REVIEW

Meningococcal A, C, Y and W-135 polysaccharide-protein conjugate vaccines

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Serogroup C meningococcal conjugate vaccines, first launched in the UK in 1999, have been used successfully in Australia, Canada and several other European countries. Combination conjugate vaccines, containing more than one meningococcal polysaccharide, have been developed to broaden protection against the disease. A tetravalent meningococcal A, C, Y and W-135 conjugate vaccine was licensed for use in 11–55 year old adolescents and adults in the US in January 2005, and subsequently also in 2–11 year old children in Canada in May 2006. This article discusses the different glycoconjugate meningococcal vaccines which have been developed and the potential for their use to control disease caused by serogroups A, C, Y and W-135 of *Neisseria meningitidis*.

This review discusses the different glycoconjugate meningococcal vaccines which have been developed and the potential for their use to control disease caused by *N meningitidis* bearing the A, C, Y and W-135 polysaccharide capsules.

EPIDEMIOLOGY OF *N MENINGITIDIS*

The incidence of meningococcal disease varies over time and geographical region due to the epidemic nature of the disease.⁷ The yearly overall endemic incidence rate per 100 000 population is 0.5–1.1 in the US⁸ and 0.39–7.41 in Europe⁹ with the highest age specific incidence rates seen in infants, 1–4 year old children and adolescents.^{8–9} Although serogroups B and C cause most meningococcal disease in developed countries, serogroup Y is now also a major cause of meningococcal disease in the US with an increase in the proportion of meningococcal cases from 2% in 1989–1991 to 19–28% in 2000–2005.^{8–10}

Serogroups W-135 and A constitute a minor proportion of the meningococcal disease burden in most industrialised countries today. However, after the first and second world wars, most cases in Europe and North America were caused by serogroup A with another peak observed in the 1970s in several countries. Recent outbreaks of serogroup A meningococcal disease in Russia¹¹ and Poland¹² highlight the proximity to Western Europe of areas with a high disease prevalence.

By contrast, the incidence of endemic meningococcal disease in developing countries is much higher, with rates of 10–25 cases per 100 000 population per year being reported.¹³ The highest rates are found in countries in the “meningitis belt” of sub-Saharan Africa where meningococcal disease occurs in seasonal annual cycles and also periodically in epidemics, rising rapidly in the dry season and usually stopping with the onset of rainfall.⁷ During these epidemics, which are mainly caused by serogroup A and more recently by serogroup W-135,^{7–14} the magnitude of the meningococcal disease burden is devastating with attack rates at times reaching up to 1000 cases per 100 000 population.⁷ This is in contrast to the epidemics which occurred in Finland and Norway in the 1970s where the annual incidence was only 15–25 per 100 000 population.⁷ International

In children, *Neisseria meningitidis* is one of the leading causes of meningitis and septicaemia. Despite appropriate treatment, the overall case fatality rate remains at 3–10%^{1–2} and survivors often sustain permanent disability.³ Vaccination against the most prevalent serogroups is the only rational strategy for prevention of meningococcal disease.

In contrast to polysaccharide vaccines, meningococcal glycoconjugate vaccines stimulate a T cell dependent immune response and immunological memory from infancy. The dramatic decline in the incidence of meningococcal C disease seen in the UK after the introduction of a serogroup C meningococcal vaccine programme, indicates that glycoconjugate meningococcal vaccines can control disease at a population level.⁴ The recent licensure of a tetravalent meningococcal A, C, Y and W-135 (MenACYW-D) conjugate vaccine (Menactra, Sanofi Pasteur, Swiftwater, PA, USA) in 2–55 year olds in Canada and children over 11 years of age in the United States is expected to provide broader protection against invasive meningococcal disease. Another tetravalent meningococcal conjugate vaccine (MenACYW-CRM₁₉₇, Novartis Vaccines, Siena, Italy), currently under development, is immunogenic from infancy,⁵ providing the potential for the use of these vaccines in the future from early infancy to adulthood. In comparison, glycoconjugate meningococcal B vaccines are poorly immunogenic because of molecular mimicry between the serogroup B capsule and neural cell adhesion molecules.⁶ Progress in the development of MenB vaccines is awaited to provide comprehensive prevention of this disease.

