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Complete List of Authors:	<p>Koukou, Dimitra; Aghia Sophia Children's Hospital, First Department of Pediatrics, Athens University</p> <p>Grivea, Ioanna; University Hospital of Larissa, Pediatric Department Roma, Eleftheria; Aghia Sophia Children's Hospital, First Department of Pediatrics, Athens University</p> <p>Tsioni, Heleni; University Hospital of Ioannina, Department of Pediatrics</p> <p>Trimis, Georgios; Aghia Sophia Children's Hospital, First Department of Pediatrics, Athens University</p> <p>Galanakis, Emmanuel; University Hospital of Heraklion, Department of Pediatrics</p> <p>Farmaki, Evagelia; Ippokration Hospital of Thessaloniki, First Department of Pediatrics, Aristotle University</p> <p>Iosifidis, Elias; Ippokration Hospital of Thessaloniki, Third Department of Pediatrics, Aristotle University</p> <p>Michos, A; Aghia Sophia Children's Hospital, First Department of Pediatrics, Athens University</p> <p>Siamopoulou-Mavridou, Antigoni; University Hospital of Ioannina, Department of Pediatrics</p> <p>Kalmanti, Maria; University Hospital of Heraklion, Department of Pediatrics</p> <p>Papadopoulou, Heleni; Ippokration Hospital of Thessaloniki, First Department of Pediatrics, Aristotle University</p> <p>Roilides, Emmanuel; Ippokration Hospital of Thessaloniki, Third Department of Pediatrics, Aristotle University</p> <p>Theodoridou, Maria; Aghia Sophia Children's Hospital, First Department of Pediatrics, Athens University</p> <p>Syrogianopoulos, George; University Hospital of Larissa, Pediatric Department</p> <p>Syriopoulou, Vassiliki; Aghia Sophia Children's Hospital, First Department of Pediatrics, Athens University</p>

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“Frequency, clinical characteristics and genotype distribution of rotavirus gastroenteritis in Greece (2007-2008)”

Dimitra Koukou,¹ Ioanna Grivea,² Eleftheria Roma,¹ Heleni Tsioni,³ Georgios Trimis,¹ Emmanuel Galanakis,⁴ Evagelia Farmaki,⁵ Elias Iosifidis,⁵ Athanassios Michos,¹ Antigoni Siamopoulou-Mavridou,³ Maria Kalmanti,⁴ Heleni Papadopoulou,⁵ Emmanuel Roilides,⁵ Maria Theodoridou,¹ George A Syrogiannopoulos,² Vassiliki Syriopoulou,¹ Greek Rotascore Extension Study Group

¹First Department of Pediatrics, Athens University, Aghia Sophia Children’s Hospital, ²Pediatric Department, University Hospital of Larissa, Larissa, Greece,

³Department of Pediatrics, University Hospital of Ioannina, Ioannina, Greece,

⁴Department of Pediatrics, University Hospital of Heraklion, Heraklion, Greece,

⁵First and Third Department of Pediatrics, Aristotle University, Ippokration Hospital of Thessaloniki, Thessaloniki, Greece

Pharmaceutical companies VIANEX, Athens-Greece and Sanofi Pasteur MSD, Lyon-France provided the test kits of rotavirus antigen stool detection.

Disclaimer: Georgios Trimis has to declare that he is Consultant in the pharmaceutical company VIANEX Athens-Greece, representative of Sanofi Pasteur MSD Lyon-France in Greece, which has the marketing authorization of RotaTeq (rotavirus vaccine) in Greece. All the other authors have not any financial relationship to disclosure.

Address of correspondence: Vassiliki Syriopoulou, M.D.

