIV according to capsid gene. The genotype GII.4 is responsible for the majority of NoV cases featuring some fashion that every 2-3 years a new GII.4 variant emerges and it becomes the predominant strain [14].

Although RoV infection mortality is higher, NoV also causes severe to moderate impact on morbidity, direct health costs and productivity losses. It is estimated that AGE in children < 5 costs around $39.8 billion [15–17]. Once this age group is the most vulnerable for severity, it deserves particular interest in prevention. Experimental vaccines against NoV have not shown satisfactory results [18], therefore most of the disease control strategy focus on hand hygiene, environmental cleaning, personal protective equipment and cases notification [19].

To our knowledge, there are no systematic reviews published in the literature that comprise NoV genotypes circulation in children < 5. Epidemiological characterization of NoV infections is an important aspect for decision-makers when elaborating control strategies against this pathogen (i.e. vaccine development). To understand the pattern of NoV circulation, we conducted a systematic review and meta-analysis to describe NoV circulating genotypes in this age group over ten years.

Methods

Search strategy and selection criteria

We performed a systematic review on MEDLINE (Medical Literature Analysis and Retrieval System Online), SCOPUS and LILACS (Latin American and Caribbean Health Sciences Literature) databases searching for studies published through the period of January 1st 2006 and December 31st 2016 using the following search terms: "Norovirus", "Norwalk-like virus", "Caliciviridae infections"; and related terms.

Two independent reviewers (H.N & C.O.) screened titles and abstracts for relevance and selected original articles that included children less than 5 years old with symptoms of AGE, reported data on norovirus genotypes or reported epidemiological information. A third independent reviewer (R.G) evaluated the result of this screening section, selecting the titles for full-text assessment. To ensure the capture of all relevant studies we cross-referenced all articles from the bibliography of the selected articles. After full-text assessment, we selected the articles that met the following criteria: (1) Conducted between 2006 and 2015; (2) English, Spanish or Portuguese as the publication language; (3) Conducted for at least 12 months; (4) Specified the location where the study was performed; (5) Included children less than 5 years old with signs and symptoms of AGE; (6) PCR-based technique for Norovirus infection diagnose from stool samples. We excluded

review or opinion publications without original data; studies that did not provide a denominator (i.e., the total number of patients with AGE in the study population); studies that did not allow the extraction of data for children < 5.

Data extraction and bias assessment

Relevant data was extracted from each article: First author, title, journal, year of publication, start date of samples gathering, end date of samples gathering, country, total number of children less than 5 years old, positive noroviruses cases in children less than 5 years old and noroviruses genotypes isolated from stool samples of infected children. When there was population overlap among two different publications, the one with less time of data collection was excluded.

Two spreadsheets were edited. The first held data of articles that was possible extracting Norovirus AGE incidence in children less than 5 years old. The second held data of articles that was possible extracting Norovirus genotypes isolated from stool samples of children less than 5 years old diagnosed with Norovirus AGE. Moreover, the second spreadsheet comprised all NoV capsid genotypes reported in each study (Genogroups I and II). Each spreadsheet had the studies information divided into three groups according to the period of samples collection (2006-2008, 2009-2011, 2012-2015)

Data synthesis

Proportion of NoV circulating genotypes were calculated using logit transformation. We used the 95% CIs to graphically represents NoV isolated genotypes in children aged 0-5 years according to the geographic region. Statistical heterogeneity was assessed by using the Cochran Q test [20] and

quantified by the I^2 index [21]. Analyzes were performed using R statistical programming language version 2.10.13.

Results

Database search was performed on March 17th, 2017. 6412 records were identified, 3576 from Scopus, 2784 Medline, and 52 LILACS. Afterwards 2011 duplicates were removed, and 4401 titles and abstracts were screened for relevance. 696 full-text articles have been assessed for eligibility, and ultimately 108 articles have been included in systematic review. 51 articles reported NoV genotypes in infected children <5 over the periods of 2006-2008, 2009-2011 and 2012-2015 (Figure 1 and S1 Table). The selected records comprised studies from four continents, including 5 countries in Africa, 4 in America, 16 in Asia, 9 in Europe. It was obtained information on 7,072 NoV specimens from children aged < 5 presenting AGE symptoms over 10 years. NoV most predominant genotypes varied over continents and periods. There were no eligible reports from Oceania identified during the entire period of study.

