

Correlates of protection against *Neisseria meningitidis*

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Over the last 2 decades, the leading cause of meningitis in childhood and the leading infectious cause of death in the UK was *N. meningitidis*. Following on from programmes since 1999 to control disease caused by capsular group C, and then more recently A,C,Y and W *N. meningitidis*, in 2015, a multi-component capsular group B meningococcal (MenB) vaccine was introduced in the United Kingdom for all infants, and the first results suggest high vaccine effectiveness (83% against all MenB strains after two doses; 95% CI 24.1–95.2) [Ref Lancet 2016]. There is now the potential for broad control of this serious disease. Because the disease is rare, these vaccines were all licensed without efficacy trials because data accumulated over the last century have shown that bactericidal antibody is the correlate of protection against this organism. In 1921 Heist and colleagues showed that meningococci isolated from cases were more resistant to killing in whole blood than bacteria taken from the throats of healthy carriers, and also observed considerable variation between individuals in the ability of their blood to control the growth of these bacteria [Ref Heist 1921]. The blood of carriers was found to be better at killing meningococci than non-carriers, suggesting immunity induced by pharyngeal exposure. In all they made observations involving 172 individuals. They also showed that defibrinated blood supported the growth of all strains and was used as a positive control in the experiments, as was the blood of “Man H” which seemed also to be an excellent growth medium. We now know that the meningococci were killed in these laboratory experiments by complement-mediate lysis directed to the bacterial surface by specific antibody among immune individuals and that susceptibility correlates with lack of specific antibody and associated strongly complement deficiency. Defibrinated blood lacks complement and supports growth of the bacteria despite presence of antibody. Man H, was the lead author of the paper, George Heist, and he died, aged 36 years, of meningococcal meningitis in the year before the paper was published despite valiant efforts to treat him with intra-spinal infusions of immune serum. Since 5 male members of his family are said to have died in a similar way, including his father at the age of 24 years, It seems quite possible that he had an X-linked complement deficiency. These carefully observed studies are a stark reminder that simple experiments in the laboratory and tragic experiments of nature provide the key information to underpin vaccine development and point to correlates of protection.