First Department of Pediatrics, First Department of Pediatrics, Athens University, Aghia Sophia Children’s Hospital, Thivon and Levadias Street, Athens, 11527, GREECE. Tel: +30 10 746 74 78, Fax: +30 210 746 7669 email: vsyriop@med.uoa.gr

Running head: Rotavirus gastroenteritis in Greece

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3 Rotavirus is the leading cause of acute gastroenteritis among young children
4 worldwide. A prospective multi-center study was conducted (2007-2008) in 5
6 Pediatric Hospitals to determine the prevalence, the clinical characteristics, and
7 genotype distribution of rotavirus infection in Greece. Faecal samples were examined
8 for the presence of group A rotavirus antigen by immunochromatography. Rotavirus
9 strains were subjected to G and P genotyping by reverse-transcriptase polymerase
10 chain reaction (PCR) and sequencing. A total of 393 children (216 boys) of median
11 age 23 months, participated in the study. Rotavirus was the cause of acute
12 gastroenteritis in 166 children, 42.3% (CI 95%, 37.4-47.1%) of non-hospitalized and
13 47.8% (CI 95%, 41.7-53.9%) of hospitalized patients. Rotavirus gastroenteritis
14 occurred between December and April in 78.6% of the cases. Most children with
15 RVG (77.8%) were between 3 months and 3 years old. The mean value of Clark
16 severity score was 12.9 ± 5.1 for RVG and 10.5 ± 4.9 for non-RVG ($p < 0.01$). Genotypes
17 were determined in 117 strains and their distribution was as following: G1P[8], 49%;
18 G2P[4], 31%; G4P[8], 10%; G9P[8], 9%; and G8P[14], 1%. *Conclusion.* Rotavirus is
19 a frequent cause of acute gastroenteritis in Greece. The genotypes circulating are
20 similar with those of other European countries.
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46 **KEY WORDS:** epidemiological study; acute gastroenteritis; rotavirus; genotypes
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INTRODUCTION

Rotavirus Gastroenteritis is the leading cause of acute gastroenteritis in children aged ≤ 5 years worldwide. Although the prevalence of the disease is similar in most geographic regions, the mortality is greater in developing countries due to malnutrition and poorer access to medical treatment [Butz et al., 1993; Cook et al., 1990; Giaquinto et al., 2007; Kavaliotis et al., 2007; Leung et al., 2005; Parashar et al., 2003; Raebel, Ou, 1999; Soriano-Gabarró et al., 2006; Van Damme et al., 2007a]. Rotaviruses are classified into G and P genotypes on the basis of the sequence diversities of the two outer layer proteins VP7 and VP4 respectively which are the two viral proteins that elicit neutralizing antibody responses [Parashar et al., 2003; Raebel, Ou, 1999]. Although genotypes G1P[8], G2P[4], G3[P8], G4 [P8] and G9[P8] are the predominant genotypes of the human strains circulating in most European countries, genotype variations have been observed among different geographic areas [Iturriza-Gómara et al., 2009]. The aim of the present study was to examine the epidemiology of rotavirus infection, the clinical characteristics and the genotype distribution in Greek children younger than 5 years of age.

MATERIAL AND METHODS

The present study was conducted in five Paediatric Hospitals located in different geographic areas of Greece (Athens, Thessaloniki, Larissa, Ioannina and Heraklion) between January 2007 and June 2008. These Hospitals cover nearly 65% of Greek pediatric population (Athens Hospital alone covers the 40%); however vast majority of mild to moderate and many severe cases of acute gastroenteritis are treated from primary care Pediatricians. Consecutive children aged ≤ 5 years who presented to the emergency room with symptoms of acute gastroenteritis were evaluated. Disease