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Abbreviations: GBS, Guillain-Barré syndrome; GMT, geometric mean antibody titre; Hib, *Haemophilus influenzae* type b; hSBA, serum bactericidal antibody assay using human complement; MenA/B/C/Y/W-135, *Neisseria meningitidis* serogroup A/B/C/Y/W-135; rSBA, serum bactericidal antibody assay using rabbit complement; SBA, serum bactericidal assay

outbreaks, with serogroup A in 1987¹⁵ and with serogroup W-135 in 2000,¹⁶ have been associated with pilgrims attending the annual Hajj pilgrimage.

Carriage

Approximately 10% of healthy adults will carry *N meningitidis* in the nasopharynx, providing a continuous reservoir for transmission, especially in crowded conditions.^{1 17} The carriage rate is lowest in children¹⁸ but rises with age, up to 25% in 15–19 year olds¹⁷ and 32% at 25 years of age, probably as a result of age-related changes in social behaviour.¹⁹ In Europe, MenB is the most frequently carried serogroup (30–40%), followed by MenY (10–15%), MenC (5–7%), MenW-135 (3–4%) and MenA (2%).^{19 20} The possibility that the use of conjugate meningococcal vaccines might result in an increase in disease burden from non-vaccine serogroups has not been observed in the UK since the introduction of the MenC vaccine.²¹

MICROBIOLOGY OF THE CAPSULAR POLYSACCHARIDES OF *N MENINGITIDIS*

The capsules of serogroups B, C, Y and W-135 *N meningitidis* are made up of polysialic acid or sialic acid linked to glucose or galactose, whilst that of serogroup A is composed of *N*-acetyl mannosamine-1-phosphate.²² A capsular operon (cps) encodes the specific capsular polysaccharide transport protein gene *CtrA* (capsular transferase) and capsular polysaccharide serogroup specific biosynthesis genes. *CtrA* is strongly conserved in all meningococcal serogroups independent of the chemical composition of the capsular polysaccharide.²³ The capsule biosynthesis genes encoding serogroup specific sialic acid polymerases are: *sia D* (related but chemically distinct in MenB or C),²⁴ *syn G* (MenW-135) and *syn F* (MenY).²⁵ The genes for the capsule of MenA are encoded by *sacB*.²⁶ Amplification of these genes by PCR²⁷ provides a rapid and reliable method of diagnosing and identifying the corresponding *N meningitidis* serogroup, a process which is crucial in guiding vaccine campaigns during epidemics.

PLAIN POLYSACCHARIDE VACCINES

Monovalent (A or C), bivalent (A/C) and tetravalent (ACYW-135) polysaccharide vaccines stimulate a B cell immune response with the production of antibodies specific to the polysaccharides included in the vaccine. Despite high seroconversion and efficacy rates, antibody responses are short lived and vary with age and with the serogroup specific polysaccharide included in the vaccines.

MenA polysaccharide is immunogenic from 3 months of age, but MenC polysaccharide is poorly immunogenic in those under 2 years of age.²⁸ Both MenC and MenA polysaccharides induce short-lasting immunity in children younger than 6 years of age.^{29–31} The poor immune response of the MenC polysaccharide in young children is presumed to be due to the T cell independent nature of the antigen and immunological immaturity.³²

Although it is classically thought that polysaccharide vaccines do not affect herd immunity, both MenA and C polysaccharides have been shown to induce a mucosal response in adolescents and young adults, suggesting a theoretical potential for interrupting transmission of *N meningitidis*.^{33 34} Further human studies are needed to explore and quantify this potential.

Booster doses of MenA/C polysaccharide vaccines have been shown to result in serological hyporesponsiveness towards the MenC polysaccharide.^{28 35} By contrast, MenA polysaccharide results in an increase in the antibody response in infants after boosting.²⁸ The observed differences in the immune response between MenA and C polysaccharides suggest that the serogroup A polysaccharide may not behave strictly as a T cell

independent antigen. The clinical significance of hyporesponsiveness towards MenC is unclear, but concerns remain about the safety of repeated doses of pure polysaccharide meningococcal vaccines incorporating the MenC polysaccharide.³⁵ In addition, the use of plain polysaccharide vaccines is further limited by the fact that, unlike conjugate vaccines, they do not generate immune memory.³²

CONJUGATE MENINGOCOCCAL VACCINES

Conjugation of bacterial capsular polysaccharide/oligosaccharide to a carrier protein results in a T cell dependent immune response allowing the production of high affinity antibodies and the formation of memory B cells specific for the carbohydrate antigens.³⁶ Following on from the success of *Haemophilus influenzae* type b conjugate vaccines,³⁷ monovalent,³⁸ bivalent³⁹ and tetravalent meningococcal conjugate vaccines^{5 40} have been formulated.

