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## ***Neisseria meningitidis* ST-11 clonal complex bearing capsule serogroups B, C, or W in Brazil**

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### **Dear Editor**

In 2000, there was an outbreak of sequence type (ST)-11, serogroup W meningococcal disease in Mecca, Saudi Arabia, with subsequent global spread. Since then, serogroup W meningococcal infection has become an increasing problem in many parts of the world, including Latin America. In this Journal, the presence of the Hajj 2000-associated clone, which is characterized as 2-145:P1.5,2:F1-1:ST-11 (cc11) and 16S type 31, was recently reported in Brazil,<sup>1</sup> as were other highly-related ST-11 serogroup W isolates in Brazil<sup>1,2</sup> and Argentina.<sup>3</sup>

In Rio de Janeiro State, Brazil, serogroup W meningococcal disease was uncommon until 2003, when a sudden increase of W:2a *Neisseria meningitidis* sporadic cases and outbreaks occurred.<sup>4</sup> From 1988 to 2009, 12,917 (1988–1999 = 8906 [3728 culture-proven] and 2000–2009 = 4011 [1060 culture-proven]) cases of meningococcal disease were reported to the Rio de Janeiro State Department of Health. Although serogroup B *N. meningitidis* was

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#### **Competing interests**

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recorded as the leading cause of invasive meningococcal disease before 2000, it has gradually been replaced by isolates of serogroup C, which have been responsible for over 80% of culture-confirmed cases since 2008. In this context, there were 34 culture-positive serogroup W cases, 14 from 1988 to 1999 and 20 from 2003 to 2009, representing an average of 1.2 and 2.9 cases per year, respectively. From 2003 to 2009, an additional 44 PCR-positive serogroup W cases were reported, 30 (68%) of which occurred during 2004–2005.

We analysed the genetic and antigenic diversity of serogroup W *N. meningitidis* and serotype 2a isolates of other serogroups from patients during 1988–2009 in Rio de Janeiro State with the goal of understanding the sudden increase in serogroup W disease and its role in meningococcal disease outbreaks. *N. meningitidis* serogroup was determined by slide agglutination with specific rabbit antisera (BD Difco, Maryland, USA). Serotyping was performed at the National Meningitis Reference Centre. MLST and antigen sequence typing of the genes encoding PorB, PorA, and FetA were performed on 31 serogroup W and 21 serotype 2a ( $B = 2$ ;  $C = 19$ ) invasive isolates and directly from 37 CSF samples available from which serogroup W *N. meningitidis* had been detected by a two-step PCR assay; 16S rRNA gene typing was also performed on selected isolates of the ST-11 clonal complex.<sup>1,5</sup>

Of the 78 cases (4 missing data) of serogroup W meningococcal disease, the average age was 15 years (range 24 days–63 years); 64% were <10 years. The disease affected more males (59%) than females (41%) ( $p = 0.01$ ). The proportion diagnosed with septicaemia increased from 7% in 1988–1999 to 22% in 2000–2009 ( $p = 0.1$ ). The case fatality rate also increased from 14% in the early period to 21% since 2000 ( $p = 0.4$ ).

All of 21 serotype 2a isolates and 98% of 57 W isolates from 1999 to 2009 belonged to the ST-11 clonal complex (Table 1). In contrast, 2 (18%) of the W isolates before 1999 belonged to the ST-11 clonal complex. Beginning in 1999, two predominant ST-11 or single locus variant [SLV] of ST-11 serogroup W clones emerged (2–145:P1.5,2:F1-1 [79% of 56 cases] and 2–69:P1.5,2:F1-1 [16%]). The 2–145:P1.5,2:F1-1:ST-11 (cc11) clone was first identified in 1997 and was found to exhibit multiple capsules, an indication of possible capsular switching, and to be 16S type 13 (Table 1). For example, two ST-11 clonal complex isolates from 1997 (one ST-11 and one ST-475, an SLV of ST-11) were found to bear serogroup B capsule. Subsequently, serogroup W and C variants of the clone were identified in 1999 and 2000, respectively.