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3 severity was assessed by 24-point severity scale (Clark's scale), based on a clinical
4 scoring system concerning the presence, intensity and duration of fever, vomiting,
5 diarrhea, and changes in behaviour due to dehydration [Rosenfeldt et al., 2005]. Stool
6 examination was performed in children after parents gave a written informed consent
7 to participate in the study. No parents refused. Ethics Committee provided its
8 approval prior to study initiation.
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18 A rapid stool immunochromatographic test for rotavirus antigen detection (test
19 VIKIA, BioMérieux) was used. Fecal samples tested within 24 hours and those
20 positive for Rotavirus Group A antigen were stored at 4°C. Viral RNA was extracted
21 from 10% faecal suspensions in balanced salt solution with the guanidinium
22 isothiocyanate/silica method [Boom et al., 1990]. Complementary DNA was
23 synthesized from the extracted viral RNA using reverse transcriptase enzyme in the
24 presence of random hexamers [Iturriza-Gómara et al., 1999] and was further
25 characterised by semi-nested multiplex polymerase chain reaction (PCR) using
26 specific primers for the VP7 and VP4 genes to identify the G and P types respectively
27 [Gentsch et al., 1992; Gouvea et al., 1990; Iturriza-Gómara et al., 2000a; Iturriza-
28 Gómara et al., 2004; Simmonds et al., 2008]. Amplification products were analysed
29 by electrophoresis using a 2% agarose gel stained with ethidium bromide in TBE
30 buffer. Specific segment sizes were visualised under ultraviolet light, and rotavirus
31 genotypes were determined. For the strains which were not P typable by second round
32 multiplex PCR, the first round PCR products were sequenced using the VP4 primers.
33 Sequencing was also carried out for PCR products of VP7 gene in one strain that
34 displayed the G12 type. Sequencing was performed in a collaborating laboratory
35 (Biogenomica, Athens, Greece) and the results were analyzed with the Bioedit
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3 software package and aligned with the BLAST nucleotide search
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6 [\http://blast.ncbi.nlm.nih.gov/Blast.cgi, 2010].
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10 RESULTS

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12 A total of 393 children of median age 23 months (range 2 months-5 years)
13 participated in the study; 139 from Athens, 75 from Larissa, 71 from Ioannina, 57
14 from Heraklion, and 51 from Thessaloniki. Boys outnumbered girls by a ratio of 1.2
15 (216/180). The proportion of rotavirus gastroenteritis per geographic region is
16 presented in Fig. 1. Rotavirus was the cause of acute gastroenteritis in 166 children,
17 42.3% (CI 95%, 37.4-47.1%) of non-hospitalized and 47.8% (CI 95%, 41.7-53.9%) of
18 hospitalized patients. The 78.6% of rotavirus gastroenteritis occurred in winter
19 months, between December and April. Most children with rotavirus gastroenteritis
20 (77.8%) were between 3 months and 3 years old. The median age of rotavirus
21 gastroenteritis diagnosis was 22 months (mean 20 ±12 months), while the median age
22 of non-rotavirus acute gastroenteritis was 25 months (mean 22±11 months).
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38 Behavioral changes (irritability, hypotonia), signs of dehydration, weight loss, fever
39 $\geq 38^{\circ}\text{C}$, vomiting, duration of diarrhea were more prevalent in rotavirus gastroenteritis
40 than in non rotavirus gastroenteritis ($p < 0.01$). Most children suffered from moderate
41 (91.7% for rotavirus gastroenteritis vs 92.4% for non rotavirus acute gastroenteritis)
42 or severe (7.1% for rotavirus gastroenteritis vs 6.1% for non rotavirus acute
43 gastroenteritis) gastroenteritis (9-16 points and 17-24 points respectively). The mean
44 value of severity was 12.9±5.1 for rotavirus gastroenteritis and 10.5±4.9 for non
45 rotavirus acute gastroenteritis ($p < 0.01$).
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57 Children with rotavirus gastroenteritis as compared to those with non-rotavirus
58 acute gastroenteritis were more likely to need clinical reevaluation during the course
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3 of the disease (85.5 vs 74.9%, $p<0.05$), get hospitalized (72.9% vs 60.8%, $p<0.05$),
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5 have greater hospitalization time (median 4 vs 3 days, mean 4.2 ± 2.7 vs 4 ± 2.4 days)
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8 and more parents' days of absence from work (median 4 vs 3 days, mean 4.5 ± 2.9 vs
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10 3.8 ± 2.6 days, $p<0.05$). No patient with rotavirus gastroenteritis had received any
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12 rotavirus vaccine.