SEROGROUP C MENINGOCOCCAL VACCINES

In the 1990s serogroup C meningococcal disease outbreaks caused by the hyperinvasive ST 11 clone, led to the licensure of effective conjugate MenC vaccines in the UK. Subsequent surveillance data showed lower rates of meningococcal disease, evidence of herd immunity²¹ and high short term vaccine effectiveness.⁴¹

Measurement of functional antibody and serum bactericidal assay (SBA) titres of $\geq 1:4$ (using human complement)⁴² and of $\geq 1:8$ (using rabbit complement) are used as a surrogate for protection.^{43 44} For serogroups A, W-135 and Y, there are no data to demonstrate that any SBA titre correlates with the protective efficacy of a vaccine but, by extrapolation, the protective MenC rSBA (serum bactericidal antibody assay using rabbit complement) titre of $\geq 1:8$ has been assumed to indicate protection.

Although there is evidence of immunological memory,^{45 46} bactericidal antibodies wane within 2–4 years in children vaccinated against MenC in the first 2 years of life, with a corresponding decline in vaccine effectiveness.^{45 47} By contrast, vaccine effectiveness persists for up to 4 years in those vaccinated after their third birthday.⁴⁸ Although such waning immunity is worrying, vaccine effectiveness also relies on the ability of these glycoconjugate MenC vaccines to induce herd immunity and therefore decreasing transmission. Conjugate MenC vaccines have been shown to stimulate specific mucosal IgA and IgG³³ and also resulted in a 66% reduction in nasopharyngeal carriage of MenC in adolescents 1 year after the introduction of the MenC immunisation campaign in the UK.²¹ The associated reduction in invasive MenC disease even in unvaccinated children provides evidence of this herd immune effect.⁴¹ In order to ensure sustained protection through the peak of meningococcal disease in adolescence, vaccination programmes that use MenC or tetravalent MenACYW conjugate vaccines will not only have to consider the waning of functional antibody in childhood but also the protective effect of herd immunity when incorporating booster schedules.

Meningococcal A vaccines

A monovalent MenA vaccine is currently being developed by the Meningitis Vaccine Project. The project is expected to result in a low-cost vaccine that could relieve much suffering from meningococcal disease but will need continued funding to break the cycle of epidemics in the meningitis belt of Africa.⁴⁹

Meningococcal A and C vaccines

Conjugate meningococcal A/C vaccines would be useful in countries with a high incidence of meningococcal A and C disease, such as many of those in sub-Saharan Africa.^{7 50} Conjugate MenA/C vaccines were shown to be safe and immunogenic in clinical trials conducted in young adults^{34 51 52}

and in infants from Niger, Gambia and Britain.^{53–55} Immunological memory to both MenA and C polysaccharides was also demonstrated in infants.^{53–55} At present there is no licensed conjugate A/C vaccine and no further development is planned. More interest has been generated in investigating tetravalent ACYW vaccines which would protect against more serogroups worldwide.

Meningococcal A, C, Y and W-135 (MenACYW) vaccines

A tetravalent MenACYW polysaccharide-diphtheria toxoid conjugate vaccine (Menactra, Sanofi Pasteur) has been licensed for use in 11–55 year olds in the US since January 2005⁸ and has been recently also approved for immunisation of 2–10 year olds in Canada since May 2006.⁵⁶ Other manufacturers are also developing multivalent meningococcal vaccines (table 1). However, the only data that have been publicly presented are for the Novartis MenACYW vaccine. An important approach in the licensure of novel conjugate vaccines is the demonstration that the immunogenicity of these vaccines is not inferior to previously licensed and widely used plain polysaccharide vaccines.

Immunogenicity

The 4 µg dose of each serogroup A, C, Y and W-135 capsular polysaccharide in MenACYW-D was selected for development in view of immunogenicity in children after infancy and in adults, and low reactogenicity in adults,⁵⁷ toddlers⁵⁸ and infants⁵⁹ (table 2). Data on the formulation of MenACYW-CRM₁₉₇ are not available at this time.