During the period of 2003–2006, there were 42 serogroup W cases caused by this clone (41 ST-11 and 1 ST-7815, another SLV of ST-11). This was due in part to an outbreak caused by the 2–145:P1.5,2:F1-1:ST-11 (cc11) clone in 16 of 68 neighbourhoods in the city of Nova Iguaçu (Fig. 1), where 31 individuals (74% <6 years) were diagnosed with meningococcal disease from April through mid-June 2004; 22 (71%) patients had a haemorrhagic rash at admission and 4 (13%) patients died. The affected neighbourhoods are contiguous areas belonging to 6 districts (260,133 inhabitants), for which the overall incidence rate was 12/100,000 (range, 5.4 in Miguel Couto to 17.9/100,000 in Centro [downtown area]). Also, there were 2 additional clusters caused by this clone, one in 2004 involving 2 military recruits during a 4 day outdoor training exercise in the city of São

Gonçalo (attack rate,  $2/94 = 2.1\%$ ) and one in 2006 affecting 2 brothers (1 year and 3 years old) living in the city of Duque de Caxias, which is adjacent to Nova Iguaçu (Fig. 1).

In this study, we found ST-11 clonal complex meningococcal isolates of multiple capsular groups, namely C, with which this clonal complex is most commonly associated, as well as B and W. This finding is within the context that Brazil has recently instituted a national program of routine childhood meningococcal vaccination with serogroup C conjugate vaccine.<sup>6</sup> Capsular switching and subsequent substantial disease from serogroup C to serogroups W and B has important public health implications. Although ST-11 serogroup W disease has been reported from southern Brazil<sup>2</sup> and Argentina,<sup>3</sup> to our knowledge neither has been associated with outbreaks in region. These capsular switching events were associated with a substantial number of clinical cases in Rio de Janeiro State, outbreak and field clusters, a preponderance of disease in children, an increase in septicaemia, and a high case fatality.

Recent studies have demonstrated that serogroup W ST-11 isolates in several countries were distinguishable from the Hajj-associated clone by means of fine molecular typing.<sup>1,7,8</sup> These results suggest the expansion of local isolates and the emergence of new genetic lineages of serogroup W that differ from the Hajj-associated clone, which is believed to have arisen from serogroup C to W capsular switching. Whether these differences reflect the evolution of the Hajj clone over time or multiple serogroup C to W capsular switches is not known but might be discernible by DNA sequencing of the capsular operon of well-selected isolates. The re-emergence of *N. meningitidis* belonging to serogroup W and to the ST-11 clonal complex has been observed globally since 2010 in regions such as the African meningitis belt, France, and Chile, giving rise to new questions about the origin and expansion of these isolates.<sup>9,10</sup> Our study underscores the need to conduct molecular surveillance of meningococcal disease to monitor the impact of meningococcal immunization programs and determine whether use of multivalent meningococcal vaccines is warranted.

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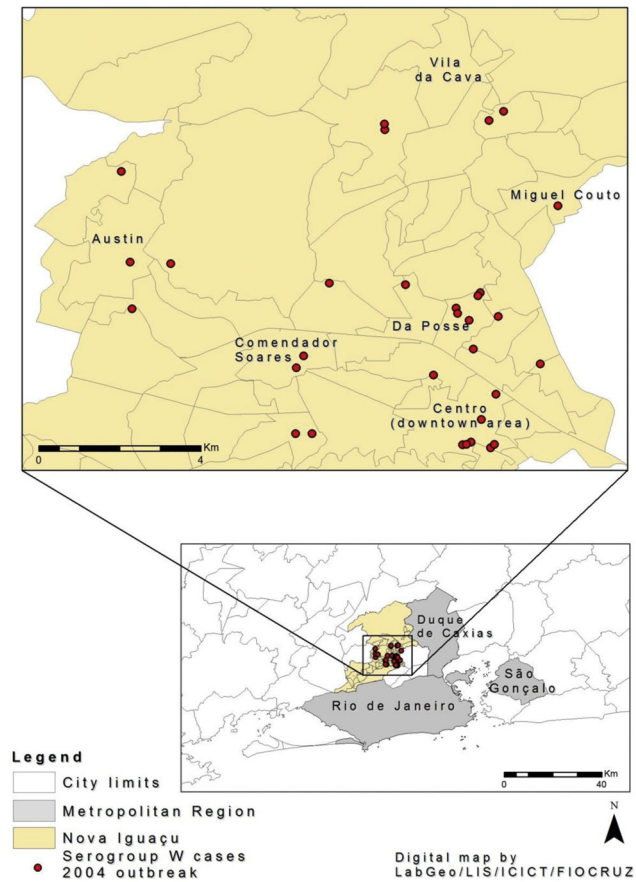
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**Figure 1.**  
Geographic location of meningococcal disease cases in the city of Nova Iguaçu during the 2004 serogroup W outbreak.