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15 One hundred seventeen of the 166 rotavirus gastroenteritis positive samples (70%)
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17 were available for genotyping. The other 49 rotavirus gastroenteritis positive samples
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19 were not properly stored or the quantity was not adequate. **All of the analyzed**
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21 **strains were successfully G typed by PCR. Sequence analysis of the VP4 gene**
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23 **was carried out for 15 strains that could not be P typed by PCR. Fourteen of**
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25 **those strains were classified as P[8] and one strain as P[14]. The last strain that**
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27 **displayed the unusual G12P[14] type was further analyzed by sequencing the**
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29 **VP7 and VP6 gene and was finally identified as G8P[14] group A rotavirus**
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31 **subgroup I. Two mutations were detected at nt 1 and 8 from the primers' 3' end**
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33 **of VP4 gene (C:A and T:G, respectively). Alignment of the VP7 sequencing**
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35 **demonstrated 3 base-pair mismatches at the positions nt 1, 10 and 15 from the**
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37 **primers' 3' end, which prevented G8 specific primer binding to the G8 primer**
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39 **binding site, whereas the great homology of the G12 primer with the**
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41 **corresponding binding site of the VP7 sequence resulted to the G12 mistype.**
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49 One hundred sixteen of the 117 (99%) strains belonged to the most common
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51 genotypes that circulate in Europe during the last years [10,20], while 1 strain (1%)
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53 belonged to an uncommon genotype, G8P[14]. The distribution of the genotypes
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55 across the country (G1P[8] 49%, G2P[4] 31%, G4P[8] 10%, G9P[8] 9% and G8P[14]
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57 1%) and differences in genotype distribution by geographic region are shown in Fig. 2
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3 (A and B). No association was observed between genotypes and patients' age,
4 severity of disease, and hospitalization rate.
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9 10 **DISCUSSION**

11 The clinical burden of rotavirus gastroenteritis in Greece has a similar profile with
12 that observed in other European countries. Rotavirus is the most common cause of
13 acute gastroenteritis in children up to 5 years old in Greece (main risk period between
14 3 months and 3 years old), it has a greater clinical burden compared to non rotavirus
15 acute gastroenteritis, and it occurs more frequently in winter months [Parashar et al.,
16 2003; Soriano-Gabarró et al., 2006; Van Damme et al., 2007a]. Rotavirus
17 gastroenteritis is responsible for nearly half of the cases visiting emergency clinics or
18 requiring hospitalization due to acute gastroenteritis in Greek children up to 5 years of
19 age (42.3% and 47.8% respectively); **prevalence that is close to that reported in**
20 **other studies conducted worldwide and in a previous study held in Greece**
21 **(Kavaliotis et al., 2007; Soriano-Gabarró et al., 2006). However, Levidiotou et al,**
22 **reported a lower prevalence (21.35%) of rotavirus infection in hospitalized**
23 **children in Northwest Greece (Levidiotou et al., 2009). The different results**
24 **obtained by the latter group may reflect differences in the screened population**
25 **(different years and geographic regions) as well as in the detection method.**
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47 Factors such as hospitalizations, emergency visits, increased mean hospitalization
48 time (4.2 days), lost working days from parents (4.5 days as a mean) indicate social
49 and economic cost, except from increased burden of Health System and suffering of
50 children and their families. A limitation of the present study is that nosocomial
51 infections, where rotavirus is the leading cause of acute gastroenteritis [Parashar et al.,
52 2003], cases visiting pediatric offices in community and domiciliary episodes are not
53 included.
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3 In this report, the preliminary results **of the first multicenter Hellenic study** to
4 determine the rotavirus genotypes circulating in Greece are presented. The
5 predominant genotype was the G1P[8] which is the commonest worldwide, followed
6 by G2P[4], G4P[8], G9P[8] that represent 99% of the circulating genotypes in this
7 geographic region and are together with the G3P[8] the 5 commonest in Europe and
8 worldwide [Iturriza-Gómara et al., 2009; Van Damme et al., 2007b]. Similarly with
9 other countries [Iturriza-Gómara et al., 2009], some genotype variation was observed
10 across the country; G2P[4] was the predominant genotype in southern and northern
11 Greece (Thessaloniki, Heraklion) and G1P[8] in central Greece (Athens, Larissa).