Adolescents

A single dose of MenACYW-D or the pure polysaccharide comparator MenACYW-PS (Menomune, Sanofi Pasteur) resulted in post-vaccination rSBA titres of $\geq 1:128$ for all serogroups in 98% of adolescents.⁶⁰ Immunity persisted for 3 years after vaccination with both vaccine formulations, however, both the geometric mean serum bactericidal antibody titres against MenC and immunologic memory to all four serogroups were better after MenACYW-D.^{60–61} When compared to naive individuals, a booster dose of MenACYW-D resulted in lower antibody titres to all four serogroups in the adolescents initially vaccinated with MenACYW-PS,⁶⁰ suggesting that the initial polysaccharide dose interfered with the immune response to the subsequently administered conjugate as has been described previously during development of MenA/C polysaccharide vaccines.

Children (2–10 years old)

The proportion of 2–10 year old children with rSBA titres $\geq 1:128$ for all four serogroups after vaccination with a single dose of either MenACYW-D or MenACYW-PS are comparable⁶²; however, population and age differences in the response to the vaccines have been shown,⁶³ suggesting the need for further

trials in children from different countries before making a global recommendation for the use of these vaccines. Functional antibody against serogroup C, as measured by antibody avidity and protection against serogroup C bacteraemia in an animal model, was higher after MenACYW-D.⁶⁴ Although after 6 months a decline in the geometric mean antibody titres (GMTs) was only noted for MenA, within 2 years most of the vaccinees had titres of $\leq 1:4$ for all serogroups.^{65–66} The waning long term immunity is similar to that already well described for monovalent MenC vaccines^{48–67} and provides justification for a booster dose. The 136-fold rise in SBA titre to serogroup C with MenACYW-D seen in 2–5 year old children who had been previously vaccinated with a monovalent conjugate MenC vaccine, supports evidence of a booster response.⁶⁸ However, further studies need to be carried out in children previously vaccinated with MenACYW-D.

Toddlers

In 12–23 month old toddlers, two doses of MenACYW-D, administered at an interval of 6–8 weeks, were needed to achieve protection, as shown by a rSBA $\geq 1:8$ in 100% of children for all serogroups, 1 month after the second dose (compared to 37.5%–100% after the first dose, depending on the serogroup).⁵⁸ Similarly, a two dose schedule in 12–16 month old children for MenACYW-CRM₁₉₇ was required to induce protective antibody levels against all serogroups, as shown by a hSBA $\geq 1:4$ in 49–70% and 91–96% of children after the first and second doses, respectively.⁶⁹ (Values for serum bactericidal antibody titres which have been accepted as correlates of protection against invasive meningococcal group C disease are taken at a cut off of $\geq 1:4$ when using human complement (hSBA) and at corresponding titre of $\geq 1:8$ when baby rabbit complement (rSBA) is used.) These data appear to indicate that a two dose schedule is highly immunogenic in toddlers and could be used to control disease in regions where these serogroups are a problem in this age group.

Infants

The percentage of infants with rSBA titres of $\geq 1:8$, 1 month following vaccination with MenACYW-D at 2, 4 and 6 months, was low for MenC (54.2%), MenY (66.7%) and MenW-135 (62.5%) but high for MenA (91.7%).⁵⁹ ELISA and SBA GMTs to MenC were much lower than previously reported with monovalent C or bivalent A/C conjugate vaccines.⁵⁹ This suggests that MenACYW-D does not stimulate adequate protective immunity in infants to serogroups C, W-135 and Y. Although immunologic priming was demonstrated by an anamnestic response to all serogroups after a MenACYW-PS booster at 15–18 months of age,⁵⁹ this might not indicate long term protection. Based on these limited data, this vaccine does not appear to be sufficiently immunogenic for use in infants.

By contrast, preliminary data indicated much higher seroconversion rates using hSBA, for MenC (84%), Y (92%) and

Table 1 Multivalent meningococcal conjugate vaccines

Components	Company	Status	Schedule/recommendation
MenACYW-D	Sanofi Pasteur	Licensed in the USA (11–55 year olds) ⁸ and in Canada (2–55 year olds) ⁵⁶	One dose after 11 years of age in the USA One dose after 2 years of age in Canada
MenACYW-CRM ₁₉₇	Novartis Vaccines	Phase II studies	Infant study*: 2 or 3 doses at 2, 3 and 4 months of age ⁵ Toddler study: 1 or 2 doses at 12–16 months ⁶⁹
MenACYW	GSK Vaccines	No published data	No published data
Hib-MenCY	GSK Vaccines	No published data	No published data
Hib-MenAC-DTwP-HB	GSK Vaccines	No published data	No published data
Hib-MenC-TT	GSK Vaccines	Licensed in the UK in December 2005	3 doses at 2, 3 and 4 months of age and/or a booster in the second year of life

*First data presented at the Meningitis Research Foundation conference, London 2005.

