BIBIOGRAFIA sul VACCINI, MENINGITE ed altro (Inglese)

Studio pubblicato su PubMed sull'incidenza di casi di meningite asettica e porpora trombocitopenica idiopatica dopo la vaccinazione antimorbillo e antiparotite:
"Enhancing global vaccine pharmacovigilance: Proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination."
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Miglioramento della farmacovigilanza vaccinale globale: studio della prova di concetto sulla meningite asettica e sulla porpora trombocitopenica immune, dopo la vaccinazione.
By Perez-Vilar S, et al. Vaccino. 2018.

Estratto
Nuovi vaccini progettati per prevenire le malattie endemiche nei paesi a basso e medio reddito (LMIC) sono ora in fase di introduzione senza precedenti registrazioni di utilizzo in paesi con solidi sistemi di farmacovigilanza. Per affrontare questo deficit, il nostro obiettivo era dimostrare la fattibilità di una rete internazionale ospedaliera per la valutazione delle potenziali associazioni epidemiologiche tra eventi avversi gravi e rari e vaccini in qualsiasi contesto. Ciò è stato fatto attraverso una valutazione proof-of-concept del rischio di porpora trombocitopenica immune (ITP) e meningite asettica (AM) in seguito alla somministrazione della prima dose di vaccini contenenti il morbillo parotite utilizzando il metodo dell'intervallo di rischio autocontrollato nell'analisi primaria. L'Organizzazione Mondiale della Sanità (OMS) ha selezionato 26 siti sentinella (49 ospedali) distribuiti in 16 paesi delle sei regioni dell'OMS. Tasso di incidenza (IRR) di 5,0 (IC 95%: 2,5-9,7) per ITP dopo la prima dose di vaccinazioni contenenti morbillo e di 10,9 (IC 95%: 4,2-27,8) per AM dopo vaccinazioni contenenti parotite sono stati trovati. Le analisi specifiche del ceppo hanno mostrato un rischio ITP significativamente elevato per i vaccini contro il morbillo contenenti Schwarz (IRR: 20,7, IC 95%: 2,7-157,6), Edmonston-Zagreb (IRR: 11,1, IC 95%: 1,4-90,3) e Enders'Edmonston (IRR: 8.5; IC 95%: 1.9-38.1). È stato anche rilevato un rischio AM significativamente elevato per i vaccini contenenti ceppo di parotite di Leningrado-Zagabria (IRR: 10,8; IC 95%: 1,3-87,4). Questo studio di proof-of-concept ha mostrato, per la prima volta, che una rete internazionale ospedaliera per lo studio di eventi avversi da vaccino raro, utilizzando procedure standardizzate comuni e con elevata partecipazione di LMIC, sia fattibile, possa produrre risultati affidabili e abbia il potenziale per caratterizzare le differenze di rischio tra i ceppi vaccinali. Il completamento di questa rete con l'aggiunta di grandi ospedali di riferimento, in particolare da paesi tropicali, e l'implementazione sistematica di questo approccio da parte dell'OMS, dovrebbe consentire una rapida valutazione post-marketing dei segnali di sicurezza per eventi avversi gravi e rari per vaccini nuovi ed esistenti in tutte le impostazioni, inclusi i LMIC.

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Abstract
Przegl Epidemiol, 1998, 52(3), 227 - 35
{Meningococcal infections in Warsaw's district}; Dulny G et al.; The epidemiological situation of meningococcal meningitis in Warsaw's district in comparison to the situation in Poland in the years 1980-1997 in discussed . In September 1997, the local population of Zielonka--small city in Warsaw's district, was alarmed by two meningococcal septicaemia cases in girls attending to the same kindergarten . Anti-epidemic measures undertaken were described.

Epidemiol Mikrobiol Imunol, 1998 Dec, 47(4), 131 - 6

{Factors affecting Neisseria meningitidis and Neisseria lactamica carrier state}; Krizova P et al.; Invasive meningococcal diseases have become in the Czech Republic since 1993 a serious epidemiological and clinical problem due to a clonus which was not present previously: Neisseria meningitidis C:2a:P1.2,P1.5, ET-15/37 . In 1996 a trial was conducted focused on the problem how this altered epidemiological and clinical situation is reflected in carriership of Neisseria meningitidis and Neisseria lactamica in the healthy population . Two age groups were followed up which were most severely affected by the new clonus of the meningococcus: 15-19 years (410 subjects) and 1-4 years (116 subjects) . The trial was implemented in Olomouc where in 1993 the new epidemiological situation of the incidence of the invasive meningococcal disease was so serious that targeted vaccination was introduced . Of 116 children in the age group from 1-4 years in none Neisseria meningitidis was detected, in 9 Neisseria lactamica was found (7.7%) . On repeated examination of children with a positive cultivation of Neisseria lactamica after two weeks in none Neisseria meningitidis nor Neisseria lactamica were found . Of 410 subjects in the age group from 15-19 years in none Neisseria lactamica was detected and in 35 Neisseria meningitidis (8.5%) . Examinations were repeated after two weeks in 33 carriers: in 31 Neisseria meningitidis was again cultivated . Analysis of factors influencing carriership revealed in Neisseria lactamica two factors in young children which significantly promote this carriership: cold and close contact/kissing . A risk factor at the limit of significance are frequent respiratory diseases . In the carriership of Neisseria meningitidis in 15-19 year-old subjects six factors were revealed which promote carriership . A significant risk factor is close contact/kissing, the existence of partnership, participation in activities of the "disco" type, living in a town, flats in the centre of the town . Effort is a risk factor at the limit of significance.

Nurs Stand, 1998 Oct 21-27, 13(5), 49 - 52; quiz 55-6
Meningococcal disease; Bowler S; This article discusses meningococcal disease and outlines the role of the nurse in treating patients who may suffer from meningitis, one of the illnesses caused by meningococcal disease . It goes on to discuss how nurses can support the relatives of these patients.

