Extended list of references and summaries for the 2011 WHO position paper and the 2015 updated guidance on the use of meningococcal A conjugate vaccine

Advisory Committee on Immunization Practices (ACIP). Licensure of a meningococcal conjugate vaccine for children aged 2 through 10 years and updated booster dose guidance for adolescents and other persons at increased risk for meningococcal disease. *Morbidity and Mortality Weekly Report*, 2011, 60: 1018-1019.

In January 2011, the Food and Drug Administration lowered the approval age range for use of MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics), a quadrivalent meningococcal conjugate vaccine, to include persons aged 2 through 55 years. One other quadrivalent meningococcal conjugate vaccine, MenACWY-D(Menactra, Sanofi Pasteur), is licensed in the United States for prevention of meningococcal disease caused by serogroups A, C, Y, and W-135 among persons aged 2 through 55 years; MenACWY-D also is licensed as a 2-dose series for children aged 9 through 23 months. The Advisory Committee on Immunization Practices (ACIP) recommends that persons aged 2 through 55 years at increased risk for meningococcal disease and all adolescents aged 11 through 18 years be immunized with meningococcal conjugate vaccine. ACIP further recommended, in January 2011, that all adolescents receive a booster dose of quadrivalent meningococcal conjugate vaccine at age 16 years. This report summarizes data supporting the extended age indication for MenACWY-CRM and the interchangeability of the two licensed meningococcal conjugate vaccines.

Al-Tawfiq J A et al. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. *Journal of travel medicine,* 2010, 17, (Supplement): 3-8.

Conclusions: The epidemiology of meningococcal disease exhibits remarkable diversity across the globe, with incidence rates ranging from less than one case per 100,000 in many industrialized countries to attack rates of 1% during meningitis belt epidemics. Meningitis remains prominent in the public consciousness both in industrialized settings and in the developing world. A limited number of countries have successfully implemented meningococcal conjugate vaccination programs, but more remains to be accomplished. No broadly protective serogroup B vaccines are yet available, and the countries of the African meningitis belt await a conjugate vaccine developed to end epidemic meningitis as a public health concern. Even as meningococcal disease epidemiology is described, the risk to travelers is incompletely understood. However, the increasing frequency and ease of travel may increase the risk of acquiring meningococcal disease for travelers, and of introducing new strains into susceptible populations.

Andrews N et al. Validation of Serological Correlate of Protection for Meningococcal C Conjugate Vaccine by Using Efficacy Estimates from Postlicensure Surveillance in England. *Clinical and Diagnostic Laboratory Immunology*, 2003, 10: 780-786.

Meningococcal C conjugate (MCC) vaccines were licensed on the basis of serological correlates of protection without efficacy data. The original correlate of protection was established by using a serum bactericidal antibody assay (SBA) with human complement (hSBA), with titers > or =4 predicting protection. However, the antibody data supporting

licensure were largely generated by SBA with rabbit complement (rSBA), which gives higher titers than hSBA. While rSBA titers > or =128 reliably predict protection, as measured by hSBA, sera with rSBA titers in the range of 8 to 64 may not have hSBA titers > or =4. For rSBA titers in this equivocal range, a fourfold rise pre- to postvaccination with the MCC vaccine and/or a characteristic booster response to a polysaccharide challenge was proposed as a correlate of protection. To validate this proposed rSBA correlate, age-specific efficacy estimates for MCC vaccines obtained from postlicensure surveillance in England were compared with the efficacy predicted by the percentage of individuals in these age groups with rSBA titers above different cutoffs at 4 weeks and at 7 to 9 months after vaccination with the MCC vaccine. The average time since vaccination in the cohorts in whom efficacy was measured ranged from 8 to 10 months. The rSBA cutoff of > or =128 was shown to significantly underestimate efficacy, with rSBA cutoffs of > or =4 or > or =8 at 4 weeks postvaccination with the MCC vaccine being the most consistent with observed efficacy. When the levels obtained 7 to 9 months postvaccination with the MCC vaccine were used, all rSBA cutoffs significantly underestimated efficacy, suggesting that continuing protection is less dependent on the SBA level at the time of exposure but is more reliant on immunologic memory.

Arguedas A et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. *Vaccine,* 2010, 28:3171-3179.

This Phase III study evaluates an investigational quadrivalent meningococcal CRM(197) conjugate vaccine, MenACWY-CRM (Novartis Vaccines), when administered concomitantly or sequentially with two other recommended adolescent vaccines; combined tetanus, reduced diphtheria and acellular pertussis (Tdap), and human papillomavirus (HPV) vaccine. In this single-centre study, 1620 subjects 11-18 years of age, were randomized to three groups (1:1:1) to receive MenACWY-CRM concomitantly or sequentially with Tdap and HPV. Meningococcal serogroup-specific serum bactericidal assay using human complement (hSBA), and antibodies to Tdap antigens and HPV virus-like particles were determined before and 1 month after study vaccinations. Proportions of subjects with hSBA titres > or =1:8 for all four meningococcal serogroups (A, C, W-135, Y) were non-inferior for both concomitant and sequential administration. Immune responses to Tdap and HPV antigens were comparable when these vaccines were given alone or concomitantly with MenACWY-CRM. All vaccines were well tolerated; concomitant or sequential administration did not increase reactogenicity. MenACWY-CRM was well tolerated and immunogenic in subjects 11-18 years of age, with comparable immune responses to the four serogroups when given alone or concomitantly with Tdap or HPV antigens. This is the first demonstration that these currently recommended adolescent vaccines could be administered concomitantly without causing increased reactogenicity.

Auckland C. Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. *The Journal of infectious diseases,* 2006, 194:1745-1752.

BACKGROUND:The meningococcal serogroup C conjugate (MCC) vaccine was introduced into the United Kingdom with licensure based on immunogenicity data not efficacy data. METHODS: All subjects with laboratory-confirmed meningococcal serogroup C (MenC) disease from January 2000 to December 2003 in England and Wales were followed up. A

vaccine failure was defined as a laboratory confirmed case of MenC disease occurring ≥10 days after the subject's last scheduled dose of MCC vaccine. Total immunoglobulins, serum bactericidal antibody (SBA) titers, MCC anticapsular antibody levels, and avidity indices (AIs) were measured in acute and convalescent serum samples from subjects with vaccine failure and unvaccinated subjects with MenC disease.
RESULTS: Of 465 subjects with confirmed MenC disease identified among those eligible for vaccination, information on vaccination history was obtained for 462 (99.4%); of these, 53 were subjects with vaccine failure. SBA titers in convalescent serum samples and AIs in acute serum samples were significantly higher in subjects with vaccine failure than in unvaccinated subjects, (6.1-fold higher for SBA titers [Pp.03] and 3.2-fold higher for AIs [Pp.001]).
CONCLUSIONS:The antibody response in the subjects with vaccine failure was consistent with an anamnestic response, suggesting that MenC disease occurred despite the MCC vaccine priming for immune memory. Persistence of antibodies may be a more appropriate correlate of long-term protection for MCC vaccines than the ability to generate a booster response on exposure.

Background paper on meningococcal vaccines. Geneva, WHO Strategic Advisory Group of Experts on Immunization, 2011
http://www.who.int/immunization/sage/1_mening_background_document_v5_3__apr_2011.pdf

Bilukha OO et al. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). CDC Surveillance Summaries: *Morbidity and Mortality Weekly Report,* 2005, 54:1–21.

In January 2005, a tetravalent meningococcal polysaccharide-protein conjugate vaccine ([MCV4] Menactra, manufactured by Sanofi Pasteur, Inc., Swiftwater, Pennsylvania) was licensed for use among persons aged 11-55 years. CDCns Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of young adolescents (defined in this report as persons aged 11-12 years) with MCV4 at the preadolescent health-care visit (at age 11-12 years). Introducing a recommendation for MCV4 vaccination among young adolescents might strengthen the role of the preadolescent visit and have a positive effect on vaccine coverage among adolescents. For those persons who have not previously received MCV4, ACIP recommends vaccination before high-school entry (at approximately age 15 years) as an effective strategy to reduce meningococcal disease incidence among adolescents and young adults. By 2008, the goal will be routine vaccination with MCV4 of all adolescents beginning at age 11 years. Routine vaccination with meningococcal vaccine also is recommended for college freshmen living in dormitories and for other populations at increased risk (i.e., military recruits, travelers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of Neisseria meningitidis, patients with anatomic or functional asplenia, and patients with terminal complement deficiency). Other adolescents, college students, and persons infected with human immunodeficiency virus who wish to decrease their risk for meningococcal disease may elect to receive vaccine. This report updates previous reports from ACIP concerning prevention and control of meningococcal disease. It also provides updated recommendations regarding use of the tetravalent meningococcal polysaccharide vaccine (MPSV4) and on antimicrobial chemoprophylaxis.

Biselli R et al. Dramatic reduction of meningococcal meningitis among military recruits in Italy after introduction of specific vaccination. *Vaccine,* 1993, 11: 578-581.

Meningococcal meningitis is still a serious infectious disease with a mortality rate that can be as high as 10% even in developed countries. Military recruits are generally a high-risk group for meningococcal disease, with a reported incidence of four to ten times greater than that of the general population. In Italy the results of the National Meningitis Surveillance Programme showed a high attack rate of the disease among recruits in 1985 as well as in 1986, with 92 and 95% of the cases, respectively, caused by serogroup C and thus preventable. These findings led to the authorities' decision to make vaccination against meningococcal disease mandatory for recruits starting from January 1987. After almost 5 years from the introduction of meningococcal vaccination, we here sum up the epidemiological and immunological effects of the vaccination. From the epidemiological point of view we have observed a dramatic reduction of the prevalence of the disease. In 1987, the year in which we had 150,000 unvaccinated and 150,000 vaccinated recruits, the protective efficacy was 91.2%. From the immunological point of view, vaccination is highly effective, as seroconversion against polysaccharide (PS) A and C is 84 and 91%, respectively. The spectrotypic analysis of the sera before and after vaccination shows that the type of response is mainly oligoclonal, like the majority of the responses to PSs, and the antibodies induced by a sole PS are not qualitatively different from the antibodies induced by natural immunization. In addition, the efficacy is not modified by environmental factors like hypoxia, as demonstrated during permanence at 16,174 feet for 20 days.(ABSTRACT TRUNCATED AT 250 WORDS)

Borrow R et al. Meningococcal surrogates of protection--serum bactericidal antibody activity. *Vaccine,* 2005, 23: 2222-2227.

Despite the availability of anti-microbial agents effective against Neisseria meningitidis, meningococcal disease continues to be a major global health problem, particularly in the very young. Serogroup A meningococci cause large epidemics in sub-Saharan Africa, whilst serogroups B and C organisms are responsible for sporadic cases and localised outbreaks of disease world-wide. For measuring functional activity, the serum bactericidal antibody (SBA) assay is the most important method. It is mediated by antibody and complement resulting in lysis of the bacterial cells. To date the SBA has proved to be the best surrogate of protection for all serogroups. For serogroup C, an SBA titre of either >/ or =4 or > or =8 has being utilised for putatively indicating protection when using either human or baby rabbit complement, respectively. For serogroup B, the proportions of vaccines with > or =4-fold rises in SBA pre- to post-vaccination or SBA titres > or =4 have been correlated with clinical efficacy in trials of outer membrane vesicle (OMV) vaccines in Cuba, Brazil and Norway. SBA activity as a correlate of protection for evaluating the immune response to meningococcal vaccines is described in this review.

Borrow R et al. Immunogenicity of, and immunologic memory to, a reduced primary schedule of meningococcal C-tetanus toxoid conjugate vaccine in infants in the United Kingdom. *Infection and Immunity, 2003,* 71:5549-5555.