HB, hepatitis B; Hib, *Haemophilus influenzae* type b; TT, tetanus toxoid; wP, whole cell pertussis.

Table 2 Immunogenicity data after primary vaccination with MenACYW-D in infants, children and adolescents

Authors	Type of clinical trial	Study population	Vaccine	% Subjects with rSBA $\geq 1:8$ (and $\geq 1:128$, when available) 1 month after last dose				% Subjects with 4-fold SBA titre increase after 1 month				SBA GMT 1 month after last dose			
				A	C	Y	W135	A	C	Y	W135	A	C	Y	W135
*Renells <i>et al</i> ⁸⁷	Phase I	90 infants 6–13 weeks old	1 μ g/4 μ g/10 μ g dose of MenACYW-D administered at 2, 4 and 6 months to one of 3 groups, with 30 infants in each group	91.7	54.2	66.7	62.5	–	–	–	–	101.6	19.6	19.6	17.4
†Renells <i>et al</i> ⁸⁸	Phase I	30 children 12–<23 months old	1 μ g/4 μ g/10 μ g dose of MenACYW-D administered as 2 doses, at an interval of 6–12 weeks, to one of 3 groups, with 10 children in each group	100	100	100	100	–	–	–	–	3158.4	304	304.4	430.5
Bashir <i>et al</i> ⁸⁸	Phase II	103 subjects 2–<5 years old vaccinated with MenC vaccine ≥ 1 year previously	52 given 1 dose of Menactra	100 (100)	100 (100)	100 (98)	100 (100)	–	–	–	–	11 404	12 535	4032	5978
‡Granoff <i>et al</i> ^{84,85}	Phase II	1398 subjects 2–10 years old	51 given 1 dose of a Hib vaccine 696 given 1 dose of Menactra 702 given 1 dose of Menomune	78 (78)	44 (31)	89 (83)	58 (36)	–	–	–	–	199	22.6	299	32
			696 given 1 dose of Menactra 702 given 1 dose of Menomune	75–80	50	60–65	35–40	–	–	–	–	20–30	5–6	10–20	5–6
			702 given 1 dose of Menactra	55	17	60	25–30	–	–	–	–	7–8	2–3	9–10	3–4
§Pichichero <i>et al</i> ⁸²	Phase II	1398 subjects 2–10 years old	696 given 1 dose of Menactra 702 given 1 dose of Menomune	98.6 (97)	87.9 (81)	86.2 (93)	96 (91)	98.6	87.9	86.2	96	1700	354	637	750
			440 given 1 dose of Menactra 441 given 1 dose of Menomune	94.7 (93)	80.1 (73)	75.0 (86)	89.6 (86)	94.7	80.1	75.0	89.6	893	231	408	426
Keyserling <i>et al</i> ⁸⁰	Phase II	881 subjects 11–18 years old	440 given 1 dose of Menactra 441 given 1 dose of Menomune	(99.8)	(98.9)	(99.6)	(98.7)	92.7	91.7	81.8	96.7	5483	1924	1322	1407
			121 sera from subjects given 1 dose of Menactra 99 sera from subjects given 1 dose of Menomune	(100)	(98.5)	(99.3)	(98.9)	92.4	88.7	80.1	95.3	3246	1639	1228	1545
¶Lagos <i>et al</i> ⁸³	Phase III	1037 subjects 2–10 years old	121 sera from subjects given 1 dose of Menactra 99 sera from subjects given 1 dose of Menomune	–	–	–	–	77	82	68	92	2109	1164	2616	1227
				–	–	–	–	78	78	66	90	1645	1222	2019	1155

*Only SBA GMTs (reciprocal) for the 4 μ g dose are shown.†Only the data for the 4 μ g dose are shown.‡SBA titres of $\geq 1:4$ (using human complement) were used to indicate protection. Values are approximate for both the percentage of subjects with hSBA $\geq 1:4$ and hSBA GMTs (reciprocal) since they were read from the published figures. Data presented are for a subset of the total study cohort.§The data on the percentage of subjects with four-fold increases in SBA titres were presented for those subjects who had undetectable SBA $< 1:8$ and subsequently seroconverted to titres $\geq 1:32$.