Fig 1. Flow diagram of study selection.

Table 1. Norovirus specimens by genogroups from 2006 to 2015.

Norovirus circulating genotypes

2006-2008

Twenty-eight studies [(6,22–44) provided data on NoV circulating genotypes from 2006 to 2008. Most of them were carried out in Asia (20), where 1402 specimens of NoV were genotyped. Europe

had 243 specimens of NoV genotyped, followed by America and Africa reaching 106 and 72 specimens respectively. Proportion of NoV Genogroup I specimens varied from 1.8% (95% CI, 0.5–6.8) in Europe to 10.8% (95% CI, 6.1–18.2) in America, the highest proportion found for this genogroup. Genogroup II specimens varied from 89.2% (95% CI, 81.8–93.4) in Asia to 98.2% (95% CI, 93.2–99.5) in Europe. Genotype GII.4 was the predominant one in the four continents over this period. Its circulation proportion varied from 63% (95% CI, 56.7-68.8) in Europe to 75% (95% CI, 66.5-82.7) in America. Genotype GII.3 presented significant circulation in Asia (17%; 95% CI, 15.3-19.2) and Europe (27%; 95% CI, 22.0-33.1), while accounted for 3% (95% CI, 0.1-8.0) of genotyped specimens in America. Genotype GII.6 also had a significant circulation in Africa (8%; 95% CI, 3.9-17.0) and Europe (4%; 95% CI, 2.3-7.4). Figure 2

Fig 2. Norovirus circulating genotypes from 2006 to 2008.

2009-2011

Twenty-eight studies (6–9,26,27,29,31–35,38,41,45–57) provided data on NoV circulating genotypes from 2009 to 2011. Most of the studies were carried out in Asia (18), where 2027 specimens of NoV were genotyped. America accounted for 463 specimens, while Africa and Europe accounted for 301 and 108 specimens respectively. Genogroup I specimens varied from 1.7% (95% CI, 0.7–3.9) in Asia to 5.1% (95% CI, 2.0–12.3) in Europe. On the other hand, Genogroup II reached the highest rates over the period varying from 94.9% (95% CI, 87.7–98.0) in Europe to 98.3% (95% CI, 96.1–99.3) in Asia. Genotype GII.4 remained as the predominant genotype in the four continents, though just in America it reached circulation proportion higher than 60% (63%; 95% CI, 58.6-67.3). Africa, Asia and Europe registered the widest variety of circulating genotypes over this period. Even though, most of these genotypes were not presented,

GII.3 remained with significant proportion of circulating specimens in Asia (23%; 95% CI, 21.1-24.8), while GII.6 was the third most common circulating genotype in this continent (2.8%; 95% CI, 2.1-3.6). Furthermore, GII.12 emerged as an important genotype in America (8%; 95% CI 5.9-10.8) and Europe (6%; 95% CI, 2.6-11.6).

Fig 3. Norovirus circulating genotypes from 2009 to 2011.

2012-2015

Over the period from 2012 to 2015, only data from America, Africa and Asia has beenwere available from 16 studies (6,31–33,35,38,46,52,53,58–64)]. Asia had 2122 specimens genotyped, followed by Africa (177) and America (51). Genogroup I proportion varied from 2.8% (95% CI, 1.2–6.0) in Asia to 7.3% (95% CI, 4.0–12.2) in Africa as Genogroup II varied from 92.7% (95% CI, 87.8–96.0) to 97.3% (95% CI, 94.0–98.8) in Asia. Genotype GII.4 remained as the predominant circulating genotype in the three continents. In America GII.4 accounted for 80% (95% CI, 67.5-89.0) of circulating genotypes, while it accounted for 57% (95% CI, 49.7-64.1) in Africa and 56% (95% CI, 53.5-57.8) in Asia. The Asian and African continent presented the same pattern of most common circulating genotypes. Genotype GII.3 re-emerged its importance once it presented as the second most common in Asia (33%; 95% CI, 30.4-34.3) and Africa (17%; 95% CI, 12.1-23.1). Besides, genotype GII.12 presented as the third most common genotype in Asia (5%; 95% CI, 3.8-5.6) and Africa (6%; 95% CI, 3.1-10.0).

Fig 4. Norovirus circulating genotypes from 2012 to 2015.