It has been previously shown that one of the three meningococcal C conjugate (MCC) vaccines introduced in the United Kingdom proved highly immunogenic after the first dose of a three-dose schedule, with evidence of immune memory after dose 3. Thus, in infants a one- or two-dose schedule of this MCC vaccine, conjugated to tetanus toxoid (TT), may suffice. Healthy infants (n _ 586) were randomized to receive either one (group 1), two (group 2), or three (group 3) doses of MCC-TT vaccine with a 10-_g polysaccharide booster given at 13 to

14 months of age. Serum bactericidal antibody (SBA) levels were measured by utilizing rabbit complement (rSBA), meningococcal C-specific immunoglobulin G (IgG), and avidity indices (AIs). For groups 1, 2, and 3, the percentages of infants with an rSBA level of >8 against strain C11 were 98.4, 100, and 99.4%, respectively. Infants in group 1 with prevaccination rSBA titers of >8 had post-primary MCC rSBA geometric mean titers (GMTs) significantly lower than those infants with prevaccination rSBA titers of <8. One dose of MCC-TT vaccine given to infants at 2 months of age yielded significantly lower SBA GMTs and geometric mean AIs (GMAIs) than two or three doses but elicited a significantly greater response after boosting, as reflected by rSBA levels and GMAI. This study provides the first evidence that the number of doses of MCC-TT used in infant immunization schedules could be decreased.

Borrow R et al. Antibody persistence and immunological memory at age 4 years after meningococcal group C conjugate vaccination in children in the United Kingdom. *Journal of Infectious Diseases,* 2002, 186: 1353-1357.

Antibody persistence and immunological priming for 2 formulations of a meningococcal group C (menC) conjugate (MCC) vaccine (containing 2 or 10 mg of menC polysaccharide) administered at 2, 3, and 4 months of age was investigated by boosting vaccine recipients at age 13–16 months or 4 years with 10 mg of unconjugated menC polysaccharide. At age 4 years, geometric mean titers (GMTs) and concentrations of menC-specific immunoglobulin G and serum bactericidal antibody (SBA) had decreased to prevaccination levels. Geometric mean avidity indices increased after the primary vaccination until age 13–16 months and then remained constant until age 4 years. One month after boosting at age 4 years, menC immunoglobulin G and SBA levels increased significantly. The postbooster SBA GMT for the 2-mg vaccination (2181.2; 95% confidence interval [CI], 975.9–4875.1) was 2-fold higher than that for the 10-mg vaccination (931.6; 95% CI, 338.0–2568.1). This is the first demonstration of immunological memory at 4 years of age in children receiving MCC vaccine on the United Kingdom's 2/3/4-month immunization schedule.

Bronská E et al. Invasive meningococcal disease and latex agglutination test--is it still beneficial for diagnosis? *Folia Microbiologica (Praha)*, 2005, 50:453-456.

We showed current clinical usefulness of the latex agglutination (LA) test for confirmation of meningococcal etiology on 32 cerebrospinal fluid, 77 serum and 93 urine samples collected during the first week of hospitalization from 19 patients with laboratory confirmed invasive meningococcal disease. The positivity of the LA test in cerebrospinal fluid was 47%, in serum 42% and in urine 24%, while the PCR of cerebrospinal fluid and serum was positive in 95 and 47% cases, respectively. The latest positivity of the LA test was detected on day 2 in cerebrospinal fluid, on day 3 in serum and on day 4 in urine. In the group of patients who had received antibiotic therapy we found nonsignificant reduction of LA positivity and also statistically significant reduction of culture positivity in CSF ($p = 0.04$); the PCR positivity changed minimally. In blood samples, nonsignificant reduction of culture positivity and no difference in LA and PCR positivity was found. We did not find any statistically significant relationship between test results and clinical forms. The LA test can be therefore considered to be an auxiliary diagnostic method, rapid and easily practicable but less sensitive than PCR. It can be recommended especially for local laboratories where PCR is not available and the patient already received antibiotics before admission to the hospital.

Campbell H et al. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: Effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clinical and Vaccine Immunology*, 2010, 17: 840-847.

Meningococcal serogroup C conjugate (MCC) vaccines were licensed in the United Kingdom more than 10 years ago based on correlates of protection that had previously been established for serogroup C-containing polysaccharide vaccines by using the serum bactericidal antibody (SBA) assay. These correlates of protection were subsequently validated against postlicensure estimates of observed vaccine effectiveness up to 7 to 9 months after the administration of the MCC vaccine. Vaccine effectiveness was, however, shown to fall significantly more than 1 year after the administration of a 3-dose course in infancy. Despite this finding, the marked impact on serogroup C disease has been sustained, with the lowest recorded incidence (0.02 case per 100,000 population) in the 2008-2009 epidemiological year, mainly due to the indirect herd immunity effect of the vaccine in reducing carriage. Updated estimates of vaccine effectiveness through 30 June 2009 confirmed high short-term protection after vaccination in infancy, at 97% (95% confidence interval [CI], 91% to 99%), falling to 68% (95% CI, -63% to 90%) more than a year after vaccination. The observed vaccine effectiveness more than 12 months postvaccination was consistent with measured declining SBA levels, but confidence intervals were imprecise; vaccine effectiveness estimates were consistent with SBA titers of 1:4 or 1:8 as correlates of long-term protection after a primary course in infants. Modeling suggested that protection against carriage persists for at least 3 years and predicted the stabilization of serogroup C disease at low levels (fewer than 50 cases per year) up to 2015-2016.

Caron F et al. From tailor-made to ready-to-wear meningococcal B vaccines: longitudinal study of a clonal meningococcal B outbreak. *Lancet Infectious Diseases*, 2011, 11:455-463.

BACKGROUND: Outer-membrane-vesicle vaccines for meningococcal B outbreaks are complex and time consuming to develop. We studied the use of already available vaccine to control an outbreak caused by a genetically close strain.
METHODS: From 2006 to 2009, all individuals younger than 20 years living in the region of Normandy, France, in which an outbreak caused by a B:14:P1.7,16 strain occurred, were eligible to receive MenBvac, a Norwegian vaccine designed 20 years earlier against a strain sharing the same serosubtype (B:15:P1.7,16). The immunogenicity (in a randomly selected cohort of 400 children aged 1-5 years), safety, and epidemiological effect of the vaccination were assessed.
FINDINGS: 26,014 individuals were eligible to receive the vaccine. Shortage of vaccine production prompted start of the campaign in the highest incidence groups (1-5 years). 16,709 (64%) received a complete vaccination schedule of whom 13,589 (81%) received a 2+1 dose schedule (week 0, week 6, and month 8). At 6 weeks after the third dose, of 235 vaccinees for whom samples were available, 206 (88%) had a seroresponse, and 108 (56 %) of 193 had a seroresponse at 15 months. These results were similar to those described for tailor-made vaccines and their homologous strain. Only previously described adverse effects occurred. The incidence of B:14:P1.7,16 cases decreased significantly in the vaccine targeted population after the primary vaccination period (from 31·6 per 100,000 to 5·9 per 100,000; p=0·001).
INTERPRETATION: The ready-to-wear approach is reliable if epidemic and vaccine strains are genetically close. Other meningococcal B clonal outbreaks might benefit from this

strategy; and previously described outer-membrane-vesicle vaccines can be effective against various strains.

Choo S et al. Immunogenicity and reactogenicity of a group C meningococcal conjugate vaccine compared with a group A+C meningococcal polysaccharide vaccine in adolescents in a randomised observer-blind controlled trial. *Vaccine,* 2000,18:2686-2692.

This study evaluated the immunogenicity and reactogenicity of a group C meningococcal conjugate vaccine (MenC) compared with a group A+C meningococcal polysaccharide vaccine (MenPS) in healthy adolescents. Subjects were randomised to receive one dose of either MenC (n=92) or MenPS (n=90). Group C meningococcal IgG antibody concentrations and bactericidal titres were higher in the MenC group than the MenPS group at 1 month (22.8 U/ml vs 4.0 U/ml, p<0.001, and 87 vs 20, p<0.001, respectively) and 12 months (6.1 U/ml vs 3.0 U/ml, p<0.001, and 81.3 vs 20.2, p<0.001, respectively). No differences in post immunisation reaction rates were noted between the two vaccinated groups. This study demonstrated the safety and enhanced immunogenicity of the candidate meningococcal conjugate vaccine as compared with the licensed polysaccharide vaccine in adolescents.

Data to be published: Meningitis Vaccine Project. Protocol No. PsA-TT-004. Final version 1- 30 October 2007-Amendment 1- 15 May 2008- Amendment 2- 23 September 2010.

Data to be published: Meningitis Vaccine Project. Protocol No. PsA-TT-007. Final version 1- 20 October 2011-Amendment 1-8 December 2011.

Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet.* 2014; 383: 40–47.

BACKGROUND:A serogroup A meningococcal polysaccharide–tetanus toxoid conjugate vaccine (PsA–TT, MenAfriVac) was licensed in India in 2009, and pre-qualified by WHO in 2010, on the basis of its safety and immunogenicity. This vaccine is now being deployed across the African meningitis belt. We studied the effect of PsA–TT on meningococcal meningitis and carriage in Chad during a serogroup A meningococcal meningitis epidemic. METHODS:We obtained data for the incidence of meningitis before and after vaccination from national records between January, 2009, and June, 2012. In 2012, surveillance was enhanced in regions where vaccination with PsA–TT had been undertaken in 2011, and in one district where a reactive vaccination campaign in response to an outbreak of meningitis was undertaken. Meningococcal carriage was studied in an age-stratified sample of residents aged 1–29 years of a rural area roughly 13–15 and 2–4 months before and 4–6 months after vaccination. Meningococci obtained from cerebrospinal fluid or oropharyngeal swabs were characterised by conventional microbiological and molecular methods. FINDINGS:Roughly 1·8 million individuals aged 1–29 years received one dose of PsA–TT during a vaccination campaign in three regions of Chad in and around the capital N'Djamena during 10 days in December, 2011. The incidence of meningitis during the 2012 meningitis season in these three regions was 2·48 per 100 000 (57 cases in the 2·3 million population), whereas in regions without mass vaccination, incidence was 43·8 per 100 000 (3809 cases per 8·7 million population), a 94% difference in crude incidence (p<0·0001), and an incidence rate ratio of 0·096 (95% CI 0·046–0·198). Despite enhanced surveillance, no case of serogroup A meningococcal meningitis was reported in the three vaccinated regions. 32

serogroup A carriers were identified in 4278 age-stratified individuals (0·75%) living in a rural area near the capital 2–4 months before vaccination, whereas only one serogroup A meningococcus was isolated in 5001 people living in the same community 4–6 months after vaccination (adjusted odds ratio 0·019, 95% CI 0·002–0·138; p<0·0001).
INTERPRETATION:PSA–TT was highly effective at prevention of serogroup A invasive meningococcal disease and carriage in Chad. How long this protection will persist needs to be established.

De Greeff SC et al. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. *The Pediatric Infectious Disease Journal,* 2006, 25:79-80.

Routine vaccination with a single dose of conjugated meningococcal C vaccine at 14 months and a catch-up campaign have reduced the incidence of meningococcal C disease in the Netherlands. In contrast to countries where routine vaccination is given in infancy, vaccine failures were not reported. This suggests that one dose of conjugated vaccine in the second year of life might offer longer lasting protection against meningococcal C disease than 3 doses in infancy.

Dellicour S et al. Impact of meningococcal vaccination on pharyngeal carriage of meningococci. *Tropical Medicine and International Health*, 2007, 12:1409-14521.

OBJECTIVE: To investigate the effect of meningococcal vaccines on pharyngeal carriage of meningococci.
METHODS: Systematic review. MEDLINE and EMBASE were searched for relevant studies. Controlled trials and observational studies which used comparison groups or compared carriage rates before and after vaccination were included in the review.
RESULTS: Twenty-nine studies satisfied the inclusion criteria. Twenty-five studies reported the effect of a polysaccharide vaccine, one the effect of a serogroup C conjugate vaccine and three the impact of serogroup B outer-membrane vaccines on overall and/or serogroup-specific meningococcal carriage rates. Ten studies of meningococcal polysaccharide vaccines found reduced serogroup-specific carriage; seven of these focussed on high-risk groups and had a short follow-up period. Only one of five studies of civilian populations in Africa showed a significantly reduced carriage. Many studies had methodological shortcomings. The one study which assessed the effect of a meningococcal conjugate vaccine on carriage showed a significant impact. Three studies of serogroup B outer-membrane protein vaccines showed no effect on carriage.
CONCLUSIONS: A few well-designed trials of the impact of meningococcal vaccines on carriage have been undertaken. Such studies should be an essential component of the evaluation of new meningococcal vaccines, particularly those introduced to control epidemic meningococcal disease in Africa.