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25 **Mismatches between the P[8] specific primer and its complementary region of**
26 **the VP4 cDNA in the P[8] isolates would explain the failure of the typing RT-**
27 **PCR of 15 strains.** Of note, one strain was identified as P[14] and was closely related
28 to human Rotavirus A P[14] strains isolated in Italy (PR/1300/04) and Hungary
29 (Hun5) (maximum identity at nucleotide level 97% and 96% respectively) [Medici et
30 al., 2008]. The VP7 gene of the same strain was identified as G8 and displayed high
31 similarity to the Egyptian human Rotavirus A strain EGY1850 (maximum identity at
32 nucleotide level 96%), while the sequence analysis of the VP6 gene identified it as
33 subgroup I and displayed high nucleotide identity (97%) to the Slovenian Human
34 Rotavirus A strain SI-R241/07 [Holmes et al., 1999]. This uncommon strain G8P[14]
35 was detected from **a non-hospitalized child living in a rural region of Larisa who**
36 **may have close contact with animals**, and is possibly the result of reassortment
37 between human and animal strains during coinfection [Holmes et al., 1999; Medici et
38 al., 2008; Santos, Hoshino, 2005]. There are few reports that associate P[14] with G
39 types in humans, because P[14] is a rotavirus type that has been detected mostly in
40 animals [Holmes et al., 1999; Matthijssens et al., 2009; Medici et al., 2008; Santos,
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3 Hoshino, 2005]. G8 is a rotavirus type that can be found in cows at relatively high
4 frequency and presents a great diversity of G-P combinations [Santos, Hoshino, 2005]
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6 In the previous decades human G8 was circulating mostly in tropical regions like
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8 Indonesia, Brazil and Africa and sporadically in some European countries like
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10 Finland, Italy and United Kingdom [Holmes et al. 1992]. Recently has reported
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12 mistyping of G8 human strains as G12 due to point mutations at the G8 specific
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14 primer binding site and the G8 and G12 primers were necessarily redesigned [Aladin
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16 et al., 2010]. Interspecies transmission events and genome reassortment are frequently
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18 reported in the evolution history of rotavirus and highlight the role of animals as a
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20 source of rotavirus infection in humans [Matthijnsens et al., 2008a]. Sequencing of
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22 its genome and adopting a new classification system are recommended to generate
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24 reliable data and elucidate the rotavirus evolutionary patterns [Matthijnsens et al.,
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26 2008b].

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29 Rotavirus strains circulating in Greece are well covered by current vaccines.
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31 However, as there is seasonal fluctuation, next years results will help to form a more
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33 representative picture for rotavirus genotypes prevalence in Greece. Surveillance
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35 studies are necessary to monitor the changes in strain distribution during the pre- and
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37 post-vaccine era and to detect the emergence of antibody escape mutants that may
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39 occur after implementation of rotavirus vaccines [Iturriza-Gómara et al., 2009;
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41 Iturriza-Gómara et al., 2000b]. Although there is a limitation from the small sample
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43 size, results confirm that there is not a constant different distribution of rotavirus
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45 genotypes in non hospitalized compared to hospitalized patients with rotavirus
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47 gastroenteritis, either a different distribution in age groups, except neonates (not any
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49 case from this group in this study) [Parashar et al., 2003].
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3 Rotavirus vaccination has diminished rotavirus activity in other countries; while,
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5 especially in USA, herd immunity has been demonstrated [CDC, 2008]. Medical
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7 societies, as ESPID and ESPGHAN, recommend introduction of routine infant
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9 rotavirus vaccination in European countries as a cost effective means of rotavirus
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11 gastroenteritis impact on society [Vesikari et al., 2008].
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15 Rotavirus gastroenteritis has a major clinical burden in children between 3 months
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17 and 3 years old, a period where rotavirus vaccines have proven their efficacy against
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19 disease related to the serotypes that seem prevalent in Greece. This study supports the
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21 need for implementation of routine rotavirus vaccination program in Greece in order
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23 to reduce rotavirus gastroenteritis clinical burden and the associated cost for health
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25 care system.
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For Peer Review

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FIG. 1. Proportion (%) of RVG per Hospital (N=393).