Discussion

Norovirus-associated acute gastroenteritis has fomented health public concernment since the decrease of Rotavirus-associated diarrhea. Once NoV has been recognized as the predominant etiologic agent of AGE in children <5, several studies have been carried out to determine clinical and epidemiological patterns resulted from this etiological change (65). To our knowledge this is the first systematic review that globally evaluates NoV genotypes circulation for the age group of children below 5 years of age. This used to be the most affected group by Rotavirus infection, and now NoV is replacing RV as the most frequent diarrhea etiologic agent in most part of the world [6–10].

It is known that NoV-associated outbreaks are influenced by the leading NoV genotype in circulation. This meta-analysis evaluated 7,072 specimens of NoV isolated from stool samples of children from 4 continents. Genogroup II Norovirus responded for the majority of specimens, reaching the lowest proportion in America 2006-2008 (89.2%) and the highest in Asia 2009-2011 (98.3%). Genotype GII.4 responded to more than 50% of circulating genotypes, excepting for 2009-2011 period in Asia, Africa and Europe. This data is consistent with previous review that suggests that hospitalizations and deaths are more likely associated with GII.4 genotype (66).

It is well observed that NoV circulating genotypes vary over time, specially through a 2-3 year period, when another genotype or a novel variant genotype emerges and displaces the dominant virus (67). This meta-analysis identified NoV GII.4 as the most common genotype involved in pathogenesis of NoV-associated AGE. During the period from 2006 to 2008, GII.4 accounted for more than 60% of NoV specimens in Asia, Africa, America and Europe, followed by GII.3, that also played a pivotal role in Asia and Europe. This predominance pattern was threatened by the increased circulation of other genotypes in the period from 2009-2011. During this period GII.4

proportion decreased, mainly in Asia and Europe, where GII.12 arose as an important genotype replacing GII.3 position in the previous period. Besides GII.13, that has been significantly recognized in Asia 2006-2008, emerged as an important genotype in America. During the last period 2012-2015, the pattern observed from 2006 to 2008 returned. GII.4 responded to the most of genotypes, followed by GII.3. Highlights for GII.12, that remained as a dominant genotype in Asia and Africa, and GII.6 that assumed an important circulation in America once it also circulated in Africa and Europe from 2006 to 2008 and Asia from 2009 to 2011.

Information provided by this systematic review.

This is a descriptive study, therefore there is no causal insight that could explain molecular epidemiological changes. Neither all continents have available data, nor all countries are comprised in the three different periods. Besides, not all studies provided NoV genotypes clustering, which limits molecular epidemiological comparison and genotypes variants evolution over the years.

Our study certainly contributes to synthesize epidemiological information regarding NoV genotypes circulation in children < 5. As described, each continent has particular features on the most identified genotypes over the periods. Excepting for GII.4, other genotypes arise or decline as pivotal etiologic specimens. These data enhance the considerations for a vaccine development once it signals that other genotypes should be targeted and that the same vaccine may not be useful for different continents. Finally, additional studies are necessary to increase the knowledge on Noroviruses epidemiological behavior.

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Supporting Information

S1 Table. Global Norovirus circulating genotypes among children <5 years old.

Supplementary Appendix. Search Strategy.

Fig 1. Flow diagram of study selection.