Goldblatt D et al. Natural and vaccine-induced immunity and immunologic memory to Neisseria meningitidis serogroup C in young adults. *Journal of Infectious Diseases, 2002,* 185: 397-400.

The immune response to polysaccharides and conjugate vaccines in adults is poorly understood. This study assessed meningococcal serogroup C responses after AC polysaccharide (MACP) and C conjugate (MCC) vaccine administration in young adults and explored immune memory by measuring antibody avidity. The geometric mean avidity indices

(GMAIs) measured 1 month after MACP vaccination were relatively high and failed to increase significantly in the 6 months before and after a second dose of MACP/MCC. Although the GMAI of naive adults increased immediately following MCC vaccination to 215.7 (95% confidence interval, 181.0–257.1), a level similar to that seen after MACP vaccination, no further maturation in the subsequent 6 months was seen. Antibody induced by polysaccharide antigens in adults is already of relatively high avidity (compared with that in infants and toddlers) and fails to mature further, probably because both MACP and MCC predominantly stimulate memory B cells.

Goldschneider I et al. Human immunity to the meningococcus. I. The role of humoral antibodies. *Journal of Experimental Medicine,* 1969, 129: 1307-1326.

Susceptibility to systemic meningococcal disease is related to a selective deficiency of humoral antibodies to pathogenic strains of meningococci. In a study of the age-specific incidence of meningococcal meningitis in the United States, it was found that the proportion of individuals with serum bactericidal activity to meningococci of serogroups A, B, and C was reciprocally related to the incidence of disease. The prevalence of bactericidal activity was highest at birth and among adults, and lowest in infants between 6 and 24 months of age. Sera from 51 of 54 prospective cases of meningococcal disease among military recruits were deficient in antibodies to homologous and heterologous strains of pathogenic meningococci as determined by serum bactericidal activity and indirect immunofluorescence. Such sera, however, could support the bactericidal activity of purified human gamma globulin (Cohn fraction II), and such individuals could respond immunologically to infection with meningococci. The implication is that susceptible persons are deficient in antimeningococcal antibodies because they have not received significant exposure to meningococcal antigens in the past. The fate of individuals who lack bactericidal antibodies to pathogenic meningococci was determined during an outbreak of group C meningitis among miHtaxy recruits. The incidence of disease was found to be primarily associated with the incidence of exposure of susceptibles to the pathogenic strains. Whereas 81.5 % of the presumed susceptibles acquired a meningococcal strain, only 24.1% acquired an organism similar to the prevalent disease-producing strains.

Goldschneider I et al. Human immunity to the meningococcus. II. The development of natural immunity. *Journal of Experimental Medicine,* 1969, 129: 1327-1348.

Results of the present study suggest that natural immunity to meningococcal disease is initiated, reinforced, and broadened by intermittent carriage of different strains of meningococci throughout life. In young adults, carriage of meningococci in the nasopharynx is an efficient process of immune sensitization. 92 % of carriers of serogroup B, C, or Bo meningococci were found to develop increased titers of serum bactericidal activity to their own meningococcal isolate, and 87 % developed bactericidal activity to heterologous strains of pathogenic meningococci. The rise in bactericidal titer occurred within 2 wk of onset of the carrier state, and was accompanied by an increase in titer of specific IgG, IgM, and IgA antibodies to meningococci. In early childhood, when few children have antibodies to pathogenic meningococci, active immunization seems to occur as a result of carriage of atypical, nonpathogenic strains. Immunity to systemic meningococcal infection among infants in the neonatal period is associated with the passive transfer of IgG antibodies from mother to fetus. The antigenic determinants which initiate the immune response to meningococci include the group-specific C polysaccharide, cross-reactlve antigens, and type-specific antigens.

Greenwood B M et al. Factors influencing susceptibility to meningococcal disease during an epidemic in the Gambia, West Africa. *The Journal of Infection,* 1987, 14:167-184.

A study was made of factors that influenced susceptibility to group A meningococcal disease during an epidemic that affected The Gambia, West Africa during the dry season of 1982-83. No explanations were found for the distribution of cases between villages or within affected villages. Socio-economic status, crowding, nutrition and previous exposure to meningococcal disease all appeared to be unimportant. Examination of serum samples obtained before the outbreak from a few children who subsequently became patients and from an equal number of age-matched controls from the same village showed a higher mean serum IgA value in children who became patients than in controls. There were not, however, any significant differences found in the concentrations of IgG, IgM, complement or meningococcal antibody between the two groups. Four children who developed culture-proven group A meningococcal disease had raised titres of bactericidal antibody to the epidemic strain 2-3 months before their illnesses. Our findings suggest that some important risk factors for group A meningococcal disease remain to be identified.

Greenwood B et al. Mortality from meningococcal disease during an epidemic in the Gambia, West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 1987, 81: 536-538.

Mortality from meningococcal disease was determined during an epidemic in a rural area of The Gambia with few medical resources, but where a system of registration of births and deaths had been established before the introduction of a primary health care programme. 33 deaths were recorded among 127 patients, a case mortality rate of 26%. 84% of deaths occurred within the first 24 h of illness and many patients died before they could reach any source of treatment. Previous studies, based on regional statistics or on hospital series, may have underestimated mortality from epidemic meningitis in Africa. Mortality from this infection will be reduced only if treatment can be made readily accessible to patients early in the course of their illness.

Greenwood BM et al. Prevention of secondary cases of meningococcal disease in household contacts by vaccination. *British medical journal*, 1978, 1:1317-1319.

Household contacts of patients with group A meningococcal infection were vaccinated with either meningococcal vaccine or tetanus toxoid. Five of the 523 subjects who received tetanus toxoid developed meningococcal meningitis and another four probably had meningococcal disease. Only one possible case of meningococcal infection occurred among 520 contacts vaccinated with meningococcal vaccine. Vaccination had no effect on nasopharyngeal carriage of meningococci. Vaccination of household contacts of patients with group A meningococcal infections is an effective way of using limited supplies of meningococcal vaccine, though its value would be limited in an epidemic. Secondary cases of meningococcal infection often occur within a few days of the index case, and, although vaccine alone seemed to provide adequate prophylaxis in these Nigerian subjects, additional chemoprophylaxis may be needed to cover this critical period.

Guerin P et al. Immunogenicity of fractional doses of tetravalent a/C/Y/W135 meningococcal polysaccharide vaccine: Results from a randomized non-inferiority controlled trial in Uganda. *PLoS Neglected Tropical Diseases*, 2008, 2: e342.

BACKGROUND: Neisseria meningitidis serogroup A is the main causative pathogen of meningitis epidemics in sub-Saharan Africa. In recent years, serogroup W135 has also been the cause of epidemics. Mass vaccination campaigns with polysaccharide vaccines are key elements in controlling these epidemics. Facing global vaccine shortage, we explored the use of fractional doses of a licensed A/C/Y/W135 polysaccharide meningococcal vaccine.
METHODS AND FINDINGS: We conducted a randomized, non-inferiority trial in 750 healthy volunteers 2-19 years old in Mbarara, Uganda, to compare the immune response of the full dose of the vaccine versus fractional doses (1/5 or 1/10). Safety and tolerability data were collected for all subjects during the 4 weeks following the injection. Pre- and post-vaccination sera were analyzed by measuring serum bactericidal activity (SBA) with baby rabbit complement. A responder was defined as a subject with a > or =4-fold increase in SBA against a target strain from each serogroup and SBA titer > or =128. For serogroup W135, 94% and 97% of the vaccinees in the 1/5- and 1/10-dose arms, respectively, were responders, versus 94% in the full-dose arm; for serogroup A, 92% and 88% were responders, respectively, versus 95%. Non-inferiority was demonstrated between the full dose and both fractional doses in SBA seroresponse against serogroups W135 and Y, in total population analysis. Non-inferiority was shown between the full and 1/5 doses for serogroup A in the population non-immune prior to vaccination. Non-inferiority was not shown for any of the fractionate doses for serogroup C. Safety and tolerability data were favourable, as observed in other studies.
CONCLUSIONS: While the advent of conjugate A vaccine is anticipated to largely contribute to control serogroup A outbreaks in Africa, the scale-up of its production will not cover the entire "Meningitis Belt" target population for at least the next 3 to 5 years. In view of the current shortage of meningococcal vaccines for Africa, the use of 1/5 fractional doses should be considered as an alternative in mass vaccination campaigns.

Harrison L H. Global epidemiology of meningococcal disease. *Vaccine,* 2009, 27 Suppl 2: B51-63.

As reviewed in this paper, meningococcal disease epidemiology varies substantially by geographic area and time. The disease can occur as sporadic cases, outbreaks, and large epidemics. Surveillance is crucial for understanding meningococcal disease epidemiology, as well as the need for and impact of vaccination. Despite limited data from some regions of the world and constant change, current meningococcal disease epidemiology can be summarized by region. By far the highest incidence of meningococcal disease occurs in the meningitis belt of sub-Saharan Africa. During epidemics, the incidence can approach 1000 per 100,000, or 1% of the population. Serogroup A has been the most important serogroup in this region. However, serogroup C disease has also occurred, as has serogroup X disease and, most recently, serogroup W-135 disease. In the Americas, the reported incidence of disease, in the range of 0.3-4 cases per 100,000 population, is much lower than in the meningitis belt. In addition, in some countries such as the United States, the incidence is at an historical low. The bulk of the disease in the Americas is caused by serogroups C and B, although serogroup Y causes a substantial proportion of infections in some countries and W-135 is becoming increasingly problematic as well. The majority of meningococcal disease in European countries, which ranges in incidence from 0.2 to 14 cases per 100,000, is caused by serogroup B strains, particularly in countries that have introduced serogroup C meningococcal conjugate vaccines. Serogroup B also predominates in Australia and New Zealand, in Australia because of the control of serogroup C disease through vaccination and in New Zealand because of a serogroup B epidemic. Based on limited data, most disease in

Asia is caused by serogroup A and C strains. Although this review summarizes the current status of meningococcal disease epidemiology, the dynamic nature of this disease requires ongoing surveillance both to provide data for vaccine formulation and vaccine policy and to monitor the impact of vaccines following introduction.

Halperin SA et al. Safety and immunogenicity of an investigational quadrivalent meningococcal conjugate vaccine after one or two doses given to infants and toddlers. *European Journal of Clininical Microbiology & Infectious Diseases,* 2010, 29:259-267.

With the emergence of multiple meningococcal serogroups in different geographic areas, broad vaccine protection from infancy is desirable. One hundred and seventy-five infants received either two doses of a meningococcal quadrivalent (A, C, W-135, Y) conjugate vaccine (MenACWY-CRM) at 6 and 12 months, one dose of MenACWY-CRM at 12 months, or MenC at 12 months and MenACWY-CRM at 18 months. Bactericidal antibody titers using human complement were measured before and 1 month after each dose. Injection-site reactions were reported by 22-45% of participants following MenACWY-CRM given at 6 or 12 months. Similar proportions of subjects had injection-site reactions following two doses of MenACWY-CRM (32-41%) or one dose of MenC (26-44%). The incidence of systemic adverse events was comparable between groups. After two doses of MenACWY-CRM, the percentages of participants reporting hSBA titers >or=8 were 100% for C, W-135, and Y, and 84% for A. Serogroup C titers were more than 10-fold higher after two doses of MenACWY-CRM than after one dose of MenC or MenACWY-CRM at 12 months. Serogroup C titers were comparable following a single dose of MenACWY-CRM or MenC at 12 months. MenACWY-CRM is well tolerated and immunogenic given at 12 months, or two doses at 6 and 12 months of age.

Halperin S et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2-10 years of age. *Vaccine,* 2010, 28:7865-7872.