¶This was a multicentre trial carried out in the US and Chile recruiting a total of 3232 children. Only data from the Chilean study have been published.

Dashes (–) indicate that no data were published for the corresponding variable. GMT, geometric mean antibody titre; Hib, *Haemophilus influenzae* type b; hSBA, serum bactericidal antibody assay using human complement; rSBA, serum bactericidal antibody assay using rabbit complement.

W-135 (96%), in infants vaccinated at 2, 3 and 4 months with MenACYW-CRM₁₉₇.⁵ Furthermore, the proportion protected against MenC was found to be comparable to that after two doses of a licensed meningococcal C vaccine.⁵ As yet there are no data available on the persistence of immune memory with MenACYW-CRM₁₉₇ vaccine administered in infants; however, a memory response has been reported in toddlers who received a polysaccharide booster 8 months after receiving a single dose of MenACYW-CRM₁₉₇.⁶⁹ The differences between the immune response elicited by the two tetravalent conjugate vaccines are likely to be due to a number of variables, including differences in size and dose of oligosaccharide, the type of carrier protein used, the use of adjuvant and the conjugation chemistry.

Safety

MenACYW-D has an acceptable safety profile in studies performed in infants,⁵⁹ children^{58, 62, 63} and adolescents.⁶⁰ Solicited local reactions, including pain, redness and swelling at the injection site, occurred in approximately two thirds of children below the age of 10 years. Although these rates are much higher than those reported in the clinical studies looking at the reactogenicity of conjugate MenC, *Haemophilus influenzae* type b (Hib) and heptavalent pneumococcal vaccines, very few were classified as severe and all resolved without sequelae. Fever >38°C was reported in 5–10% of the vaccinees in all age groups, with the lowest rates seen in infants and toddlers.^{58, 59} These rates are similar to those reported for other conjugate vaccines. In the adolescent study, rates of local adverse reactions were higher with MenACYW-D, possibly due to the inclusion of diphtheria toxoid as a carrier protein in the conjugate vaccine.⁶⁰ The number of adolescent cases of Guillain-Barré syndrome (GBS) reported after introduction of MenACYW-D in the US did not exceed the estimated background incidence rate for this disease. However, MenACYW-D is not recommended for individuals with a history of GBS unless they are at an increased risk of meningococcal disease.⁷⁰

No data have been published on the safety of MenACYW-CRM₁₉₇.

CONCLUSION AND FUTURE DIRECTIONS

The formulation of multivalent meningococcal vaccines has provided the potential for broader protection against meningococcal disease. Tetravalent meningococcal vaccines could be used in various at-risk groups (table 3) and, due to induction of immunological memory and better duration of bactericidal antibody, might be more suitable than plain polysaccharide vaccines in these situations. Multivalent conjugate vaccines should be used as a response to epidemics caused by specific serogroups in countries that have access to these vaccines, but pre-emptive vaccination in response to endemic disease and hyperendemic disease might be considered.

Table 3 At-risk groups who might benefit from a tetravalent MenACYW vaccine

- a) Microbiologists and other laboratory staff
- b) Close contacts of an index case of A, C, Y or W-135 disease
- c) Immunocompromised individuals such as those who are asplenic/hyposplenic or have terminal complement deficiencies⁸
- d) Students starting high school and college freshmen living in dormitories⁸
- e) Military recruits⁸
- f) Travellers to high risk areas, such as countries in the African meningitis belt
- g) Hajj pilgrims
- h) Individuals residing in epidemic or hyperendemic areas
- i) Infants, toddlers or adolescents in routine immunisation programmes

Several questions remain about the introduction of MenACYW conjugate vaccines in immunisation programmes in developed and especially in developing countries. For routine vaccination of infants and toddlers younger than 2 years of age, the number of doses and scheduling of these tetravalent meningococcal vaccines cannot be determined without the availability of further data from clinical trials in this age group. There are currently no alternatives for immunisation against serogroups Y and W-135 at these ages (since the plain polysaccharide vaccine for Y and W-135 is not immunogenic in those under the age of 2) and these new vaccines would offer the possibility of some protection where there are high rates of disease caused by A and W-135, as in Asia, Middle East and Africa or in countries experiencing an increase in MenY disease, as in the US. Where serogroup C meningococcal disease has been controlled with monovalent MenC vaccines, there is now hope that broader protection may be possible with these combination vaccines. However, the scheduling of the ACYW dose(s) in the primary schedule would have to fit in with the highly variable schedules currently used in different countries,^{71–73} perhaps requiring further study to ensure that there is no predictable loss in MenC effectiveness caused by a switch.