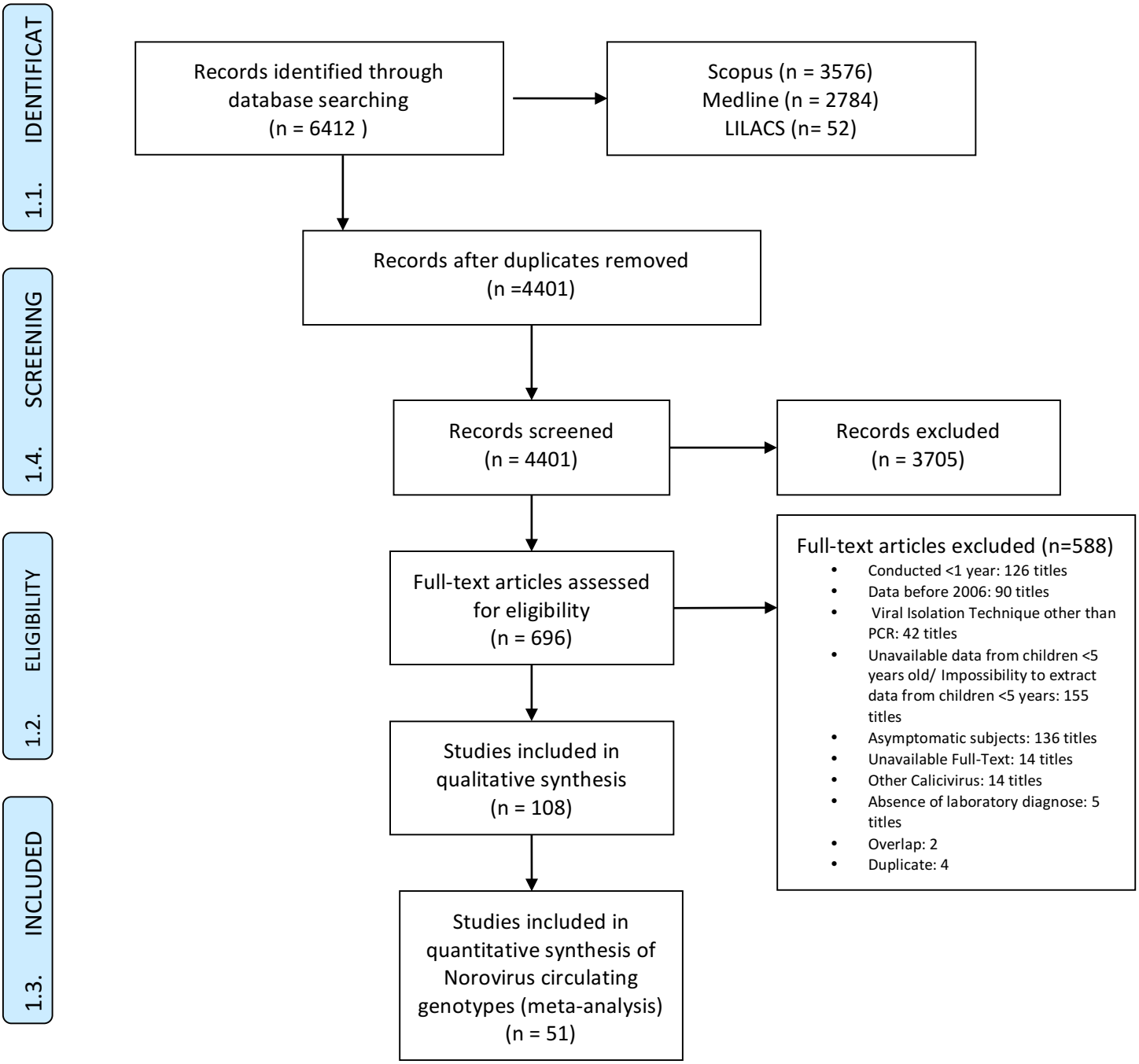

Table 1. Norovirus specimens by genogroups from 2006 to 2015.

Region	GI			GII		
	2006-2008	**2009-2011**	**2012-2015**	**2006-2008**	**2009-2011**	**2012-2015**
America	10.8% (6.1–18.2)	3.4% (0.7–14.7)	6.5% (0.4–56.6)	89.2% (81.8–93.4)	96.6% (85.3–99.3)	93.5% (43.4–99.6)
Africa	7.0% (3.7–12.9)	4.4% (2.0–9.4)	7.3% (4.0–12.2)	93.0% (87.1–96.3)	95.6% (91.2–98.0)	92.7% (87.8–96.0)
Asia	4.7% (2.7–7.9)	1.7% (0.7–3.9)	2.8% (1.2–6.0)	95.3% (92.1–97.3)	98.3% (96.1–99.3)	97.3% (94.0–98.8)
Europe	1.8% (0.5–6.8)	5.1% (2.0–12.3)	-	98.2% (93.2–99.5)	94.9% (87.7–98.0)	-

Fig 2. Norovirus circulating genotypes from 2006 to 2008.