BACKGROUND: Routine administration of quadrivalent meningococcal conjugate vaccine to adolescents and certain high risk groups is recommended in the United States and Canada. We compared the immunogenicity and safety of an investigational quadrivalent meningococcal vaccine conjugated to CRM-197 (MenACWY-CRM) with a licensed quadrivalent vaccine conjugated to diphtheria toxoid (MCV4) in children aged 2-10 years. METHODS: Eligible 2-5-year-olds were randomized 1:2:2 to receive either 2 doses of MenACWY-CRM, or 1 dose of MenACWY-CRM or MCV4; 6-10-year-olds were randomized 1:1 to receive a single dose of MenACWY-CRM or MCV4. The primary immunogenicity assessment was seroresponse separately for the two age cohorts 28 days following a single dose of MenACWY-CRM or MCV4. Noninferiority and superiority criteria were predefined. Solicited injection-site and systemic reactions were collected for the 7 days postvaccination. RESULTS: A total of 2907 children were randomized to receive study vaccine. MenACWY-CRM met statistical superiority criteria vs. MCV4 for groups W and Y and was noninferior for group C in both age strata. For group A, noninferiority criteria were not met; the group A seroresponse rates for MenACWY-CRM and MCV4, respectively were 72% (95% confidence interval 68-75%) and 77% (73-80%) in 2-5-year-olds and 77% (73-80%) and 83% (79-86%) in 6-10-year-olds. When the two age strata were combined (2-10-year-old children), MenACWY-CRM was noninferior to MCV4 for all four groups, and statistically superior for groups C, W, and Y. Safety parameters were similar across age cohorts and vaccines groups. CONCLUSIONS: MenACWY-CRM and MCV4 were immunogenic and well tolerated in

children aged 2-10 years. Seroresponse to MenACWY-CRM was statistically noninferior to MCV4 for all groups, and statistically superior for groups C, W, and Y.

Halperin SA et al. Simultaneous administration of meningococcal C conjugate vaccine and diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b conjugate vaccine in children: A randomized double-blind study. *Clinical and Investigative Medicine,* 2002, 25:243-251.

BACKGROUND: Meningococcal C disease can be life-threatening in infants, young children and adolescents. New conjugate vaccines are immunogenic in young infants and induce immunologic memory, so we should consider incorporating them into the routine childhood immunization program. The objective of this study was to measure the safety and immunogenicity of a meningococcal C conjugate vaccine when given with routine childhood vaccines.
METHODS: We carried out a randomized, double-blind, controlled clinical trial at children's hospitals in 3 Canadian cities. A convenience sample of 351 healthy 2-month-old infants was enrolled from the community and randomly allocated to receive either meningococcal C conjugate vaccine or the control (hepatitis B) vaccine. All participants received a concurrent injection of the combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b (DTaP-IPV-Hib) conjugate vaccine in the opposite limb. Participants were immunized at 2, 4, 6 and 15 months of age; adverse events were recorded after each dose. Serum bactericidal and ELISA meningococcal antibody levels in the participants were measured at 6, 7, 15 and 16 months of age; diphtheria, tetanus, H. influenzae type b, poliovirus and pertussis antibodies were measured at 7 months of age. A total of 323 (92%) participants completed all aspects of the study. The proportion of participants who suffered adverse events after each vaccine dose was the primary safety outcome. Geometric mean antibody titres and the proportion of participants with protective antibody levels after immunization were the primary immunologic outcomes.
RESULTS: After 2 doses of the meningococcal C conjugate vaccine 99% of participants achieved a protective (> or = 1:8) bactericidal meningococcal serogroup C antibody level, and after 3 doses this rate increased to 100%. Antibody levels to the concomitant vaccine antigens in the group receiving meningococcal C vaccine were similar to those in the control group except for higher antidiphtheria antibody titres ($p < 0.001$). Local injection site reactions (redness and induration) after the meningococcal conjugate vaccine were more frequent than after hepatitis B vaccine but less frequent than after the DTaP-IPV-Hib vaccine.
CONCLUSIONS: The meningococcal C conjugate vaccine can be safely and effectively administered at the same visit as the other vaccine antigens routinely given to infants in Canada.

Hassan-King MK, Wall RA, Greenwood BM. Meningococcal carriage, meningococcal disease and vaccination. *The Journal of Infection*, 1988, 16:55-59.

Group A meningococcal carriage rates were determined 6 months before and 6 and 18 months after a mass vaccination campaign with a combined group A and group C meningococcal polysaccharide vaccine in a rural area of The Gambia. During the first pre-vaccination survey, performed during an outbreak of meningococcal disease, the carriage rate was high (16%). The carriage rate remained high during a second survey made 6 months after a vaccination campaign that covered approximately 90% of the study population. A year later very few group A meningococcal carriers were found. Membrane protein patterns of isolates obtained before and after vaccination were similar. We conclude that vaccination had

little influence on the carriage rate of group A meningococci but that this was influenced by changes in herd immunity or by other unidentified factors.

International travel and health. Chapter 6. Vaccine-preventable diseases and vaccines. http://www.who.int/ith/chapters/ith2011chap6.pdf

Jolley KA et al. Molecular typing of meningococci: recommendations for target choice and nomenclature. *FEMS microbiology reviews*, 2007, 31: 89-96.

The diversity and dynamics of Neisseria meningitidis populations generate a requirement for high resolution, comprehensive, and portable typing schemes for meningococcal disease surveillance. Molecular approaches, specifically DNA amplification and sequencing, are the methods of choice for various reasons, including: their generic nature and portability, comprehensive coverage, and ready implementation to culture negative clinical specimens. The following target genes are recommended: (1) the variable regions of the antigen-encoding genes porA and fetA and, if additional resolution is required, the porB gene for rapid investigation of disease outbreaks and investigating the distribution of antigenic variants; (2) the seven multilocus sequence typing loci-these data are essential for the most effective national, and international management of meningococcal disease, as well as being invaluable in studies of meningococcal population biology and evolution. These targets have been employed extensively in reference laboratories throughout the world and validated protocols have been published. It is further recommended that a modified nomenclature be adopted of the form: serogroup: PorA type: FetA type: sequence type (clonal complex), thus: B: P1.19,15: F5-1: ST-33 (cc32).

Johnson DR. Menactra®. Infant Indication. ACIP Presentation Slides: June 2011 Meeting. http://www.cdc.gov/vaccines/recs/acip/slides-jun11.htm

Karachaliou A, Trotter C. Modelling long-term vaccination strategies with MenAfriVac® in the African meningitis belt: Executive summary prepared for SAGE, October 2014. Geneva, World Health Organization, 2014 (http://www.who.int/immunization/sage/meetings/2014/october/2_Modelling_MenAfriVac_SAGE_summary_30Sep2014.pdf?ua=1, accessed November 2014).

Khatami A et al. Persistence of immunity following a booster dose of *Haemophilus influenzae* type b-meningococcal serogroup C glycoconjugate vaccine: follow-up of a randomized controlled trial. *The Pediatric infectious disease journal*, 2011, 30:197-202.

BACKGROUND: Antibodies against Haemophilus influenzae type b (Hib) and serogroup C Neisseria meningitidis (MenC) wane after early infant immunization.
METHODS: Children previously immunized in a randomized controlled trial at ages 2, 3, and 4 months with DTPa-IPV-Hib and MenC-CRM197 (MenC-CRM group) or DTPa-IPV and Hib-MenC-TT (Hib-MenC-TT group) had blood samples drawn at 1 and 2 years following a booster dose of Hib-MenC-TT at 12 to 15 months of age. A blood sample was also drawn at the year 2 follow-up from a separately recruited age-matched control group who had not received a booster.
RESULTS: In 271 children at year 1, mean 14.6 months (range: 12-18 months) following the Hib-MenC-TT booster, MenC bactericidal titers above the protective threshold (rSBA ≥ 1:8) was demonstrated in 89.0% of the Hib-MenC-TT group and 69.5% of MenC-CRM participants. Antipolyribosylribitol phosphate Ig ≥ 1.0 μg/mL (Hib correlate for long-term

protection) was seen in 94.9% and 82.5%, respectively.In 379 participants (including 72 control children) at year 2 (age: 39-43 months, 25-31 months post Hib-MenC-TT) persistence of MenC antibodies was demonstrated in 67.1% of the Hib-MenC-TT group and 40.5% of the MenC-CRM group, compared with 44.1% of control group participants. Antipolyribosylribitol phosphate Ig ≥ 1.0 μg/mL was seen in 89.0%, 74.7%, and 38.9%, respectively.
CONCLUSIONS: A toddler Hib-MenC-TT booster helps sustain immunity against Hib to 3½ years of age. Persistence of MenC antibody is similar in children primed with MenC-CRM197 in infancy who receive a booster Hib-MenC-TT, to those who receive no booster. Persistence of MenC antibody is better when primed and boosted with Hib-MenC-TT.

Koch S et al. Meningococcal disease in travelers: Vaccination recommendations. *Journal of Travel Medicine,* 1994,1:4-7.

The object of the study was to determine the incidence rate of meningococcal disease in travelers originating in industrialized countries and visiting developing countries. Subjects were intercontinental travelers with meningococcal diseases acquired from 1986 to 1989. Health authorities in 108 countries were contacted; data obtained by postal survey were analyzed. The 56 replying health authorities reported 13 cases of meningococcal disease in tourist or business persons as well as 40 primary and 26 secondary cases in pilgrims in Mecca. The majority of cases were due to serogroup A. The case fatality rate in both groups of patients slightly exceeded 20%. Among the tourists and business persons, several patients had stayed in hotels; in several the onset of symptoms occurred during the flight home. The incidence rate per month of stay was estimated to be 0.4 per million travelers in this group, but 2000 per million in pilgrims to Mecca. Vaccination of pilgrims to Mecca is highly recommended, presently even compulsory. For the usual traveler to endemic countries, the risk of infection abroad seems not to exceed the one at home, thus vaccination may be limited to high-risk groups, such as trekkers.

Kshirsagar N et al. Safety, immunogenicity, and antibody persistence of a new meningococcal group A conjugate vaccine in healthy Indian adults. *Vaccine,* 2007, 25: Supplement 1: A101-107.

We performed a double-blind, randomized, controlled phase I study to assess safety, immunogenicity, and antibody persistence of the new meningococcal group A conjugate vaccine (PsA-TT) in healthy volunteers aged 18-35 years. Of the 74 male subjects enrolled, 24 received the PsA-TT vaccine (Group 1), 25 received the Meningococcal Polysaccharide Vaccine A+C, Pasteur, Lyon, France (Group 2), and 25 received the Tetanus Toxoid Vaccine Adsorbed, SIIL, Pune India (Group 3). No immediate reactions were observed. Local and systemic solicited reactions within 7 days post-vaccination and unsolicited adverse events (AEs) were mild and similar among the three groups and resolved without sequelae. No serious AEs were notified up to 1 year post-vaccination. Four weeks post-vaccination, a slightly higher proportion of Group 1 subjects had a four-fold increase in SBA titers compared to Group 2 subjects (83% versus 72%, $p>0.05$). SBA GMTs in Groups 2 and 3 were higher than in Group 3 ($p<0.05$). Serogroup A-specific IgG GMCs were significantly higher in Group 1 than in Groups 2 ($p<0.05$) and 3 ($p<0.05$). After 1 year SBA titers were significantly higher in Group 1 than in Group 2 ($p<0.05$). The new PsA-TT vaccine was shown to be safe, immunogenic, and able to elicit persistent functional antibody titers in adults. This opens the prospective for further development and licensure of this vaccine to eliminate epidemic meningitis in sub-Saharan Africa.

Larrauri A et al. Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. *Vaccine*, 2005, 23: 4097-4100.