Infect Immun, 1999 Feb, 67(2), 954 - 7
Role of lipopolysaccharide sialylation in serum resistance of serogroup B and C meningococcal disease isolates; Vogel U et al.; alpha-2,3-Sialyltransferase mutants of three genetically and phenotypically diverse Neisseria meningitidis strains were compared with regard to resistance to human serum and systemic spread in the infant rat . Lipopolysaccharide sialylation was found to be of minor importance for the resistance of serogroup B and C meningococcal disease isolates to complement attack.

Infect Immun, 1999 Feb, 67(2), 921 - 7
Antigen-specific T-cell responses in humans after intranasal immunization with a meningococcal serogroup B outer membrane vesicle vaccine; Oftung F et al.; We have studied the ability of the Norwegian group B meningococcal outer membrane vesicle (OMV) vaccine, when administered intranasally without adjuvant, to induce T-cell responses in humans . A group of 12 vaccinees was immunized with four doses of OMVs (250 micrograms of protein/dose) at weekly intervals, and a single booster dose was given 5 months later . In vitro T-cell proliferation in response to the OMV vaccine, purified PorA (class 1) protein, PorB (class 3) protein, and one unrelated control antigen (Mycobacterium bovis BCG) was measured by {3H}thymidine incorporation into peripheral blood mononuclear cells obtained from the vaccinees before and after the immunizations . The nasal OMV immunizations induced antigen-specific T-cell responses in the majority of the vaccinees when tested against OMVs (7 of 12) and the PorA antigen (11 of 12) . None of the vaccinees showed a vaccine-induced T-cell response to the PorB antigen after the initial four doses . Although some individuals responded to all the vaccine antigens after the booster dose, this response was not significant when the vaccinees were analyzed as a group . We have also demonstrated that the PorA antigen-specific T-cell responses correlated with anti-OMV immunoglobulin A (IgA) levels in nasal secretions, with anti-OMV IgG levels in serum, and with serum bactericidal activity . In conclusion, we have shown that it is possible to

induce antigen-specific T-cell responses in humans by intranasal administration of a meningococcal OMV vaccine without adjuvant.

Schweiz Med Wochenschr, 1998 Dec 12, 128(50), 1988 - 93
{Chronic meningococcemia--a rare, but characteristic disease picture}; Grob H et al.; Chronic meningococcaemia is a rare clinical manifestation of invasive infection by Neisseria meningitidis . The clinical signs and symptoms are recurrent fever, skin rash, arthralgias and headache . This constellation is rather typical and may enable the clinician to establish the diagnosis . The clinical diagnosis is confirmed by the growth of Neisseria meningitidis in the blood culture . In addition, the clinical course under antibiotic treatment leads to a dramatic improvement within 24-48 hours . Positive cultures may be obtained by needle aspiration or skin biopsy . There are a few reports on patients with deficiency of late complement components or immunoglobulin deficiency . We report on two patients with the typical findings of chronic meningococcaemia.

Crit Rev Microbiol, 1998, 24(4), 281 - 334
Genetic basis for biosynthesis, structure, and function of meningococcal lipooligosaccharide (endotoxin); Kahler CM et al.; The exclusive human pathogen Neisseria meningitidis expresses lipooligosaccharide (LOS), an endotoxin that is structurally distinct from the lipopolysaccharides (LPS) of enteric Gram-negative bacilli . Differences that appear to be biologically important occur in the composition and attachment of acyl chains to lipid A, phosphorylation patterns of lipid A, and the incorporation and phosphorylation of sugar residues in the LOS inner core . Further, unlike most enteric LPS, only two to five sugar residues are attached to the meningococcal LOS inner core, and there are no multiple repeating units of O-antigens . In contrast to Escherichia coli, where the LPS biosynthesis genes are organized as large operons, the meningococcal LOS biosynthesis genes are organized into small operons or are located individually in the chromosome . Some of these genetic loci in meningococci and gonococci display polymorphisms caused by localized chromosomal rearrangements . One mechanism of antigenic variation of meningococci LOS is the regulation of glycosyltransferase activity by slipped strand mispairing of homopolymeric tracts within the 5' end of the genes encoding these enzymes, resulting in the addition of different sugar residues to the LOS molecule . Meningococcal LOS is a critical virulence factor in N . meningitidis infections and is involved in many aspects of pathogenesis, including the colonization of the human nasopharynx, survival after bloodstream invasion, and the inflammation associated with the morbidity and mortality of meningococcemia and meningitis . Meningococcal LOS, which is a component of serogroup B meningococcal vaccines currently in clinical trials, has been proposed as a candidate for a new generation of meningococcal vaccines . The rapidly expanding knowledge of the genetic basis for biosynthesis, structure, and regulation of meningococcal LOS provides insights into unique endotoxin structures and the precise role of LOS in the pathogenesis of meningococcal disease.

Burns, 1998 Nov, 24(7), 680 - 2
Purpura fulminans localising to a recent burn injury; Wharton SM et al.; The development of progressive, severe skin changes (purpura fulminans) is a serious complication of septicaemia, particularly meningococcal septicaemia . Purpura fulminans almost invariably leads to some full thickness skin loss and may lead to limb amputation . The pathophysiology may involve microemboli, endotoxins and direct bacterial damage to the vessels . We describe a case of purpura fulminans, probably as a result of meningococcal septicaemia, localising to a recent, healed burn with complete resolution . We can find no other record of the skin manifestations of meningococcal septicaemia localising to a previous injury.