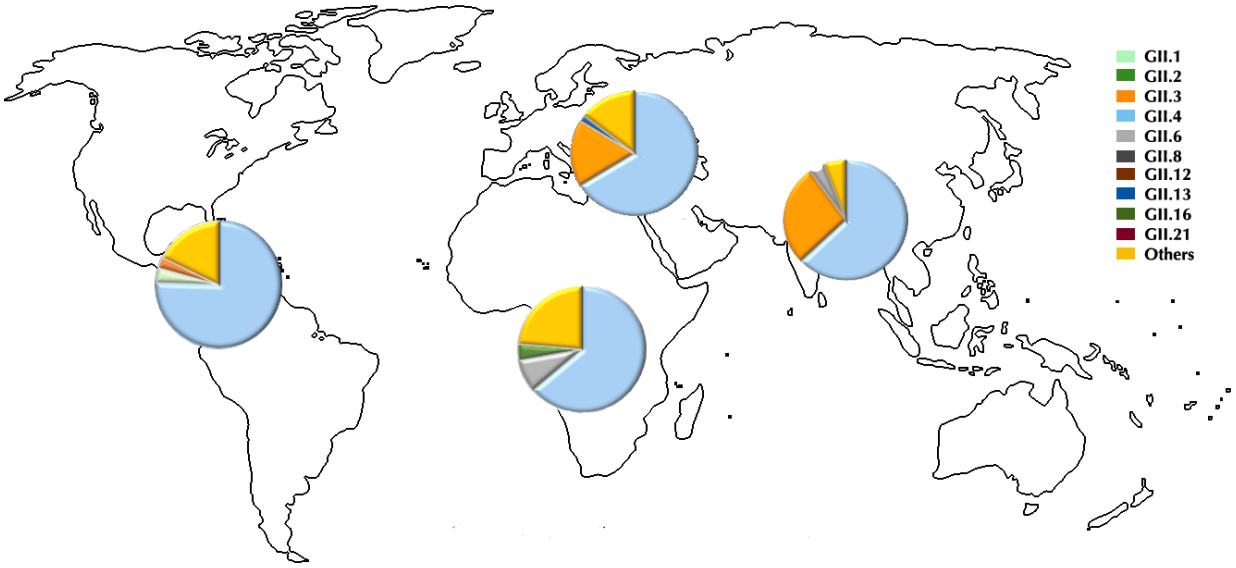

Fig 3. Norovirus circulating genotypes from 2009 to 2011.

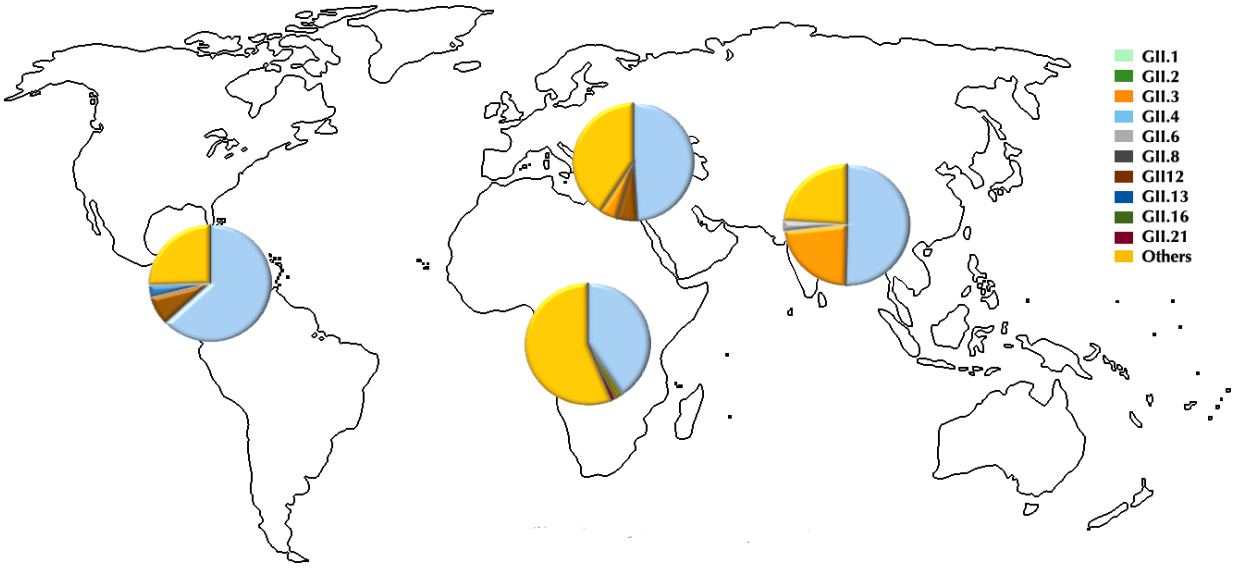

Fig 4. Norovirus circulating genotypes from 2012 to 2015.