This study describes the epidemiological impact of meningococcal C conjugate vaccine on age groups targeted by this vaccination programme in Spain, and estimates high short-term vaccine effectiveness values under field conditions in the 4 years following its introduction. Meningococcal C conjugate vaccine has led to a substantial reduction in incidence of meningococcal serogroup C disease in Spain among age groups targeted for intervention nationwide. Disease surveillance in the 4 years since the vaccine was introduced has enabled vaccine effectiveness (VE) to be estimated. The vaccine registered high short-term VE values but there has been some loss of VE with time. Four years after vaccination, vaccine protection levels exceeded 94% in cohorts immunised during the campaign. Among children vaccinated in routine childhood immunisation programmes, however, long-term VE loss was greater. Accordingly, there is a need for ongoing re-evaluation of VE and ascertainment of long-term vaccine protection. The findings reported would allow to decide on the advisability of revising current vaccination guidelines.

Macneil J R. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. *The Pediatric infectious disease journal,* 2011, 30: 451-455.

BACKGROUND: In January 2005, a quadrivalent meningococcal conjugate vaccine (MenACWYD) was licensed for use in the United States. The Advisory Committee on Immunization Practices recommends MenACWYD for all adolescents 11 to 18 years of age and others at increased risk for meningococcal disease.
METHODS: Reports of breakthrough meningococcal disease after vaccination with MenACWYD were collected. A simulation approach was used to estimate the expected number of cases in vaccinated persons.
RESULTS: Between 2005 and 2008, 14 breakthrough cases, including 3 deaths occurred. At a vaccine effectiveness (VE) of 90%, 7 breakthrough cases would be expected (range, 1-17); at VE of 85%, 11 cases (range, 2-30); at VE of 80%, 15 cases (range, 5-28); and at VE of 75%, 18 cases (range, 7-32) would be expected. The probability of the ≥14 observed cases occurring was 2.9% at VE of 90%, 29.3% at VE of 85%, 66.1% at VE of 80%, and 83.0% at VE of 75%.
CONCLUSIONS: This report provides an early estimate of MenACWYD effectiveness within 3 to 4 years after vaccination, and suggests that MenACWYD effectiveness is 80% to 85%, similar to the VE reported for meningococcal polysaccharide vaccine.

Maiden MC et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. *Journal of Infectious Diseases*, 2008,197:737-743.

BACKGROUND: In 1999, meningococcal serogroup C conjugate (MCC) vaccines were introduced in the United Kingdom for those under 19 years of age. The impact of this intervention on asymptomatic carriage of meningococci was investigated to establish whether serogroup replacement or protection by herd immunity occurred.
METHODS: Multicenter surveys of carriage were conducted during vaccine introduction and on 2 successive years, resulting in a total of 48,309 samples, from which 8599 meningococci were isolated and characterized by genotyping and phenotyping.
RESULTS: A reduction in serogroup C carriage (rate ratio, 0.19) was observed that lasted at least 2 years with no evidence of serogroup replacement. Vaccine efficacy against carriage was 75%, and vaccination had a disproportionate impact on the carriage of sequence type

(ST)-11 complex serogroup C meningococci that (rate ratio, 0.06); these meningococci also exhibited high rates of capsule expression.
CONCLUSIONS: The impact of vaccination with MCC vaccine on the prevalence of carriage of group C meningococci was consistent with herd immunity. The high impact on the carriage of ST-11 complex serogroup C could be attributed to high levels of capsule expression. High vaccine efficacy against disease in young children, who were not protected long-term by the schedule initially used, is attributed to the high vaccine efficacy against carriage in older age groups.

Maiden MC et al. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet*, 2002,359:1829-1831.

The UK was the first place to introduce meningococcal serogroup C conjugate (MCC) vaccines. From November, 1999, all people younger than 18 years, about 14 million individuals, were offered MCC immunisation. The uptake rate was more than 70% by November, 2000. We compared the carriage of meningococci in isolates we obtained from 14,064 students aged 15-17 years during vaccination in 1999, with those from 16,583 students of the same age surveyed 1 year later. Carriage of serogroup C meningococci was reduced by 66% (p=0.004). Our results show that MCC vaccines protect against carriage of meningococci that express serogroup C polysaccharide capsules.

MacLennan JM et al. Safety, immunogenicity, and induction of immunologic memory by a serogroup C meningococcal conjugate vaccine in infants: A randomized controlled trial. *JAMA, the journal of the American Medical Association,* 2000, 283:2795-2801.

CONTEXT: Neisseria meningitidis is a common cause of meningitis and septicemia in infants worldwide. Whether a meningococcal C conjugate vaccine protects infants against the serogroup C strain is unknown.
OBJECTIVES: To determine whether a meningococcal C conjugate vaccine is safe and immunogenic and induces immunologic memory in infants.
DESIGN: Single-center, double-blind, randomized controlled trial in 1995 and 1996.
SETTING: Community, Oxfordshire, England.
PARTICIPANTS: One hundred eighty-two healthy infants.
INTERVENTIONS: Participants were randomly assigned to receive vaccination with 0. 5-mL doses of 1 of 2 lots of meningococcal C conjugate vaccine (groups 1 and 2; n=60 in each group) or a hepatitis B control vaccine (group 3; n=62), administered with routine immunizations at 2, 3, and 4 months of age. Approximately half of each group received meningococcal C conjugate vaccine and half received plain meningococcal polysaccharide vaccine (MPS) at 12 months of age.
MAIN OUTCOME MEASURES:Serum antibodies to meningococcal C polysaccharide, assayed by enzyme-linked immunosorbent assay, and serum bactericidal activity (SBA), at 2, 3, 4, 5, 12, and 13 months of age; local and systemic reactions, recorded for 6 days after each vaccination, compared by intervention group.
RESULTS: Meningococcal C conjugate vaccine was well tolerated. After 3 doses, children in groups 1 and 2 achieved significantly higher meningococcal C IgG geometric mean concentrations (21 and 17 U/mL, respectively, vs 0.20 U/mL; P<.001) and SBA titers (629 and 420, respectively, vs 4.1; P<. 001) than controls. At 12 months, antibody concentrations had decreased in all groups but remained significantly higher in children vaccinated with meningococcal C conjugate vaccine (SBA, 24 and 16 in groups 1 and 2, respectively, vs 4.2 in group 3; P<.001). Following vaccination with MPS at 12 months of age, SBA in the

meningococcal C conjugate vaccine group was significantly higher than in controls (SBA, 789 vs 4.5; P<.001).
CONCLUSIONS: Our data indicate that meningococcal C conjugate vaccine is safe and immunogenic and results in immunologic memory when given with other routinely administered vaccines to infants at 2, 3, and 4 months of age.

Meeting of the Global Advisory Committee on Vaccine Safety, June 2011. Weekly Epidemiological Record, 2011, 86: 317–324.

Meningitis Vaccine Project. (http://www.meningvax.org/index.php, accessed December 2014)

Meningitis Vaccine Project and Partners. Results from the MenA conjugate vaccine (PsA-TT) randomized controlled trials in infants and young children: Executive summary. Geneva, World Health Organization, 2014 (http://www.who.int/immunization/sage/meetings/2014/october/3_MenA_vaccine_trials_SAGE_01Oct2014.pdf?ua=1, accessed November 2014).

Molesworth A M et al. Where is the meningitis belt? Defining an area at risk of epidemic meningitis in Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 2002, 96: 242-249.

Mapping an area at risk of epidemics of meningococcal meningitis in Africa has significant implications for their prevention and case treatment, through the targeted development of improved surveillance systems and control policies. Such an area was described using information obtained from published and unpublished reports of meningitis epidemics between 1980 and 1999 and cases of meningococcal disease reported by surveillance systems to WHO. The Sahel bore the greatest epidemic burden, with over two-thirds of documented outbreaks and high attack rates. In addition to those already in the Meningitis Belt, countries affected included Guinea-Bissau, Guinea, Côte d'Ivoire, Togo, the Central African Republic and Eritrea. Elsewhere epidemics were reported from a band of countries around the Rift Valley and Great Lakes regions extending as far south as Mozambique and from here west to Angola and Namibia in southern Africa. The cumulative pan-continental analysis provided evidence of an epidemic-susceptible area which extends beyond the region accepted as the Meningitis Belt and which, moreover, may be partially determined by the physical environment, as shown by a striking correspondence to the 300-1100-mm mean annual rainfall isohyets.

Ortega-Sanchez IR et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clinical Infectious Diseases,* 2008, 46:1-13.

BACKGROUND: In June 2005, the Advisory Committee on Immunization Practices recommended the newly licensed quadrivalent meningococcal conjugate vaccine for routine use among all US children aged 11 years. A 1-time catch-up vaccination campaign for children and adolescents aged 11-17 years, followed by routine annual immunization of each child aged 11 years, could generate immediate herd immunity benefits. The objective of our study was to analyze the cost-effectiveness of a catch-up vaccination campaign with quadrivalent meningococcal conjugate vaccine for children and adolescents aged 11-17 years.

METHODS: We built a probabilistic model of disease burden and economic impacts for a 10-year period with and without a program of adolescent catch-up meningococcal vaccination, followed by 9 years of routine immunization of children aged 11 years. We used US age- and serogroup-specific surveillance data on incidence and mortality. Assumptions related to the impact of herd immunity were drawn from experience with routine meningococcal vaccination in the United Kingdom. We estimated costs per case, deaths prevented, life-years saved, and quality-adjusted life-years saved.
RESULTS: With herd immunity, the catch-up and routine vaccination program for adolescents would prevent 8251 cases of meningococcal disease in a 10-year period (a 48% decrease). Excluding program costs, this catch-up and routine vaccination program would save US$551 million in direct costs and $920 million in indirect costs, including costs associated with permanent disability and premature death. At $83 per vaccinee, the catch-up vaccination would cost society approximately $223,000 per case averted, approximately $2.6 million per death prevented, approximately $127,000 per life-year saved, and approximately $88,000 per quality-adjusted life-year saved. Targeting counties with a high incidence of disease decreased the cost per life-year saved by two-thirds.
CONCLUSIONS: Although costly, catch-up and routine vaccination of adolescents can have a substantial impact on meningococcal disease burden. Because of herd immunity, catch-up and routine vaccination cost per life-year saved could be up to one-third less than that previously assessed for routine vaccination of children aged 11 years.

Pace P et al. A new combination *Haemophilus influenzae* type B and *Neisseria meningitidis* serogroup C-tetanus toxoid conjugate vaccine for primary immunization of infants. *The Pediatric infectious disease journal*, 2007, 26:1057-1059.

We conducted a phase 3 randomized controlled trial looking at the immunogenicity and safety of a novel combined Haemophilus influenzae type b and Neisseria meningitidis serogroup C tetanus toxoid conjugate vaccine, Hib-MenC-TT in a 2-, 3-, and 4-month primary infant immunization schedule. SBA MenC titers > or =1:8 and anti-PRP concentrations > or =0.15 microg/mL were measured in 99.2% and 100%, respectively, of the infants receiving Hib-MenC-TT.

Pace D et al. A novel combined Hib-MenC-TT glycoconjugate vaccine as a booster dose for toddlers: A Phase 3 open randomised controlled trial. *Archives of disease in childhood*, 2008, 93: 963-970.

OBJECTIVE: To study the immunogenicity and reactogenicity of a combined Haemophilus influenzae type b and Neisseria meningitidis serogroup C tetanus toxoid conjugate vaccine (Hib-MenC-TT) when administered as a booster dose in combination with a measles, mumps and rubella vaccine (MMR).
DESIGN: A phase 3 open randomised controlled trial.
SETTING: One centre in Oxford, UK and nine centres in Poland.
SUBJECTS: 12-15-month-old healthy children.
INTERVENTIONS: In the primary stage of the study 500 healthy 6-12-week-old infants were randomised in a 3:1 ratio to receive Hib-MenC-TT+DTPa-IPV or MenC-CRM197 vaccine+DTPa-IPV-Hib. In the booster stage, 476 participants (190 in the UK and 286 in Poland) were vaccinated with Hib-MenC-TT and MMR.
MAIN OUTCOME MEASURES: The proportion of children with protective serum antibody levels against MenC and Hib 6 weeks following a Hib-MenC-TT booster dose.
RESULTS: The co-primary objectives were met: the Hib-MenC-TT booster dose induced

protective antibody titres in children vaccinated with Hib-MenC-TT+DTPa-IPV or MenC-CRM197+DTPa-IPV-Hib at 2, 3 and 4 months of age. 94.8% (lower limit of (LL) 95% CI 92.4) of participants had rSBA-MenC >or=1:128 and 100% (LL 95% CI 99.2) achieved anti-PRP concentrations >or=1.0 microg/ml. The percentage of toddlers with a post boost rSBA-MenC of 1:128 was significantly higher after priming with Hib-MenC-TT (97.7%) than after MenC-CRM197 (86%) (difference: 11.7%; 95% CI 6.2 to 19.4).
CONCLUSION: The waning antibody titres against Hib and MenC following primary immunisation can be boosted to protective levels by administering the Hib-MenC-TT vaccine at 12-15 months of age, supporting the recent introduction of this vaccine in the UK immunisation schedule to sustain protection of children against Hib and MenC disease.