J Biol Chem, 1999 Jan 15, 274(3), 1495 - 501
Bactericidal antibody recognition of meningococcal PorA by induced fit . Comparison of liganded and unliganded Fab structures; van den Elsen J et al.; MN12H2 is a bactericidal antibody directed against outer

membrane protein PorA epitope P1.16 of Neisseria meningitidis . Binding of MN12H2 to PorA at the meningococcal surface activates the classical complement pathway resulting in bacterial lysis . We have determined the crystal structure of the unliganded MN12H2 Fab fragment in two different crystal forms and compared it with the structure of the Fab in complex with a P1.16-derived peptide . The unliganded Fabs have elbow bend angles of 155 degrees and 159 degrees, whereas the liganded Fab has a more closed elbow bend of 143 degrees . Substantial differences in quaternary and tertiary structure of the antigen binding site are observed between the unliganded and liganded MN12H2 Fab structures that can be attributed to peptide binding . The variable light and heavy chain interface of the liganded Fab is twisted by a 5 degrees rotation along an axis approximately perpendicular to the plane of the interface . Hypervariable loops H1, H2, and framework loop FR-H3 follow this rotation . The hypervariable loop H3 undergoes conformational changes but remains closely linked to hypervariable loop L1 . In contrast with the binding site expansion seen in other Fab-peptide structures, the MN12H2 binding site is narrowed upon peptide binding due to the formation of a "false floor" mediated by arginine residue 101 of the light chain . These results indicate that PorA epitope P1.16 of N . meningitidis is recognized by the complement-activating antibody MN12H2 through induced fit, allowing the formation of a highly complementary immune complex.

JAMA, 1998 Dec 23-30, 280(24), 2094 - 8
Serogroup Y meningococcal disease in Chicago, 1991-1997; Racoosin JA et al.; CONTEXT: In 1994, surveillance by the Chicago Department of Public Health detected a growing trend in the proportion of invasive meningococcal infections caused by serogroup Y . OBJECTIVE: To examine the emergence of serogroup Y meningococcal disease and compare its clinical characteristics with those of other meningococcal serogroups . DESIGN: Population-based retrospective review of surveillance records; medical record review and cohort analysis of serogroup Y vs non-serogroup Y case patients . SETTING: Chicago, III . PARTICIPANTS: City residents with Neisseria meningitidis isolated from a normally sterile site from January 1, 1991, through December 31, 1997; cohort analysis included those identified through March 31, 1996 . MAIN OUTCOME MEASURES: Serogroup-specific incidence, demographics, and clinical outcomes . RESULTS: We identified 214 case patients; 53 (25%) had serogroup Y . The attack rate of serogroup Y meningococcal disease increased from 0.04 cases per 100000 in 1991 to a peak of 0.82 cases per 100000 in 1995 and subsequently decreased to 0.26 cases per 100000 and 0.34 cases per 100000 in 1996 and 1997, respectively . Compared with patients infected by other serogroups, patients with serogroup Y were older (median age, 16 years vs 1 year; P = .001) and more likely to have a chronic underlying illness (prevalence ratio, 2.3; 95% confidence interval, 1.2-4.4) . Outcome did not differ significantly between the 2 groups . Multilocus enzyme electrophoresis typing of isolates from 19 case patients identified 5 different types . We found no clustering among the enzyme types by age, race/ethnicity, community area, or time . CONCLUSIONS: Serogroup Y emerged as the most frequent cause of meningococcal disease in Chicago in 1995 and accounted for a substantial proportion of cases in 1996 and 1997 . Current data suggest that the magnitude of serogroup Y meningococcal disease is sufficient for vaccine developers to incorporate serogroup Y into new vaccines.

Intern Med, 1998 Nov, 37(11), 990 - 4
Adrenal hemorrhage associated with Klebsiella oxytoca bacteremia; Hori K et al.; Septic adrenal hemorrhage is classically caused by meningococcemia . An autopsied case is presented of a 45-year-old man with adrenal hemorrhage due to Klebsiella oxytoca bacteremia following placement of a central venous catheter . He died 5 hours after developing disseminated intravascular coagulation (DIC) . The bacterial entry site may have been the catheter . The cause of death was considered to be pulmonary edema due to bacteremia rather than adrenal insufficiency due to hemorrhage . Septic adrenal hemorrhage should be recognized as a subtype of sepsis rather than adrenal insufficiency, and may be caused in conditions of severe sepsis with DIC, independent of the microorganic variety.

Eur J Clin Microbiol Infect Dis, 1998 Oct, 17(10), 690 - 4
Trend in incidence and case fatality of meningococcal disease over 16 years in Northern Denmark; Sorensen HT et al.; The incidence and case fatality rates of meningococcal disease were assessed in the county of Northern Jutland, Denmark, during the 16-year period from 1980 to 1995 . A total of 320 patients were identified from the Meningococcal Research Database, which comprises information from the following sources: (i) the Department of Public Health, to whom notification of meningococcal disease is obligatory; (ii) the Regional Hospital Discharge Registry; and (iii) the register of the regional department of clinical microbiology . In order to assess prognostic indicators assessable at admission, information was collected for each patient from hospital records regarding contacts, symptoms and signs on arrival, laboratory data, and course of disease . The mean incidence was 4.3 cases per 100000 persons per year (range, 2.7-7.7) . The incidence increased slightly during the period studied . Overall, the case fatality rate was 9.7%, with a significant rise occurring during the period (P=0.016) and a peak occurring in 1992 . Advanced age (> or = 50 years), seizures, impaired consciousness, and skin bleeding on arrival at hospital were predictors of death.