Furthermore, interactions with concurrently administered vaccines used in the primary infant immunisation schedule, such as with the heptavalent pneumococcal conjugate, and with combination vaccines against diphtheria, tetanus, acellular pertussis, inactivated polio, Hib and hepatitis B, still need to be studied.

For countries considering the use of ACYW vaccines, economic issues will have a major bearing on the decision to introduce MenACYW conjugates, in the absence of the media interest generated by a possible sustained outbreak of disease caused by one of these serogroups. Nevertheless, if pricing is similar to the monovalent MenC product currently used, the added benefit of the tetravalent conjugate makes this an attractive option.

MenACYW conjugate vaccines might also be used for travellers or high risk groups (table 3). The introduction of combination conjugates in low income and developing countries will require substantial subsidy or tiered pricing, and bivalent MenA/C or MenA/W-135 conjugate vaccines might be more cost effective, depending on the local epidemiology and the risk of outbreaks from imported serogroups.

The development of multivalent conjugate MenACYW vaccines reflects a major advance in the prevention of meningococcal disease but their introduction in routine vaccination schedules faces several challenges. Unfortunately, without an effective MenB vaccine, comprehensive protection against this pathogen remains elusive.

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Competing interests: DP has received travel grants from GlaxoSmithKline Vaccines to attend scientific meetings. AJP acts as chief investigator for clinical trials conducted on behalf of Oxford University and sponsored by vaccine manufacturers (Sanofi Pasteur MSD, Novartis Vaccines, GlaxoSmithKline Biologicals, Sanofi Pasteur and Wyeth Vaccines), and has directed trials of MenACYW vaccines, manufactured by Novartis Vaccines, and a Hib-MenC vaccine, manufactured by GlaxoSmithKline Vaccines. He has received assistance from vaccine manufacturers to attend scientific meetings. Industry-sourced consultancies and honoraria for lecturing or writing are paid directly to an independent charity or a fund held by the Department of Paediatrics, University of Oxford. He is an inventor on patents in the area of MenB vaccines.

Search strategy: Data for this review were identified by searching PubMed and Medline databases up to and including October 2006. Only English language papers were reviewed. The following were the search terms used:

"conjugate", "meningococcal vaccine", "serogroup A", "serogroup C", "serogroup Y", "serogroup W-135", "bivalent", "quadrivalent" and "tetraivalent". Other sources were references identified in retrieved articles and online publications by health authorities of different countries.

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ARCHIVIST

Acute renal failure in cystic fibrosis

Reports of acute renal failure in patients with cystic fibrosis began to appear around the turn of the millennium. Now a survey of UK cystic fibrosis centres (Carol Bertenshaw and colleagues. *Thorax*. Published online 18 Jan 2007; doi: 10.1136/thx.2006.067595) has provided more reports of patients with cystic fibrosis and acute renal failure.

A questionnaire was sent to 99 doctors in 56 centres (30 paediatric and 26 adult centres). Replies were received from 94 doctors in 55 centres and information was obtained about 55 possible cases of acute renal failure between 1997 and 2004. Study consent was obtained for 26 of these and the diagnosis of acute renal failure was confirmed in 24 (19 children under the age of 16 years). The oldest patient was 31 years old. The estimated incidence was 4.6–10.5 cases of acute renal failure per 10 000 cases of cystic fibrosis per year. In 21 cases an aminoglycoside antibiotic had been given in the week before the onset of acute renal failure (gentamicin in 16 cases). Six cases had cystic fibrosis related diabetes. Renal biopsy in seven cases showed acute tubular necrosis in six, all associated with gentamicin. Thirteen patients (54%) needed renal dialysis, and 22 patients (92%) made a full recovery. One patient, with diabetic nephropathy, needed long-term dialysis, and one needed long-term antihypertensive treatment.

Acute renal failure in patients with cystic fibrosis is usually related to use of an aminoglycoside, particularly gentamicin. A case-control study is planned to delineate risk factors more fully.