Patel MS. Australia's century of meningococcal disease: development and the changing ecology of an accidental pathogen. *The Medical journal of Australia*, 2007,186:136-141.

Trends in meningococcal disease (MD) over the 20th century in Australia, as in other industrialised countries, have been characterised by epidemics during the two World Wars, a transient rise in incidence in the 1950s followed by endemic disease, and in the 1980s the emergence of a sustained hypersporadic phase. Epidemics occur at times of social upheaval and among marginalised populations, and resolve when living conditions improve. Periodic serogroup A epidemics have been replaced since the 1950s by endemic disease caused mainly by serogroups B and C meningococci. The current hypersporadic plateau in Australia, as in other industrialised countries, is associated with the intercontinental spread of hypervirulent clones of meningococci. The conjugate serogroup C vaccine has reduced the incidence of MD and carriage rates of serogroup C meningococci. However, the vaccine is expensive and its long-term impact on the emergence of non-vaccine strains and on nasopharyngeal microecology is unknown. A rising incidence of MD should not be viewed as the action of a virulent microbe exploiting a vulnerable population, but as the emergence of an "accidental pathogen" from an evolving host-microbial ecology. While it is essential to monitor the impact of vaccines on this ecology, we must find ways that can optimise our coexistence with microbes.

Patel M et al. Polysaccharide vaccines for preventing serogroup A meningococcal meningitis. *Cochrane database of systematic reviews*, 2005: CD001093.

BACKGROUND: Randomised trials carried out over two decades ago showed that the polysaccharide vaccine prevented serogroup A meningococcal meningitis. Subsequent non-randomised studies, however, suggested significant variations in the age-specific duration of protection among young children.
OBJECTIVES: The aim of the review was to determine the effect of polysaccharide serogroup A vaccine for preventing serogroup A meningococcal meningitis. The specific objectives were to assess the age-specific effects of the vaccine, the effect of booster doses in children under five years of age, and the duration of protection in children and adults.
SEARCH STRATEGY: In 2004, the review was updated. The following databases were searched for records of new trials: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004); MEDLINE (January 1966 to November Week 1 2004); and EMBASE (January 1990 to September 2004).
SELECTION CRITERIA: The first stage of the review included randomised trials. The second stage included non- randomised studies that addressed specific outcomes not answered by the randomised trials.
DATA COLLECTION AND ANALYSIS: One reviewer assessed the methodological quality of

the randomised trials and two reviewers independently identified and assessed the non-randomised studies. Of the twelve eligible Randomized trials, four were excluded because of the high risk of bias in assessing vaccine efficacy. Data from the trials were pooled using the Exact method to assess vaccine efficacy at one, two and three years post vaccination. Of the 15 non-randomised studies, only two addressed the specific objectives not answered by the randomised trials but were assessed to be at high risk of bias.
MAIN RESULTS: The protective effect within the first year of vaccination was consistent across the randomised trials, and the summary vaccine efficacy was 95% (95% confidence interval (CI) 87% to 99%). Protection extended into the second and third year after vaccination but the results did not attain statistical significance. The vaccine was protective in Finnish children aged 3 months to five years. The latter was also the only trial that assessed the effect of a booster dose in children under two years of age but lacked power to yield statistically significant results. The vaccine was protective in one- to five-year old children in developing countries (Nigeria and Sudan) but the age-specific efficacy in strata between one and five years of age could not be determined.
AUTHORS' CONCLUSIONS: For the first year after vaccination, the polysaccharide serogroup A vaccine was strongly protective against serogroup A meningococcal meningitis in participants over five years of age. It was also protective beyond the first year after vaccination in this age group but the level of vaccine efficacy could not be determined with precision. Children aged one to five years in developing countries were also protected but the level of efficacy in this age group could not be determined. While the vaccine was strongly protective among children aged three months to five years in developed countries the level of efficacy across age strata within this age group could not be determined. The number of children aged under two years was too small to draw conclusions on the protective effect of a booster dose of vaccine.

Perrett K P et al. Antibody persistence after serogroup C meningococcal conjugate immunization of United Kingdom primary-school children in 1999-2000 and response to a booster: A phase 4 clinical trial. *Clinical and Vaccine Immunology,* 2010, 50: 1601-1610.

BACKGROUND:After immunization with serogroup C meningococcal (MenC) conjugate vaccine, antibody responses and vaccine effectiveness are sustained in adolescents, in contrast to rapid waning in young children. We investigated the persistence of serum bactericidal antibody (SBA) titers in children 6 years after immunization with MenC vaccine (primed between 2 months and 6 years of age). The response to a Haemophilus influenza type b–MenC conjugate (Hib-MenC) booster was also measured.
METHODS: A phase 4 clinical trial was conducted among 250 healthy 6–12-year-old children. SBA titers were measured before, 1 month after, and 1 year after Hib-MenC administration. The correlate of protection was an SBA titer of _8.
RESULTS: An SBA titer of _8 was observed in 61 (25% [95% confidence interval {CI}, 20%–30%]) of 244 participants (mean age, 9.1 years; mean interval since MenC immunization, 6.75 years). The proportion with an SBA titer of _8 and the SBA geometric mean titer increased with age, from 12% (95% CI, 4%–23%) to 48% (95% CI, 29%–67%) and from 2.90 (95% CI, 2.11–3.99) to 17.20 (95% CI, 6.80–43.5), respectively, from a mean age of 7.0 to 12.1 years. One month after the Hib-MenC booster, all participants had an SBA titer of _8, which was sustained in 99.6% at 1 year.
CONCLUSIONS:As a result of waning antibody, the majority of 6–12-year-old children in the United Kingdom have inadequate serological protection against MenC. The persistence of MenC immunity and the response to a Hib-MenC booster is dependent on age at priming. A

booster was highly effective in this cohort and could sustain population immunity against MenC disease.
TRIAL REGISTRATION: Current Controlled Trials (http://www.controlled-trials.com) identifier: ISRCTN72858898.

PsA-TT-004 In Meningitis Vaccine Project and Partners. *Results from the MenA conjugate vaccine (PsA-TT) randomized controlled trials in infants and young children: Executive summary*. Geneva, World Health Organization, 2014 (http://www.who.int/immunization/sage/meetings/2014/october/3_MenA_vaccine_trials_SAGE_01Oct2014.pdf?ua=1, accessed November 2014).

PsA-TT-007 In Meningitis Vaccine Project and Partners. *Results from the MenA conjugate vaccine (PsA-TT) randomized controlled trials in infants and young children: Executive summary*. Geneva, World Health Organization, 2014 (http://www.who.int/immunization/sage/meetings/2014/october/3_MenA_vaccine_trials_SAGE_01Oct2014.pdf?ua=1, accessed November 2014).

Ramakrishnan M et al. Sequelae due to bacterial *meningitis* among African children: a systematic literature review. *BMC Medicine,* 2009, 7:47.
BACKGROUND: African children have some of the highest rates of bacterial meningitis in the world. Bacterial meningitis in Africa is associated with high case fatality and frequent neuropsychological sequelae. The objective of this study is to present a comprehensive review of data on bacterial meningitis sequelae in children from the African continent.
METHODS: We conducted a systematic literature search to identify studies from Africa focusing on children aged between 1 month to 15 years with laboratory-confirmed bacterial meningitis. We extracted data on neuropsychological sequelae (hearing loss, vision loss, cognitive delay, speech/language disorder, behavioural problems, motor delay/impairment, and seizures) and mortality, by pathogen.
RESULTS: A total of 37 articles were included in the final analysis representing 21 African countries and 6,029 children with confirmed meningitis. In these studies, nearly one fifth of bacterial meningitis survivors experienced in-hospital sequelae (median = 18%, interquartile range (IQR) = 13% to 27%). About a quarter of children surviving pneumococcal meningitis and Haemophilus influenzae type b (Hib) meningitis had neuropsychological sequelae by the time of hospital discharge, a risk higher than in meningococcal meningitis cases (median = 7%). The highest in-hospital case fatality ratios observed were for pneumococcal meningitis (median = 35%) and Hib meningitis (median = 25%) compared to meningococcal meningitis (median = 4%). The 10 post-discharge studies of children surviving bacterial meningitis were of varying quality. In these studies, 10% of children followed-up post discharge died (range = 0% to 18%) and a quarter of survivors had neuropsychological sequelae (range = 3% to 47%) during an average follow-up period of 3 to 60 months.
CONCLUSION: Bacterial meningitis in Africa is associated with high mortality and risk of neuropsychological sequelae. Pneumococcal and Hib meningitis kill approximately one third of affected children and cause clinically evident sequelae in a quarter of survivors prior to hospital discharge. The three leading causes of bacterial meningitis are vaccine preventable, and routine use of conjugate vaccines could provide substantial health and economic benefits through the prevention of childhood meningitis cases, deaths and disability.

Ramsay M E et al. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet,* 2001, 357:195-196.

The UK was the first country to use meningococcal serogroup C conjugate (MCC) vaccines, which were licensed on the basis of immunogenicity and safety data but without a formal efficacy study. Increased surveillance during the first 9 months since introduction has shown that short-term efficacy of the MCC vaccine in England was 97% (95% CI 77-99) for teenagers and 92% (65-98) for toddlers. These early results confirm the superiority of MCC over plain C polysaccharide vaccines, which are ineffective in young children.

Reisinger K S et al. Quadrivalent Meningococcal Vaccination of Adults: Phase Iii Comparison of an Investigational Conjugate Vaccine, Menacwy-Crm, with the Licensed Vaccine, Menactra. *Clinical and Vaccine Immunology,* 2009, 16: 1810-1815.

Neisseria meningitidis is a leading cause of bacterial meningitis in the United States, with the highest case fatality rates reported for individuals > or = 15 years of age. This study compares the safety and immunogenicity of the Novartis Vaccines investigational quadrivalent meningococcal CRM(197) conjugate vaccine, MenACWY-CRM, to those of the licensed meningococcal conjugate vaccine, Menactra, when administered to healthy adults. In this phase III multicenter study, 1,359 adults 19 to 55 years of age were randomly assigned to one of four groups (1:1:1:1 ratio) to receive a single dose of one of three lots of MenACWY-CRM or a single dose of Menactra. Serum samples obtained at baseline and 1 month postvaccination were tested for serogroup-specific serum bactericidal activity using human complement (hSBA). The hSBA titers following vaccination with MenACWY-CRM and Menactra were compared in noninferiority and prespecified superiority analyses. Reactogenicity was similar in the MenACWY-CRM and Menactra groups, and neither vaccine was associated with a serious adverse event. When compared with Menactra, MenACWY-CRM met the superiority criteria for the proportions of recipients achieving a seroresponse against serogroups C, W-135, and Y and the proportion of subjects achieving postvaccination titers of > or = 1:8 for serogroups C and Y. MenACWY-CRM's immunogenicity was statistically noninferior (the lower limit of the two-sided 95% confidence interval was more than -10%) to that of Menactra for all four serogroups, with the postvaccination hSBA geometric mean titers being consistently higher for MenACWY-CRM than for Menactra. MenACWY-CRM is well tolerated in adults 19 to 55 years of age, with immune responses to each of the serogroups noninferior and, in some cases, statistically superior to those to Menactra.