Infect Immun, 1999 Jan, 67(1), 113 - 9
Immunogenicity of intranasally administered meningococcal native outer membrane vesicles in mice; Saunders NB et al.; Colonization of the human nasopharyngeal region by Neisseria meningitidis is believed to lead to natural immunity . Although the presence of bactericidal antibody in serum has been correlated with immunity to meningococcal disease, mucosal immunity at the portal of entry may also play an important role . This study was undertaken to examine in mice the possibility of safely using native outer membrane vesicles (NOMV) not exposed to detergent as an intranasal (i.n.) vaccine . The mucosal and systemic responses of mice to intranasal and intraperitoneal (i.p.) vaccination with NOMV were compared over a range of doses from 0.1 to 20 microgram . Intranasal vaccination of mice with NOMV induced a strong systemic bactericidal antibody response, as well as a strong local immunoglobulin A immune response in the lung as determined by assay of lung lavage fluid by enzyme-linked immunosorbent assay and lung antibody secreting cells by enzyme-linked immunospot assay . However, 8- to 10-fold-higher doses of NOMV were required i.n . compared to i.p . to elicit an equivalent bactericidal antibody response in serum . Some NOMV vaccine was aspirated into the lungs of mice during i.n . immunization and resulted in an acute inflammatory response that peaked at 1 to 2 days postimmunization and was cleared by day 7 . These results indicate that i.n . delivery of meningococcal NOMV in mice is highly effective in eliciting the production of both a mucosal immune response and a systemic bactericidal antibody response.

Hum Genet, 1998 Oct, 103(4), 506 - 12
The molecular basis of C6 deficiency in the western Cape, South Africa; Hobart MJ et al.; Deficiency of the sixth component of human complement (C6) has been reported in a number of families from the western Cape, South Africa . Meningococcal disease is endemic in the Cape and almost all pedigrees of total C6 deficiency (C6Q0) have been ascertained because of recurrent disease . We have sequenced the expressed exons of the C6 gene from selected cases and have found three molecular defects leading to total deficiency: 879delG, which is the common defect in the Cape and hitherto unreported, and 1195delC and 1936delG, which have been previously reported in African-Americans . We also show that the 879delG and 1195delC defects are associated with characteristic C6/C7 region DNA marker haplotypes, although small variations were observed . The 1936delG defect was observed only once in the Cape, but its associated haplotype could be deduced . The data from the haplotypes indicate that these three molecular defects account for the defects in all the 38 unrelated C6Q0 individuals we have studied from the Cape . We have also observed the 879delG defect in two Dutch C6-deficient kindreds, but the 879delG defect in the Cape probably did not come from The Netherlands.

Scott Med J . 1998 Oct;43(5):148.
Neisseria meningitidis W135 pneumonia with sepicaemia in a nonogenarian; Cadwgan AM et al.; Neisseria

meningitidis infection is generally considered a disease of children or young adults, classically presenting as meningitis or sepicaemia . This infection is rare but recognised in the elderly . We present the case of a nonogenarian with meningococcal pneumonia and sinusitis with bacteraemia caused by N.meningitidis W135 a rare serogroup . We therefore thought this unusual situation of interest and worthwhile reporting.

Arch Pediatr, 1998 Nov, 5(11), 1232 - 5
{Chronic meningococcemia: 3 cases in the immunocompetent child}; Grouteau E et al.; Chronic meningococcemia is a part of extra meningeal manifestations of meningococcal disease . Its diagnosis can be difficult because of lack of sensitivity of blood cultures . CASE REPORT: Three cases, concerning immunocompetent children, respectively aged of 14, 10 and 4 years are reported . The clinical course was characterized by recurrent fever, inflammatory joint manifestations and diffuse maculopapules secondary centered by petechiae . Microbiological findings revealed in one case a positive throat culture and presence of meningococcal soluble antigens in blood and urine . In the other two cases, diagnosis was done after done after positive blood culture at the 7th, and 13th days of course . CONCLUSION: The diagnosis should be considered in any children with a prolonged, recurrent fever and cutaneous and joint manifestations even if blood cultures remain negative . The response to therapy by usual antimeningococcal antibiotics is dramatic and curative while a prolonged untreated course may be complicated by metastatic infection.

Ann Med Interne (Paris), 1998 Oct, 149(6), 332 - 9
{Vaccinations of the traveller}; Marchou B et al.; Travelers' immunization has 2 aims: for the traveler, to prevent the risk of contracting an endemic disease during his stay abroad; for the community to prevent the risk of importing an infectious agent yet unknown in the country . Travelling offers an opportunity to update routine immunizations: tetanus, diphtheria, poliomyelitis, hepatitis B; for young people: measles and rubella; for elderly people: influenza . Two vaccinations are compulsory: yellow fever for travelers to tropical Africa and Amazonian forest; meningococcus A + C for Mecca pilgrims . Other vaccines are recommended for travelers to specific areas: typhoid fever, hepatitis A, cholera in countries with poor hygiene; rabies for exposed travelers (expatriates, trekkers...); Japanese encephalitis for persons spending a month or longer in rural agricultural areas during the monsoon season; tickborne encephalitis for persons visiting forested areas of central Europe from may to september . Yet, most of travelers' diseases such as malaria cannot be prevented by vaccination and appropriate preventive measures (chemoprophylaxis and protection against insects) should be taken.

FEMS Microbiol Lett, 1998 Dec 1, 169(1), 171 - 7
Both the full-length and the N-terminal domain of the meningococcal transferrin-binding protein B discriminate between human iron-loaded and apo-transferrin; Renauld-Mongenie G et al.; We have readdressed the ability of the transferrin-binding protein B (TbpB) from Neisseria meningitidis to discriminate between the iron-loaded and the iron-free human transferrin (hTf) by using the BIAcore technology, a powerful experimental technique for the observation of direct interactions between a receptor and its ligands, without the use of labels . Recombinant full-length TbpB from five N . meningitidis strains were produced and purified from Escherichia coli as fusion proteins . They showed a preference for the binding to iron-loaded hTf . As for the full-length molecule, we have demonstrated that the minimal N-terminal hTf binding domain of meningococcal TbpB from B16B6 and M982 strains was able to discriminate between both hTf forms.