**Table 1**

Distribution of the outer membrane protein (OMP) gene sequence profiles (*porB*, *porA*, and *fetA*) and sequence types (STs) of *Neisseria meningitidis*, by serogroup (serotype) and MLST clonal complex, 1988–2009.

Year	Genotype	No. of isolates
Serogroup B (2a)	ST-11 clonal complex	
1997	2-145:P1.5,2:F1-1:ST-11 <sup>a</sup>	1 <sup>b</sup>
	2-145:P1.5-2:F1-1:ST-475 <sup>a</sup>	1
Serogroup C (2a)	ST-11 clonal complex	
1990	2-184:P1.5-1,2-2:F1-1:ST-5121	1
1995–1997	2-2:P1.5,2:F3-6:ST-11	5
1997	2-60:P1.5,2:F3-6:ST-7849	1
2000	2-145:P1.5,2:F1-1:ST-11 <sup>a</sup>	1 <sup>b</sup>
2001	2-184:P1.5-1,2-2:F1-1:ST-5121	1
2007–2009	2-2:P1.5-1,10-8:F3-6:ST-11	10
Serogroup W (2a)	ST-11 clonal complex	
1988	2-2:P1.5,2:F1-46:ST-11	1
1993	2-2:P1.5,2:F1-1:ST-11	1
1999	2-145:P1.5,2:F1-1:ST-11 <sup>a</sup>	2 <sup>b</sup>
2003–2005	2-69:P1.5,2:F1-1:ST-11	8
	2-69:P1.5,2:F1-1:ST-4091	1
2003–2006	2-145:P1.5,2:F1-1:ST-11 <sup>a</sup>	41 <sup>b</sup>
	2-145:P1.5,2:F1-1:ST-7815 <sup>a</sup>	1
2009	2-2:P1.5-1,10-8:F3-6:ST-7816	1
Serogroup W (2b, NT)	ST-11 clonal complex	
2005	2-3:P1.5,2:F1-1:ST-11	1
2009	2-148:P1.5,2:F1-1:ST-11	1
Serogroup W (19)	ST-174 clonal complex	
1988	3-35:P1.21,16:F5-13:ST-6302	1
1990	3-35:P1.21,16:F5-13:ST-2914	1
	3-35:P1.21,16:F5-13:ST-6307	1
	3-35:P1.21,16:F5-13:ST-7715	1
1991–1993	3-35:P1.21,16:F5-13:ST-174	1
	3-35:P1.21,16:F5-13:ST-6307	2
2003	3-292:P1.7-2,13:F5-13:ST-7707	1
Serogroup W (NT)	ST-22 clonal complex	
1991	2-23:P1.18-1,3:F4-1:ST-22	1
Serogroup W (7)	No clonal complex	
1990	3-296:P1.5-1,10-4:F1-7:ST-7706	1

<sup>a</sup>16S rRNA type 13.

<sup>b</sup>Successful clone exhibiting multiple capsules associated with outbreak and field clusters (see text).