Richmond P et al. Safety and immunogenicity of a new Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine in healthy adults. *Vaccine,* 1999,18:641-646.

We evaluated the safety and immunogenicity of a single dose of a new serogroup C O-deacetylated meningococcal polysaccharide-tetanus toxoid conjugate vaccine in 30 healthy adult volunteers. The vaccine was well tolerated with no serious adverse events and minimal local reactions and systemic symptoms. All subjects developed a fourfold or greater increase in serum bactericidal antibody (SBA) to serogroup C meningococcus. SBA geometric mean titre increased from 11 to 3649 ($p<0.001$). Serogroup C-specific IgG levels increased postvaccination from 0.65 to 17.02 microg/ml ($p<0.001$). Bactericidal titres pre- and postimmunisation showed significant correlation with serogroup C-specific IgG ($r(2)=0.693$). Antibody levels fell by 6 months postvaccination, however, meningococcal C IgG avidity increased indicating the successful induction of a T-cell-dependent antibody response. Conclusion: meningococcal C-tetanus toxoid conjugate vaccine is immunogenic and well tolerated in healthy adults.

Rosenstein N et al. Efficacy of meningococcal vaccine and barriers to vaccination. *JAMA: the journal of the American Medical Association,* 1998, 279:435-439.

CONTEXT: Use of the quadrivalent meningococcal vaccine for control of outbreaks has increased in recent years, but the efficacy of meningococcal vaccine during mass vaccination campaigns in US civilian populations has not been assessed.
OBJECTIVES: To evaluate the efficacy of the quadrivalent meningococcal vaccine against serogroup C meningococcal disease in a community outbreak setting and to evaluate potentially modifiable barriers to vaccination in an area with persistent meningococcal disease following immunization.
DESIGN: Matched case-control study of vaccine efficacy using cases of serogroup C meningococcal disease in persons eligible for vaccination during mass vaccination campaigns. Control patients were matched by neighborhood and age. The control group was used to identify possible barriers to vaccination.
SETTING: Gregg County, Texas, population 106076, from 1993 to 1995.
PARTICIPANTS: A total of 17 case patients with serogroup C meningococcal disease eligible for vaccine and 84 control patients.
MAIN OUTCOME MEASURES: Vaccine efficacy and risk factors associated with nonvaccination.
RESULTS: Vaccine efficacy among 2- to 29-year-olds was 85% (95% confidence interval, 27%-97%) and did not change in bivariate analyses with other risk factors that were significant in univariate analysis. Among control patients, older age was strongly associated with nonvaccination; vaccination rates for 2- to 4-year-olds, 5- to 18-year-olds, and 19- to 29-year-olds were 67%, 48%, and 20%, respectively (chi2 for linear trend, P=.01).
CONCLUSIONS: The meningococcal polysaccharide vaccine was effective against serogroup C meningococcal disease in this community outbreak. Although specific barriers to vaccination were not identified, older age was a risk factor for nonvaccination in the target population of 2- to 29-year-olds. In future outbreaks, emphasis should be placed on achieving high vaccination coverage, with special efforts to vaccinate young adults.

SAGE meeting of 6-9 Novemer 2007. Update on epidemiological situation and supply of meningococcal vaccine.
http://www.who.int/immunization/sage/previous_november2007/en/

Scott R D et al. Vaccinating first-year college students living in dormitories for meningococcal disease: An economic analysis. *American Journal of Preventive Medicine,* 2002, 23: 98-105.

BACKGROUND: Surveillance of meningococcal disease among U.S. college students found an elevated rate of this disease among first-year students living in dormitories.
OBJECTIVE: This study examines the economics of routinely vaccinating a cohort of 591,587 incoming first-year students who will live in dormitories for > or =1 years.
METHODS: A cost-benefit model (societal perspective) was constructed to measure the net present value (NPV) of various vaccination scenarios, as well as the cost/case and cost/death averted. Input values included hospitalization costs from $10,924 to $24,030 per hospitalization; immunization costs (vaccine plus administration costs) from $54 to $88 per vaccine; 30 nonfatal, vaccine-preventable cases over a 4-year period (includes 3 with sequelae); 3 premature deaths; value of human life from $1.2 million to $4.8 million; and long-run sequelae costs from $1298 to $14,600. Sensitivity analyses were also conducted on vaccine efficacy (80% to 90%); discount rate (0% to 5%); and coverage (60% to 100%).

RESULTS: The costs of vaccination outweighed the benefits gained with NPVs ranging from -$11 million to -$49 million. The net cost per case averted ranged from $0.6 million to $1.9 million. The net cost per death averted ranged from $7 million to $20 million. The break-even costs of vaccination (when NPV=$0) at 60% coverage ranged from $23 (90% vaccine efficacy) to $5 (80% efficacy).
CONCLUSIONS:The model showed that the vaccination program is not cost-saving. Key variables influencing the results were the low number of vaccine-preventable cases and the high cost of vaccination. However, from the perspective of students and parents, the cost of vaccination might be worth the real or perceived benefit of reducing the risk to an individual student of developing meningococcal disease.

Shepard C W et al. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. *Pediatrics, 2005,* 115: 1220-1232.

CONTEXT: The US Food and Drug Administration approved a meningococcal conjugate A/C/Y/W-135 vaccine (MCV-4) for use in persons aged 11 to 55 years in January, 2005; licensure for use in younger age groups is expected in 2 to 4 years.
OBJECTIVE: To evaluate and compare the projected health and economic impact of MCV-4 vaccination of US adolescents, toddlers, and infants.
DESIGN: Cost-effectiveness analysis from a societal perspective based on data from Active Bacterial Core Surveillance (ABCs) and other published and unpublished sources. Sensitivity analyses in which key input measures were varied over plausible ranges were performed.
SETTING AND PATIENTS: A hypothetical 2003 US population cohort of children 11 years of age and a 2003 US birth cohort.
INTERVENTIONS: Hypothetical routine vaccination of adolescents (1 dose at 11 years of age), toddlers (1 dose at 1 year of age), and infants (3 doses at 2, 4, and 6 months of age). Each vaccination scenario was compared with a "no-vaccination" scenario.
MAIN OUTCOME MEASURES: Meningococcal cases and deaths prevented, cost per case prevented, cost per life-year saved, and cost per quality-adjusted life-year saved.
RESULTS: Routine MCV-4 vaccination of US adolescents (11 years of age) would prevent 270 meningococcal cases and 36 deaths in the vaccinated cohort over 22 years, a decrease of 46% in the expected burden of disease. Before program costs are counted, adolescent vaccination would reduce direct disease costs by $18 million and decrease productivity losses by $50 million. At a cost per vaccination (average public-private price per dose plus administration fees) of $82.50, adolescent vaccination would cost society $633000 per meningococcal case prevented and $121000 per life-year saved. Key variables influencing results were disease incidence, case-fatality ratio, and cost per vaccination. The cost-effectiveness of toddler vaccination is essentially equivalent to adolescent vaccination, whereas infant vaccination would be much less cost-effective.
CONCLUSIONS: Routine MCV-4 vaccination of US children would reduce the burden of disease in vaccinated cohorts but at a relatively high net societal cost. The projected cost-effectiveness of adolescent vaccination approaches that of recently adopted childhood vaccines under conditions of above-average meningococcal disease incidence or at a lower cost per vaccination.

Southern J et al. Immunogenicity of a reduced schedule of meningococcal group C conjugate vaccine given concomitantly with the Prevenar and.Pediacel vaccines in healthy infants in the United Kingdom. *Clinical and Vaccine Immunolology, 2009,* 16:194-199.

This study investigated the use of two doses of three different meningococcal group C conjugate (MCC) vaccines when given for primary immunization with a seven-valent pneumococcal conjugate vaccine (PCV7) and Pediacel, a combination product containing five acellular pertussis components, diphtheria and tetanus toxoids, Haemophilus influenzae type b (Hib) conjugate, and inactivated-poliovirus vaccine. The immune response after a single dose of MCC is also presented. Infants were randomized to receive two doses of one of the MCC vaccines and PCV7 at 2 and 3 months or at 2 and 4 months of age. Meningococcal group C serum bactericidal antibody (SBA) geometric mean titers, Hib-polyribosylribitol phosphate (PRP) immunoglobulin G (IgG) geometric mean concentrations (GMCs), and diphtheria and tetanus antitoxin GMCs, together with the proportions of infants achieving putative protective levels, were determined. A total of 393 infants were recruited. Following the first dose of NeisVac-C (MCC conjugated to tetanus toxoid), 97% of infants achieved protective levels (SBA titer of >or=8), compared with 80% and 53%, respectively, for Menjugate and Meningitec (both of which are conjugated to CRM(197)). SBA responses to MCC vaccines were not significantly different when administered at 2 and 3 or 2 and 4 months of age. Following two doses of each MCC, 98 to 100% of infants achieved protective levels. Both PRP IgG and tetanus responses were significantly enhanced when Pediacel was coadministered with NeisVac-C. This study demonstrates that NeisVac-C and Menjugate generate good immunogenicity after the first dose at 2 months of age when coadministered with PCV7 and Pediacel and merit further investigation in single-dose priming strategies.
4. Southern J, Deane S, Ashton L, Borrow R, Goldblatt D, Andrews N, et al. Effects of prior polysaccharide vaccination on magnitude, duration, and quality of immune responses to and safety profile of a meningococcal serogroup C tetanus toxoid conjugate vaccination in adults. Clin Diagn Lab Immunol. 2004 Nov;11(6):1100-4.

Southern J et al. Effects of prior polysaccharide vaccination on magnitude, duration, and quality of immune responses to and safety profile of a meningococcal serogroup C tetanus toxoid conjugate vaccination in adults. *Clinical and Diagnostic Laboratory Immunology,* 2004, 11:1100-1104.

Extensive use of meningococcal AC polysaccharide (MACP) vaccines has raised concerns about induction of immunologic hyporesponsiveness to C polysaccharide. We investigated the immunogenicity and safety of a meningococcal C-tetanus conjugate (MCC-TT) vaccine in naive adults and prior MACP vaccinees. Laboratory staff (n = 113) were recruited; 73 were naive to meningococcal vaccination, and 40 had previously received > or =1 dose of MACP vaccine. Blood was taken prior to MCC-TT vaccination and 1 week, 1 month, and 6 months later. At each time point, proportions of subjects with serum bactericidal antibody (SBA) titers of > or =8 or > or =128 were similar (P > 0.46); >94% of subjects achieved titers of > or =128 at 1 month. However, the geometric mean titer (GMT) of SBA at 1 month was higher in the naive (1,757; 95% confidence interval [95% CI], 1,102 to 2,803) than in the previously vaccinated (662; 95% CI, 363 to 1,207) group (P = 0.02), and similarly at 6 months (P < 0.001). Conversely, geometric mean concentrations (GMCs) of serogroup C-specific immunoglobulin G (IgG) were significantly higher in the previously vaccinated group pre-MCC-TT and at 1 week; the groups were similar at 1 month, and there was some evidence that the GMC for the previously vaccinated group was higher at 6 months. Qualitative differences in antibodies between groups were demonstrated by using the SBA/IgG ratio, though avidity measures were similar for the two groups throughout the study. MCC-TT was well tolerated, with similar safety profiles in the two groups. Pain in the arm and headache were the most frequently reported events following vaccination. The study shows that MCC-

TT is safe and immunogenic in naive and previously MACP-vaccinated adults, though the magnitude and persistence of postvaccination SBA responses in the latter group were lower.

Sow S O et al. Immunogenicity and safety of a meningococcal a conjugate vaccine in Africans. *New England Journal of Medicine*, 2011, 364: 2293-2304.