Commun Dis Rep CDR Suppl, 1998 Nov, 8(5), S1 - 12
PHLS overview of communicable diseases 1997: results of a priority setting exercise; Rushdy A et al.; In early 1997, the PHLS Overview of Communicable Diseases (OVCD) Committee carried out a consultation exercise to inform the development of PHLS priorities in communicable diseases for the years 1997 to 1999 . The views of PHLS senior staff and scientific committees and consultants in communicable disease control in

district health authorities were sought by postal questionnaire, and several organisations of health professionals were asked for their views on the initial findings . The main findings of the exercise are summarised in three areas of priority . Priority 1 diseases--those of major importance to public health--included food poisoning, meningitis, tuberculosis, sexually transmitted diseases, vaccine preventable diseases, hospital acquired infections, and antimicrobial resistance . Priority 2 diseases--those of moderate importance to public health--included respiratory syncytial virus and varicella zoster virus infections and emerging problems such as travel associated infections . Priority 3 diseases included those whose prevalence is declining as a result of public health action, such as listeriosis, and diseases of low prevalence and/or associated morbidity . The exercise identified four areas of possible future work for the PHLS: activities in prion diseases, helping to tackle inequalities in health, taking a more active approach to documenting the socioeconomic burden of disease, and engaging more with those consulted . The PHLS has used the results of the priority setting exercise to guide major programme initiatives in tuberculosis, measles, mumps, and rubella, meningococcal and pneumococcal diseases, and in antibiotic resistance . In addition, they have helped to shape agenda in service delivery and research in hospital acquired infections, sexually transmitted diseases, and gastrointestinal diseases . This exercise of engaging corporately with key professionals in communicable disease has paved the way for a wider engagement with stakeholders in the setting of future priorities.

Eur J Emerg Med, 1998 Jun, 5(2), 225 - 30
Evaluation of scoring systems in acute meningococcaemia; Hachimi-Idrissi S et al.; Patients expected to develop life-threatening complications in acute meningococcal infections require early recognition and appropriate monitoring . Different prognostic scoring systems have been developed . Three of them, chosen according to their bedside availability, were compared with our clinical observations . Twenty consecutive cases of proven meningococcal infection were admitted to the paediatric intensive care unit (PICU) of the Free University of Brussels (AZ-VUB) . Biological and clinical features required for prognostic scoring were evaluated as soon as possible after admission . Glasgow meningococcal sepsis prognostic score (GMSPS), Neisseria sepsis index (NESI) and Algren criteria were retrospectively calculated and evaluated for their prognostic significance . Neisseria meningitidis was cultured from blood and cerebrospinal fluid in 11 patients and from blood in only nine patients . The age of the patients was between 1 and 15 years (mean 4.1 years) . All patients received the same therapy on admission . Four patients died with a multiorgan failure within 18 hours . The three scoring systems in these four patients predicted death . Overall, the GMSPS score, the NESI score and the Algren criteria predicted death in respectively 10, nine and five patients . Death was falsely predicted in six patients by the GMSPS score, in five patients by the NESI score and in one patient by the Algren criteria . The Algren criteria predicted the severity of the clinical process more accurately than did the GMSPS and NESI scores . However, such predictability should be cautiously used even when 100% mortality is predicted . It might be used in decision-making in regard to the following issues: patient transfer to tertiary centres and mode of transportation, monitoring of patients in intensive care units, early insertion of invasive cardiovascular monitoring catheters and consideration of new or even experimental therapy . However, one should be extremely cautious of taking any therapeutically or ethical decision on the basis of one or more of the described scoring system, since we showed the lack of precision concerning the outcome of paediatric patients with meningococcaemia.

Microbiology, 1998 Nov, 144 (Pt 11), 3027 - 37
Immunization with recombinant class 1 outer-membrane protein from Neisseria meningitidis: influence of liposomes and adjuvants on antibody avidity, recognition of native protein and the induction of a bactericidal immune response against meningococci; Christodoulides M et al.; The porA gene from Neisseria meningitidis was cloned into the pRSETA vector and recombinant class 1 outer-membrane protein expressed at high levels in Escherichia coli . The protein was readily purified by affinity chromatography on a Ni2+ matrix and used for immunization of mice with conventional Al(OH)3 adjuvant, with experimental

adjuvants which have the potential for human use, and with liposomes . The resulting sera were analysed for the magnitude, subclass distribution and antigenic specificity of the immune response . In addition, surface plasmon resonance (SPR) was used to quantify antibody avidity by analysis of the kinetics of binding to native class 1 protein . Immunization with conventional and experimental adjuvants induced antibodies of low avidity that did not recognize native class 1 protein . In contrast, immunization with recombinant protein in liposomes induced antibodies of high avidity which recognized native class 1 protein, as measured by their ability to label meningococcal cells in immunofluorescence assays and to inhibit the binding of a protective mAb . These properties were associated with the presence in sera of high levels of antibodies with the ability to induce complement-mediated killing of meningococci . These data show that liposomes containing recombinant class 1 protein represent a potential basis of future vaccines, of defined composition, designed for the prevention of group B meningococcal infections.

Cytometry, 1998 Dec 1, 33(4), 406 - 13
Flow cytometric quantitation of human opsonin-dependent phagocytosis and oxidative burst responses to meningococcal antigens; Lehmann AK et al.; A one-step flow cytometric (FCM) assay has been developed to quantify both opsonin- and antigen-dependent phagocytosis and intraphagocyte oxidative burst responses . Meningococcal outer membrane structures (OMV) were adsorbed to fluorescent polystyrene beads, opsonized with serum, and exposed to leukocytes . FCM parameters of phagocytosis were evaluated in combinations with oxidative burst indicators . Rhodamine-123 was the most sensitive indicator and was compatible with quantitation of phagocytosis . The phagocytosis and oxidative burst responses induced by OMV beads were dependent on both antigens and opsonins . Increased human opsonic responses against OMV were induced during clinical meningococcal disease . A dissociation was noted between phagocytosis and oxidative burst in individual cells, indicating that functional opsonins against OMV components may differ in their ability to stimulate phagocytosis and oxidative burst responses . The method facilitates evaluation of purified bacterial structures as mediators of opsonin-dependent phagocytosis and intracellular oxidative microbicidal mechanisms, which is of interest in the complex process of selecting bacterial antigens as constituents of certain vaccines.

