Lack of coverage or vaccine failure? A difficult question for monitoring of Bexsero®, the new meningococcal vaccine

A significant reduction in serogroup B (MenB) meningococcal disease cases in UK infants is anticipated following introduction of Bexsero® into the infant immunisation schedule. This vaccine is not, however, a panacea. Strain coverage is estimated at 88% for UK MenB strains,[1] allowing for the possibility of MenB disease in Bexsero® immunised individuals due to strains not covered by the vaccine (Figure 1). But how easy is it to distinguish if disease case is caused by a covered or non-covered strain? Bexsero® comprises three recombinant proteins (fHbp, NHBA and NadA) and detergent-extracted outer membrane vesicles containing native PorA protein and several minor proteins.[2] The recombinant proteins exhibit significant diversity in both sequence and levels of expression between meningococcal strains, so that protection only occurs if a strain has medium-to-high expression of one or more homologous antigens. Monitoring requires detection of whether antigens have the requisite homology and expression to render an infective strain sensitive to protection by Bexsero®. Homology can be determined by sequencing vaccine antigens in DNA extracted from either the 'live' strain or directly from the clinical sample. Currently, however, expression levels can only be assessed with assays requiring a 'live' bacterial isolate and are unusable in cases wherein confirmation is solely based on PCR direct from clinical samples.[3] Since 1998/99, 47% of the 18,141 confirmed cases of MenB disease were by PCR only without isolation of the 'live' infective strain. Why is precise monitoring required? All cases of meningococcal disease in Bexsero® immunised individuals could be classified as vaccine failures but this approach would underestimate the vaccine's effectiveness.

So how will coverage be assessed in the Bexsero® era? Firstly, for every suspected case of meningococcal disease in immunised individuals, extensive efforts will be necessary to isolate the causative meningococcal strain and run a full battery of tests for monitoring whether strains were covered or not covered (Figure 1A). This will have to include sampling of contacts prior to prophylaxis as potential sources of a 'live' isolate of the infecting strain. If confirmation is solely by PCR, running of gene-specific PCRs/DNA sequencing reactions can determine if the disease-causing strain has antigens homologous to the vaccine antigens and hence is covered (Figure 1B). If there are no matches, a case can be marked as due to a non-covered strain. Conversely, a good match will indicate a 'true' vaccine failure by a covered strain, except that strains with low expression of a homologous fHbp allele should be marked as non-covered strains.

Can monitoring be improved? There is potential for estimating target antigen expression in clinical samples by the indirect approach of analysing promoter sequences in extracted DNA or the direct approach of measuring RNA/peptide levels for target antigens. But for now, separating lack of coverage from vaccine failure for Bexsero® immunized individuals may have to rely on improving isolation of the 'live' infective strain.

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Figure 1. Depiction of pathways for determining the basis of a vaccine failure with Bexsero®. A case of meningococcal disease in an infant immunised with Bexsero® could be due to a *Neisseria meningitidis* strain that is either covered or not covered by the vaccine. Panel A shows the pathways available if an infective strain has been isolated whereas Panel B is for cases where no strain was isolated. DNA sequences can be generated from the infective isolate (Panel A) or residual bacterial DNA in clinical samples (Panel B). A 'match' occurs when the sequence of the bacterial strain is very similar to that of the vaccine antigen. For fHbp, levels of expression can vary so that a strain with low expression of a 'matched' fHbp antigen would be classified as a non-covered strain. Dashed lines indicate methods that have not been tested or developed. MATS, Meningococcal Antigen Typing System.[3]