BACKGROUND: Group A meningococci are the source of major epidemics of meningitis in Africa. An affordable, highly immunogenic meningococcal A conjugate vaccine is needed.
METHODS: We conducted two studies in Africa to evaluate a new MenA conjugate vaccine (PsA-TT). In study A, 601 children, 12 to 23 months of age, were randomly assigned to receive PsA-TT, a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (Haemophilus influenzae type b conjugate vaccine [Hib-TT]). Ten months later, these children underwent another round of randomization within each group to receive a full dose of PsA-TT, a one-fifth dose of PsACWY, or a full dose of Hib-TT, with 589 of the original participants receiving a booster dose. In study B, 900 subjects between 2 and 29 years of age were randomly assigned to receive PsA-TT or PsACWY. Safety and reactogenicity were evaluated, and immunogenicity was assessed by measuring the activity of group A serum bactericidal antibody (SBA) with rabbit complement and performing an IgG group A-specific enzyme-linked immunosorbent assay.
RESULTS:In study A, 96.0% of the subjects in the PsA-TT group and 63.7% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline; in study B, 78.2% of the subjects in the PsA-TT group and 46.2% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline. The geometric mean SBA titers in the PsA-TT groups in studies A and B were greater by factors of 16 and 3, respectively, than they were in the PsACWY groups ($P<0.001$). In study A, the PsA-TT group had higher antibody titers at week 40 than the PsACWY group and had obvious immunologic memory after receiving a polysaccharide booster vaccine. Safety profiles were similar across vaccine groups, although PsA-TT recipients were more likely than PsACWY recipients to have tenderness and induration at the vaccination site. Adverse events were consistent with age-specific morbidity in the study areas; no serious vaccine-related adverse events were reported.
CONCLUSIONS: The PsA-TT vaccine elicited a stronger response to group A antibody than the PsACWY vaccine. (Funded by the Meningitis Vaccine Project through a grant from the Bill and Melinda Gates Foundation; Controlled-Trials.com numbers, ISRCTN78147026 and ISRCTN87739946.).

Stefanelli P et al. First report of capsule replacement among electrophoretic type 37 *Neisseria meningitidis* strains in Italy." *Journal of Clinical Microbiology*, 2003, 41:5783-5786.

This report describes the C-to-B capsular switching in four Neisseria meningitidis strains belonging to the electrophoretic type 37 (ET-37) complex. In particular, one strain belonged to the new sequence type 1860, which was first detected in the year 2000 in Italy and is now frequently isolated. The presence of switched serogroup B strains deserves special attention if they prove as able to spread as their serogroup C progenitors belonging to the hypervirulent ET-37 complex.

Stephens D S. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium neisseria meningitidis. *Vaccine*, 2009, 27 (Suppl 2): B71-7.

For at least two hundred years, Neisseria meningitidis (the meningococcus), the cause of epidemic meningitis and sepsis, has inflicted rapid death, disability and fear on disparate human populations. The meningococcus is also recognized as a highly successful commensal organism exclusively found in humans. The evolution of N. meningitidis to an exclusive human commensal and to a sometimes fulminant and fatal pathogen represents an important case study in microbial pathogenesis. We review the general status of our knowledge of pathogenesis of meningococcal carriage, transmission and virulence behavior with particular emphasis on the relevance of research on this topic to vaccine development.

Technical Note: MenAfriVac vaccine campaigns in the African meningitis belt: Use of vaccine in pregnant and lactating women, 22 November 2010. Geneva, World Health Organization, 2010 (http://www.who.int/immunization/sage/4_WHO_Note_Vaccination__Pregnant_Women__during_MenA__conj_Campaigns_22Nov10_april_2011.pdf, Accessed November 2014).

Trotter CL et al. Meningococcal vaccines and herd immunity: Lessons learned from serogroup C conjugate vaccination programs. *Expert Review of Vaccines*, 2009, 8: 851-861.

Effective vaccines provide direct protection to immunized individuals, but may also provide benefits to unvaccinated individuals by reducing transmission and thereby lowering the risk of infection. Such herd immunity effects have been demonstrated following the introduction of meningococcal serogroup C conjugate (MCC) vaccines, with reductions in disease attack rates in unimmunized individuals and significantly lower serogroup C carriage attributable to the vaccine introduction. In the UK, targeting teenagers for immunization was crucial in maximizing indirect effects, as most meningococcal transmission occurs in this age group. Questions remain regarding the duration of herd protection and the most appropriate long-term immunization strategies. The magnitude of the herd effects following MCC vaccination was largely unanticipated, and has important consequences for the design and evaluation of new meningococcal vaccines.

Trotter CL et al. Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. *Medical decision making*, 2006, 26:38-47.

BACKGROUND: The meningococcal serogroup C conjugate (MCC) vaccination program has successfully reduced morbidity and mortality from serogroup C disease in England and Wales, owing to high short-term vaccine effectiveness and substantial herd immunity. The latter effect was not accounted for in the previous economic analysis of the MCC program.
METHODS: The authors applied a transmission dynamic model, which accounts for herd immunity, to reevaluate the cost-effectiveness of MCC vaccination. The direct and indirect benefits of the MCC vaccine strategy implemented in England and Wales were compared. The cost-effectiveness of alternative MCC vaccine strategies, including future changes to the current schedule, were evaluated.
RESULTS: The authors found that including herd immunity improved the average cost-effectiveness ratio in all cases, although the extent depended on the vaccine strategy considered. Incremental analysis showed that those strategies that offered 1 dose early in the 2nd year of life dominated strategies that offered 3 doses of vaccine in infancy and that catch-up vaccination up to the age of 18 years was also highly attractive. Furthermore, the authors

analyzed the effect of future changes to the routine vaccine schedule and predicted that shifting the age at routine vaccination from 2, 3, and 4 months (3 doses) to 12 months (1 dose) resulted in a net gain in the total number of cases prevented with only a few extra cases occurring in children under 1 year of age. This program dominated the current strategy. CONCLUSIONS: Models that do not include the indirect effects of vaccination will underestimate the impact of MCC vaccination and may lead to distorted decision making.

Trotter CL et al No evidence for capsule replacement following mass immunisation with meningococcal serogroup C conjugate vaccines in England and Wales. *Lancet Infectious Diseases*, 2006, 6: 616-617.
(No abstract)

Vicente D et al. Influence of two vaccination campaigns on genetic diversity of invasive *Neisseria meningitidis* isolates in Northern Spain (1997-2008). *PLoS One,* 2009, 4: e8501.

BACKGROUND:Neisseria meningitidis diversifies rapidly, due to its high recombination rates. The aim of this study was to analyze the possible impact of two vaccination campaigns (a once-off A/C polysaccharide vaccination campaign in people aged 18 months to 20 years old in 1997, and a meningococcal C conjugate vaccination campaign in children aged #6 years
old from 2000 to 2008) on diversification of the population of invasive isolates obtained between 1997 and 2008. All of the 461 available isolates were included (2, 319, 123, 11 and 6 belonging to serogroups A, B, C, Y and W-135, respectively).
METHODOLOGY/PRINCIPALFINDINGS: The isolates were analyzed for diversity using multilocus sequence typing, eBURST and the S.T.A.R.T.2 program. One hundred and seven sequence types (ST) and 20 clonal complexes were obtained. Five different STs (ST11, ST8, ST33, ST1163 and ST3496) included 56.4% of the isolates. With the exception of ST11, all other STs were associated with a specific serogroup. Epidemic circulation of serogroup C ST8 isolates was detected in 1997–1998, as well as epidemic circulation of ST11 isolates (serogroups B and C) in 2002–2004. The epidemic behavior of serogroup B ST11 (ST11_B:2a:P1.5) was similar, although with lesser intensity, to that of ST11 of serogroup C. Although clonality increased during epidemic years, the overall diversity of the meningococcal population did not increase throughout the 12 years of the study.
CONCLUSION: The overall diversity of the meningococcal population, measured by the frequency of STs and clonal complexes, numbers of alleles, polymorphic sites, and index of association, remained relatively constant throughout the study period, contradicting previous findings by other researchers.

Welte R et al. The role of economic evaluation in vaccine decision making: focus on meningococcal group C conjugate vaccine. *Pharmacoeconomics*, 2005, 23:855-874.

In recent years, several countries have experienced increases in the incidence of serogroup C meningococcal disease. It can be controlled with older polysaccharide vaccines and particularly the recently developed conjugate vaccines. For 21 developed countries, we investigated the role that economic evaluation played in the decision to introduce the conjugate vaccine into either the routine childhood vaccination schedule, as a mass vaccination 'catch-up' campaign or not at all. A literature review was performed and experts from these countries were contacted. For six countries, we identified published economic evaluations for meningococcal C conjugate vaccination. In four of them (Australia, Canada [Quebec], The Netherlands and the UK) the analyses were performed before a decision about the use of the conjugate vaccine was made. In all of these countries, the economic evaluation

offered guidance as to the most efficient way to add the conjugate vaccine to the routine infant immunisation schedule and, in three countries, this advice was adopted by decision makers. In Portugal and Switzerland, initial vaccination decisions were made without the economic evaluations that are influencing current decision making. Of the countries without economic evaluations, six implemented vaccination programmes. Overall, there was a positive correlation between the reported incidence of meningococcal C disease and (a) the decision to vaccinate and (b) performing an economic evaluation. All economic evaluations were modelling studies. The reported cost-effectiveness ratios were sensitive to the age of vaccination, the future meningococcal incidence, vaccine price and some methodological characteristics that varied widely between studies making direct comparisons difficult. In conclusion, in almost all countries where economic evaluations for meningococcal C conjugate vaccinations have been conducted, their results had an important role in the decision-making process. However, in most countries with strongly increasing meningococcal incidence, public health considerations took precedence. In order to improve the international comparability of such studies, firmer national and international modelling guidelines and better adherence to such guidelines seem necessary.

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Zalmanovici Trestioreanu A et al. Antibiotics for preventing meningococcal infections. *Cochrane Database Systemic Review*, 2011, CD004785.

BACKGROUND: Meningococcal disease is a contagious bacterial infection caused by Neisseria meningitidis (N. meningitidis). Household contacts have the highest risk of

contracting the disease during the first week of a case being detected. Prophylaxis is considered for close contacts of people with a meningococcal infection and populations with known high carriage rates.
OBJECTIVES: To study the effectiveness of different prophylactic treatment regimens.
SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 2) which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (January 1966 to May Week 3, 2011), EMBASE (1980 to May 2011) and LILACS (1982 to May 2011).
SELECTION CRITERIA: Randomised controlled trials (RCTs) or quasi-RCTs addressing the effectiveness of different antibiotics for: (a) prophylaxis against meningococcal disease; (b) eradication of N. meningitidis.
DATA COLLECTION AND ANALYSIS: Two review authors independently appraised the quality and extracted data from the included trials. We analysed dichotomous data by calculating the risk ratio (RR) and 95% confidence interval (CI) for each trial.
MAIN RESULTS: We included 24 studies; 19 including 2531 randomised participants and five including 4354 cluster-randomised participants. There were no cases of meningococcal disease during follow up in the trials, thus effectiveness regarding prevention of future disease cannot be directly assessed.Ciprofloxacin (RR 0.04; 95% CI 0.01 to 0.12), rifampin (rifampicin) (RR 0.17; 95% CI 0.13 to 0.24), minocycline (RR 0.28; 95% CI 0.21 to 0.37) and penicillin (RR 0.47; 95% CI 0.24 to 0.94) proved effective at eradicating N. meningitidis one week after treatment when compared with placebo. Rifampin (RR 0.20; 95% CI 0.14 to 0.29), ciprofloxacin (RR 0.03; 95% CI 0.00 to 0.42) and penicillin (RR 0.63; 95% CI 0.51 to 0.79) still proved effective at one to two weeks. Rifampin was effective compared to placebo up to four weeks after treatment but resistant isolates were seen following prophylactic treatment. No trials evaluated ceftriaxone against placebo but ceftriaxone was more effective than rifampin after one to two weeks of follow up (RR 5.93; 95% CI 1.22 to 28.68). Mild adverse events associated with treatment were observed.
AUTHORS' CONCLUSIONS: Using rifampin during an outbreak may lead to the circulation of resistant isolates. Use of ciprofloxacin, ceftriaxone or penicillin should be considered. All four agents were effective for up to two weeks follow up, though more trials comparing the effectiveness of these agents for eradicating N. meningitidis would provide important insights.