Clin Exp Immunol, 1998 Dec, 114(3), 362 - 9
Protection against meningococcal serogroup ACYW disease in complement-deficient individuals vaccinated with the tetravalent meningococcal capsular polysaccharide vaccine; Fijen CA et al.; Individuals with properdin, C3 or late complement component deficiency (LCCD) frequently develop meningococcal disease . Vaccination of these persons has been recommended, although reports on efficacy are scarce and not conclusive . We immunized 53 complement-deficient persons, of whom 19 had properdin deficiency, seven a C3 deficiency syndrome and 27 had LCCD with the tetravalent (ACYW) meningococcal capsular polysaccharide vaccine . Serological studies were performed in 43 of them . As controls 25 non-complement-deficient relatives of the complement-deficient vaccinees and 21 healthy non-related controls were vaccinated . Post-vaccination, complement-deficient individuals and controls developed a significant immunoglobulin-specific antibody response to capsular polysaccharides group A, C, Y, W135, but a great individual variation was noticed . Also, the proportion of vaccinees of the various vaccinated groups with a significant increase in bactericidal titre (assayed with heterologous complement) was similar . Opsonization of meningococci A and W135 with sera of the 20 LCCD individuals yielded in 11 (55%) and eight (40%) sera a significant increase of phagocytic activity after vaccination, respectively . Despite vaccination, four complement-deficient patients experienced six episodes of meningococcal disease in the 6 years post-vaccination . Four episodes were due to serogroup B, not included in the vaccine . Despite good response to serogroup Y upon vaccination, disease due to serogroup Y occurred in two C8beta-deficient patients, 3.5 and 5 years post-vaccination . These results support the recommendation to vaccinate complement-deficient individuals and to revaccinate them every 3 years.

Clin Exp Immunol, 1998 Dec, 114(3), 355 - 61
C7 deficiency in an Irish family: a deletion defect which is predominant in the Irish; O'Hara AM et al.; Human deficiencies of terminal complement components are known to be associated with increased susceptibility to Neisseria meningitidis infection . Polymorphic DNA marker studies in complement deficient investigations allow identification of haplotypes associated with the deficiency and enable the possible identification of heterozygote carriers of the defect . We report studies of an Irish family in which the index case had suffered recurrent meningococcal disease and was found to be deficient in the seventh component of complement (C7) . The availability of all family members enabled us to determine the segregating haplotypes . The defects in the family segregated with two very closely related C6 and C7 DNA haplotypes, one of which is known to be associated with the large Irish C7 DNA deletion defect . The index case and two C7 deficient siblings were found to be homozygous for this defect, a deletion that spans approx . 6.8 kbp and encompasses exons 7 and 8 . The deletion defect of exons 7 and 8 of C7 has been found in homozygous form in another C7 deficient Irish individual, and is present in heterozygous form in C7 deficient members of a third Irish family . Therefore, this deletion defect occurs in five of the six deficient chromosomes of these three unrelated Irish families, raising the interesting question of how prevalent this defect may be within the Irish community.

Commun Dis Rep CDR Wkly, 1998 Nov, 8 Suppl 5, S1 - 12
PHLS overview of communicable diseases 1997: results of a priority setting exercise; Rushdy A et al.; In early 1997, the PHLS Overview of Communicable Diseases (OVCD) Committee carried out a consultation exercise to inform the development of PHLS priorities in communicable diseases for the years 1997 to 1999 . The views of PHLS senior staff and scientific committees and consultants in communicable disease control in district health authorities were sought by postal questionnaire, and several organisations of health professionals were asked for their views on the initial findings . The main findings of the exercise are summarised in three areas of priority . Priority 1 diseases-those of major importance to public health-included food poisoning, meningitis, tuberculosis, sexually transmitted diseases, vaccine preventable diseases, hospital acquired infections, and antimicrobial resistance . Priority 2 diseases-those of moderate importance to public health-included respiratory syncytial virus and varicella zoster virus infections and emerging problems such as travel associated infections . Priority 3 diseases included those whose prevalence is declining as a result of public health action, such as listeriosis, and diseases of low prevalence and/or associated morbidity . The exercise identified four areas of possible future work for the PHLS: activities in prion diseases, helping to tackle inequalities in health, taking a more active approach to documenting the socioeconomic burden of diseases, and engaging more with those consulted . The PHLS has used the results of the priority setting exercise to guide major programme initiatives in tuberculosis, measles, mumps, and rubella, meningococcal and pneumococcal diseases, and in antibiotic resistance . In addition, they have helped to shape agenda in service delivery and research in hospital acquired infections, sexually transmitted diseases, and gastrointestinal diseases . This exercise of engaging corporately with key professionals in communicable disease has paved the way for a wider engagement with stakeholders in the setting of future priorities.

Eur J Pediatr, 1998 Nov, 157(11), 869 - 80
Pathophysiology of meningococcal sepsis in children; de Kleijn ED et al.; Septic shock with purpura is a syndrome frequently diagnosed in children and predominantly caused by Neisseria meningitidis . Despite improvements in management and therapy the mortality and morbidity in these patients are still high . During the last few years much effort has been put into understanding of the systemic host response during this acute infectious disease . This host response can be divided into the process of recognition of endotoxin, the cascade of pro- and counter inflammatory mediators, the endothelial damage resulting in capillary leakage and inappropriate vascular tone, and the procoagulant state . CONCLUSION: This paper reviews the recent insights in the pathophysiology of the host response and their possible consequences for

novel therapies in meningococcal sepsis.

