the authors of this study postulated that the mutants that failed to establish systemic meningococcal infection may have a role in the pathogenesis of *N. meningitidis* septicaemia. Phenotypic analysis of these genes may reveal that their products encode conserved vaccine candidate proteins, or potentially the attenuated mutants themselves could be considered as vaccine candidates (see later).

DNA microarrays spanning the genome of the MC58 meningococcal strain have been used to analyze changes in gene expression during interaction with human epithelial cells (88). Host-cell contact was found to induce 347 gene alterations. One hundred and eighty-nine genes were upregulated; more than 40% of these encoded peripherally located proteins, suggesting that when in host contact, *N. meningitidis* undergoes substantial cell membrane remodeling. Twelve new adhesion-induced surface antigens were discovered; five were capable of inducing bactericidal activity against the homologous strain in mice. These bactericidal antigens were highly conserved across 11 isolates, including the main hyperinvasive lineages, and were able to induce some cross-protective immunity.

Expression library immunization (ELI) has been used to make an expression library of the meningococcal genome for immunization of mice (89). The library was divided into 10 sublibraries (L1–L10) and used to immunize 10 groups of mice with plasmid DNA. Bactericidal antibody was induced in three groups of mice against the homologous strain, and pooled sera from one group (L8) elicited some protection from *N. meningitidis* challenge. After a whole-cell (live *N. meningitidis)* antigenic challenge, bactericidal antibodies were elicited in 9 out of 10 sublibraries (89).

COMMENSAL NEISSERIAE AND ATTENUATED BACTERIA

Neisseria lactamica is a commensal species found in the human nasopharynx, predominantly in early childhood, that is thought to generate immunity that is cross-protective against meningococci. Live *N. lactamica*, killed whole cells, OMVs, or OMP pools when used as immunogen-protected mice against lethal challenge by a number of meningococcal serogroup B and C isolates (90,91). *N. lactamica* OMVs induced antibody responses that passively protected animals and are being evaluated in a phase I safety and immunogenicity study in adult volunteers (92). The protective responses appear to arise through opsonophagocytic antibody.

Plasmid transformation has been used to express high levels of heterologous proteins in *Neisseria flavescens* (93). NspA was expressed in its native form and OMVs prepared from the modified organism induced protection in mice against a lethal challenge with *N. meningitidis* without bactericidal activity being present.

The two-component regulatory system PhoP-PhoQ controls virulence genes of *N. meningitidis*. Mice infected with a live serogroup C *phoP* mutant of the meningococcus developed bactericidal and opsonophagocytic activity against a range of meningococci from serogroups B, Y, and W135 with different serotypes and serosubtypes (94). Further development is awaited.

Two attenuated serogroup B *N. meningitidis* strains, YH102 and YH103, were identified by STM (see the preceding text) (95). Two mutations were inserted into each attenuated strain to reduce the possibility of reversion to wild-type B and the attenuated strains used to immunize mice. Bactericidal antibodies developed after immunization, providing protection against homologous strains and partial protection against heterologous strains. Although the use of live attenuated bacteria provides the possibility of a more natural development of immunity if administered at mucosal surfaces, concerns about the possibility of wild-type reversion is likely to hamper development of this approach.

CONCLUSIONS

PS vaccines against serogroups A, C, Y, and W135 of meningococcus have been available for decades and have been useful for immunization of at-risk groups and to control outbreaks. They have never been used for general immunization because they provide short-term immunity with no immunologic memory, and in most of the cases (with the exception of serogroup A) they do not work in infants and children. A CV against meningococcus C, licensed in the United Kingdom in 1999 has been extremely effective in controlling the disease in all ages, showing that CVs are an excellent solution for the prevention of meningococcal disease. In fact, they induce immunological memory and are efficacious at all ages. Conjugates against serogroups A, Y, W135 are now available, providing the possibility of further disease reduction in all regions with a problem from these serogroups.

A CV using serogroup B meningococcal capsular PS is unlikely to be successful because of the chemical identity with human antigens, poor immunogenicity in clinical studies, even after clinical modification, and the expectations of regulatory concern over the potential for generation of autoimmunity. The use of OMVs, the use of the core structure of the LPS, or surface proteins either alone or in combination could be successful if able to induce a broadly protective bactericidal response. Several different vaccines are currently in clinical trials, providing some hope that there may be improvements in the control of meningococcal disease just around the corner.

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