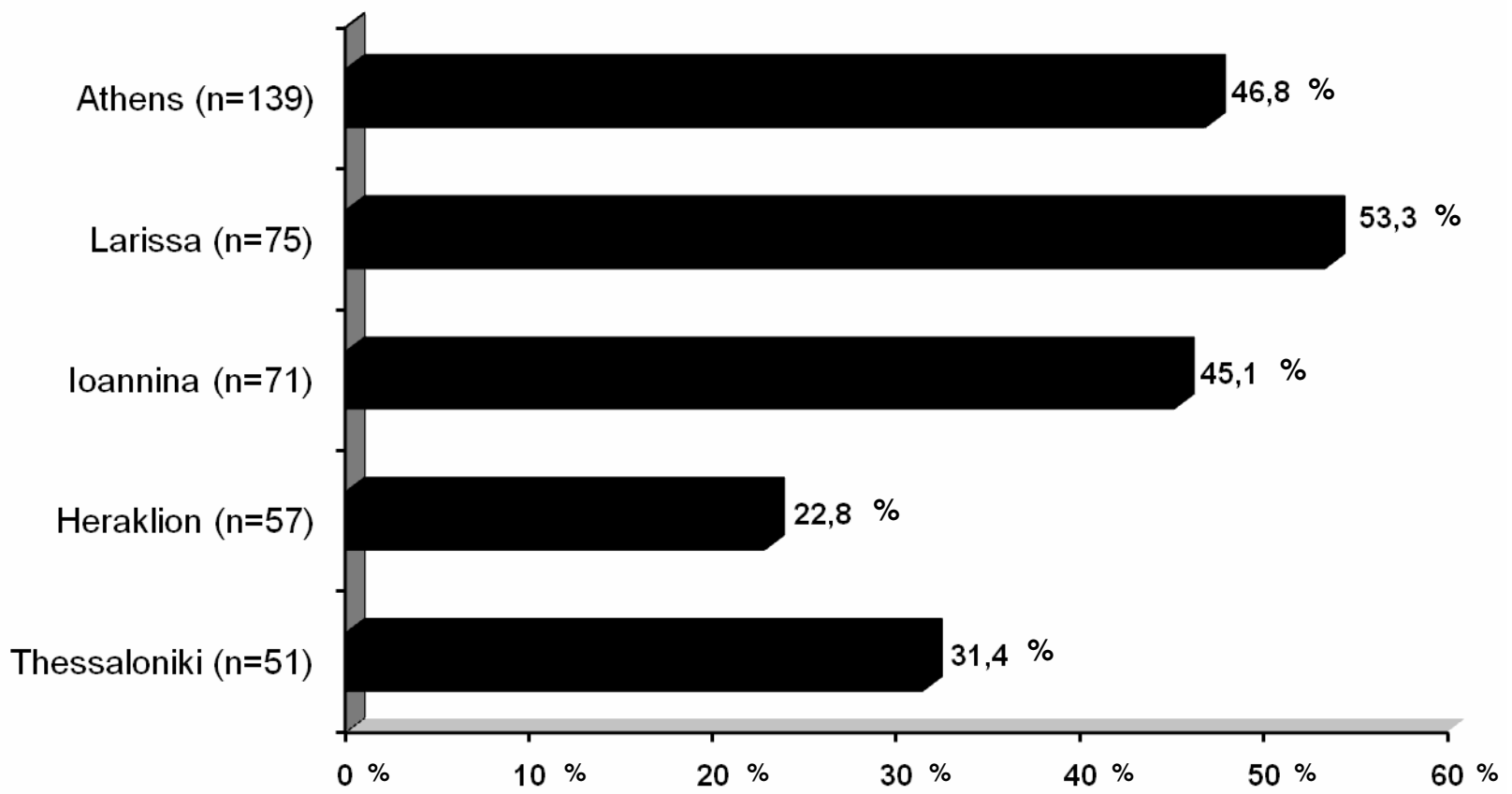


Fig. 2. Distribution of Rotavirus Group A genotypes (%) in Greece during 2007-2008 (N=117)