JAMA, 1998 Nov 18, 280(19), 1685 - 9
Induction of immunologic memory by conjugated vs plain meningococcal C polysaccharide vaccine in toddlers: a randomized controlled trial; MacDonald NE et al.; CONTEXT: Meningococcal polysaccharide vaccines are not used routinely in infants and toddlers, the groups at highest risk of invasive disease, because of poor immunologic responses to the Neisseria meningitidis serogroup C polysaccharide in these age groups . Meningococcal C conjugate vaccines offer the prospect of circumventing this problem . OBJECTIVE: To assess the immunogenicity and the induction of immunologic memory in toddlers by meningococcal C conjugate vaccine . DESIGN: A multicenter, randomized, observer-blinded controlled trial . SETTING: Urban and suburban family medicine or pediatric practices . PARTICIPANTS: Two hundred eleven healthy toddlers aged 15 to 23 months . INTERVENTION: Two injections at 2 months apart of meningococcal C conjugate (group 1, n = 69), plain meningococcal polysaccharide (group 2, n = 72), or hepatitis B virus vaccine (group 3, n = 70) . All toddlers received a follow-up dose of plain meningococcal polysaccharide vaccine 12 months later . MAIN OUTCOME MEASURES: IgG meningococcal C anticapsular antibody concentrations determined by enzyme-linked immunosorbent assay and complement-mediated bactericidal antibody . RESULTS: In group 1, the magnitude of the IgG response to meningococcal C conjugate vaccine was more than 4-fold higher after dose 1 and more than 10-fold higher after dose 2 compared with meningococcal polysaccharide vaccine (group 2) (P<.001) . Higher titers persisted in the meningococcal C conjugate group for at least 12 months (P<.001) . Group 1, primed with meningococcal C conjugate, had 25-fold higher IgG responses to the meningococcal polysaccharide 1-year booster dose than the controls who had received hepatitis B virus vaccine initially and were given meningococcal polysaccharide vaccine 1 year later for the first time (P<.001) . In contrast, group 2, primed with meningococcal polysaccharide, had a 2-fold lower response to the 1-year booster meningococcal polysaccharide dose than the hepatitis B virus control group (P = .006) . Serum bactericidal responses paralleled the enzyme-linked immunosorbent assay responses . CONCLUSIONS: Immunization of toddlers with meningococcal C conjugate vaccine induces high titers of anticapsular and bactericidal antibody . Furthermore, this vaccine induces immunologic memory to meningococcal C polysaccharide . In contrast, meningococcal polysaccharide vaccine is less immunogenic than the conjugate vaccine and also induces a hyporesponsive state that persists for at least 12 months.

Infect Immun, 1998 Dec, 66(12), 5939 - 47
The (alpha2-->8)-linked polysialic acid capsule and lipooligosaccharide structure both contribute to the ability of serogroup B Neisseria meningitidis to resist the bactericidal activity of normal human serum; Kahler CM et al.; The molecular basis for the resistance of serogroup B Neisseria meningitidis to the bactericidal activity of normal human sera (NHS) was examined with a NHS-resistant, invasive serogroup B meningococcal isolate and genetically and structurally defined capsule-, lipooligosaccharide (LOS)-, and sialylation-altered mutants of the wild-type strain . Expression of the (alpha2-->8)-linked polysialic acid serogroup B capsule was essential for meningococcal resistance to NHS . The very NHS-sensitive phenotype of acapsular mutants (99.9 to 100% killed in 10, 25, and 50% NHS) was not rescued by complete LOS sialylation or changes in LOS structure . However, expression of the capsule was necessary but not sufficient for a fully NHS-resistant phenotype . In an encapsulated background, loss of LOS sialylation by interrupting the alpha2,3 sialyltransferase gene, lst, increased sensitivity to 50% NHS . In contrast, replacement of the lacto-N-neotetraose alpha-chain (Galbeta1-4GlcNAcbeta1-3Galbeta1-4Glc) with glucose extensions (GlcN) in a galE mutant resulted in a strain resistant to killing by 50% NHS at all time points . Encapsulated meningococci expressing a Hep2(GlcNAc)-->KDO2-->lipid A LOS without an alpha-chain demonstrated enhanced sensitivity to 50% NHS (98% killed at 30 min) mediated through the antibody-dependent classical complement pathway . Encapsulated LOS mutants expressing truncated Hep2-->KDO2-->lipid A and KDO2-->lipid A structures were also sensitive to 50% NHS (98 to 100% killed at 30 min) but, unlike the wild-type strain and mutants with larger oligosaccharide structures, they were killed by hypogammaglobulinemic sera

. These data indicate that encapsulation is essential but that the LOS structure contributes to the ability of serogroup B N . meningitidis to resist the bactericidal activity of NHS.

Mol Microbiol, 1998 Nov, 30(3), 647 - 56
A gonococcal porA pseudogene: implications for understanding the evolution and pathogenicity of Neisseria gonorrhoeae; Feavers IM et al.; Members of the genus Neisseria, including the human pathogens Neisseria meningitidis and Neisseria gonorrhoeae, express at least one member of a family of related porins . N . meningitidis is the only species known to express a second porin, the meningococcal serosubtyping antigen PorA, the most divergent member of this family . Unexpectedly, a porA gene was identified in the gonococcal genome . Both the gonococcal and meningococcal porA loci were adjacent to a homologue of the Escherichia coli greA gene, although the IS1106 element downstream of porA in some meningococci was absent in the gonococcus . Almost identical porA loci were present in four unrelated gonococcal isolates and clinical specimens from patients with gonorrhoea . Lack of PorA expression in the gonococcus resulted from mutations in the promoter region, which prevented transcription, and frameshift mutations in the coding region of the porA gene . Hybridization and amplification experiments, showing the absence of a porA gene in seven other Neisseria species, suggested that porA was acquired by a common ancestor of the gonococcus and meningococcus but inactivated in the gonococcus on speciation . This implies that, while advantageous during colonization of the upper respiratory tract, this protein has no function in, or hinders, colonization of the urogenital tract.

