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Letters to the Editor

Neisseria meningitidis Subtype Nomenclature

We believe the novel subtyping nomenclature proposed for *Neisseria meningitidis* (7) is flawed and, if adopted, will create chaos for meningococcal epidemiology with serious implications for public health monitoring and vaccine development. The meningococcal subtype is determined by amino acid sequence variation in the cell-surface-exposed loops I and IV of the porin protein PorA (5, 10). The antigenically variable loops are encoded by variable regions 1 and 2 (VR1 and VR2) of the *porA* gene, respectively. Although this variation was first recognized by the use of murine monoclonal antibodies (MAbs) (1), it is more reliably deduced from the nucleotide sequence of the *porA* gene, considering the deficiencies inherent in the serological approach: the panel of MAb subtyping reagents is not comprehensive (4, 7, 9); it is becoming increasingly obsolete, as the antigenic composition of PorA continually evolves under the immune selection imposed by the host (6); murine MAbs have limited relevance to vaccine design, when epitopes recognized in the human immune response are required (3, 9); and the early use of antibiotic therapy in meningococcal disease has increased the dependence on PCR-based diagnoses and subtyping (2).

Sacchi et al. (7) propose a nomenclature that attempts to encompass both genotypic, or DNA-based, subtyping data and phenotypic subtyping data which is based on the reactions of PorA with a panel of MAbs. The proposal is unsound for a number of important reasons: (i) it is unnecessary, and potentially confusing, to attempt to convey different types of information in a single nomenclature; (ii) the proposed nomenclature ignores the fundamental relationship between genotype and phenotype, naming genetically related antigens disparately contingent upon the availability of MAb reagents; (iii) their assignment of VRs to families on the basis of our 80% amino acid identity cutoff using a denominator that makes no allowance for genetic insertions, duplications, and deletions results in genetically related PorA proteins having unrelated names; and (iv) such radical changes to the previously published names of meningococcal PorA epitopes will create unnecessary confusion in meningococcal epidemiology. Finally, the combined use of uppercase, lowercase, and underlined letters for the nomenclature is excessively complicated and difficult to understand, even for those familiar with meningococci.

We maintain that the meningococcal subtype nomenclature should be based primarily on the amino acid sequence deduced from the nucleotide sequence of *porA* but should accommodate existing names assigned originally from serological data (8). This scheme has several advantages: closely related VR sequences have similar names regardless of their reactivity with a specific MAb; the potential for a nontypeable result is eliminated; it can be readily expanded to include novel sequences; and, since *porA* is under immune selection in humans, it provides more reliable information for the design of candidate vaccines based on PorA than analyses based on murine MAbs. The genetic relationships between the *porA* genes of the meningococcus are best conveyed by using the conventional genetic designation *porA* followed by a number representing each unique allele. We have made a comprehensive collection of these data available on a website, http://mlst.zoo.ox.ac.uk/Meningococcus, that is regularly updated to accommodate novel sequences. New VR and allele numbers can be obtained on request.

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Author's Reply

We view the letter to the editor concerning our article as a healthy sign of a continuation of a long-standing tradition in the scientific community for open discussions and disagreement on the *Neisseria* nomenclature (1, 2, 4).

Several points raised in the letter highlight the problematic nature of *Neisseria meningitidis* nomenclature, which we believe are well-addressed in our approach. Most importantly, we

must disagree with the statement that it is "unnecessary, and potentially confusing, to attempt to convey different types of information in a single nomenclature . . ." From the public health point of view, it is quite necessary to relate serosubtyping and VR typing by using the same nomenclature. Indeed, sequence-based approaches, such as VR typing will most likely be a method of choice in the future. However, in light of our extensive hands-on experience with the laboratory activities of developing countries, we believe that, for economic and other reasons, serotyping will continue to be their main method of subtyping *N. meningitidis* for many years to come. After all, the great majority of the meningococcal disease cases are occurring in the developing world, and the scientific community would be at a loss without the ability to correlate these two systems. With that in mind, our nomenclature was designed to allow one to instantly correlate serosubtyping and VR typing. Since our approach does not mandate the use of monoclonal antibodies (MAbs), our proposed nomenclature will not need to be changed when serotyping is no longer used.

The comment on the use of 80% amino acid identity is somewhat unexpected, as this cutoff was used directly from the article by Suker et al. (3), who reported that "the 80% cutoff distinguished the two most closely related VR sequences that contained epitopes identified by different MAbs." The authors of the letter are correct in saying that our system ". . . makes no allowance for genetic insertions, duplications, and deletions. . ." Perhaps the rule about 80% amino acid identity for the PorA VR family will have to be modified to include variants which may have been created by one or a limited number of genetic events. We agree that, as with all other rules, exceptions may well be found.

The public availability of the data is crucially important for global communications and exchange of data. The web site mentioned in the letter remains a significant and important resource; however, more than half of the sequences found there are not available at GenBank. Furthermore, naming of novel variants is under their discretion, and no precise description of the criteria or guidelines used is provided. Our use of GenBank allows everyone the benefit of cross-checking their sequences with those already released. Therefore, researchers are allowed to name their novel variants at the time of submission.

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