J Trop Pediatr, 1998 Oct, 44(5), 263 - 5
Changing patterns of antibiotic sensitivity and resistance during an outbreak of meningococcal infection in Jos, Nigeria; Angyo IA et al.; Isolates of Neisseria meningitidis from blood and cerebrospinal fluid (CSF) of 87 children admitted to the emergency paediatric unit (EPU) at the Jos University Teaching Hospital (JUTH) during an outbreak of meningococcal infection (between February and April 1996) were tested against the commonly used antibiotics in an attempt to determine the sensitivity and resistance pattern . There were 11 (15.1 per cent) positive for N . meningitidis out of 73 blood cultures and 61 (70 per cent) positive out of 87 CSF cultures . Seventy-seven and thirty-eight per cent respectively of the CSF isolates were resistant to benzylpenicillin and ampicillin . Sensitivity to chloramphenicol and erythromycin was 97 and 95 per cent, respectively . Out of the 11 positive blood cultures, 82 and 27 per cent were resistant to benzylpenicillin and ampicillin, respectively, while all the isolates (100 per cent) were sensitive to chloramphenicol and erythromycin . It is concluded that in view of the high level of resistance of the meningococci to benzylpenicillin in our environment, this drug should no longer be the drug of choice for the empirical and initial treatment of meningococcal infection . We recommend that chloramphenicol be the drug of choice for the empirical and initial treatment of meningococcal infection in our environment.

J Med Microbiol, 1998 Nov, 47(11), 993 - 8
Identification of nasopharyngeal carriage of an outbreak strain of Neisseria meningitidis by pulsed-field gel electrophoresis versus phenotypic methods; Bevanger L et al.; The clustering of four cases of meningococcal disease during a 3-month period in a small community with 2233 inhabitants prompted an interventional carrier survey in persons < 19 years old and in family members of the patients . The aims of the survey were to identify the nasopharyngeal carriers and the carriage rate of the outbreak strain, to offer chemoprophylaxis to those carrying the outbreak strain, and to study the discriminatory power of phenotypic methods versus pulsed-field gel electrophoresis (PFGE) on carrier isolates during an outbreak . A high percentage of the population in the age group 0-19 years (73.7%) participated in the study . Among the 469 samples collected in this age group, meningococci were grown from 43 (9.2%) . The highest carriage rates were in the age group 18-19 years (36.4%) . With a provisional definition of the outbreak strain (group B or non-groupable Neisseria meningitidis with reduced sulphonamide sensitivity), six carriers were identified . All were treated with a single dose of ofloxacin . Four of these persons (0.76% of all tested) were

later shown to have harboured the outbreak strain when analysed by PFGE . Three of them were epidemiologically closely related to one of the index cases . Serogrouping alone is not sufficient for the identification of an epidemic strain of N . meningitidis . Complete concordance of type and subtype antigens correctly identified the outbreak strain in this study . PFGE is well suited for the identification of an outbreak strain of N . meningitidis versus non-epidemic strains in tonsillo-pharyngeal specimens.

Clin Exp Immunol, 1998 Nov, 114(2), 215 - 9
Endotoxin release and cytokine production in acute and chronic meningococcaemia; Prins JM et al.; Chronic meningococcaemia is a relatively benign manifestation of meningococcal disease . Whether bacterial virulence factors are responsible for this benign course has not been studied . We compared the in vitro endotoxin-liberating ability and cytokine-inducing potential of 31 Neisseria meninigitidis isolates obtained from children with acute septic shock with that of nine isolates obtained from patients with chronic meningococcaemia and 12 isolates obtained from carriers with respiratory symptoms . The median endotoxin level released in vitro after 3 h of incubation was significantly higher for isolates causing septic shock compared with isolates from the other two groups (P=0.01 and 0.02, Mann-Whitney test) . This was not explained by differences in bacterial growth rate in vitro . The median IL-6 levels in whole blood ex vivo after 4 h of incubation were also significantly lower for isolates causing chronic meningococcaemia (P=0.04, Mann-Whitney test) . The endotoxin and cytokine levels measured on admission in the 31 children with acute meningococcal septic shock showed a 1000-fold variation . No relationship was established between the amount of endotoxin released by the causative microorganisms in vitro and the endotoxin or cytokine levels in the corresponding 31 children . These results suggest a diminished bacterial virulence for isolates causing chronic meningococcaemia . However, other factors than the endotoxin-releasing potential of the microorganism involved are responsible for the wide variation in endotoxin and therefore cytokine levels in patients with acute meningococcal septic shock.

J Immunol, 1998 Nov 15, 161(10), 5525 - 33
IL-12 enhances antibody responses to T-independent polysaccharide vaccines in the absence of T and NK cells; Buchanan RM et al.; Polysaccharide vaccines to encapsulated bacteria such as Neisseria meningitidis and Streptococcus pneumoniae are weakly immunogenic due to their T-independent (TI) nature . Even when converted to T-dependent forms through conjugation to foreign proteins, polysaccharides induce responses that are deficient in many respects, such as induction of murine IgG2a Ab, the isotype that mediates optimal complement fixation and opsonization . We now show that IL-12 treatment of mice induces significantly increased levels of IgG2a Ab to the model TI-2 Ag, DNP-Ficoll, and to vaccines composed of polysaccharides from pneumococci and meningococci . Use of immunodeficient mice lacking T cells and/or NK cells demonstrated that such cells were not responsible for the observed Ab enhancement . Furthermore, the use of IFN-gamma knockout mice showed that stimulation of TI-2 Ab responses by IL-12 was only partially dependent on IFN-gamma . The ability of IL-12 to dramatically enhance TI Ab responses suggests that IL-12 will be useful as a powerful vaccine adjuvant to induce protective immune responses against encapsulated pathogens.

Cas Lek Cesk, 1998 Oct 5, 137(19), 598 - 600
{Association of class I HLA antigens with invasive meningococcal disease}; Holub M et al.; BACKGROUND: The majority of meningococcal infections are characterized by nasopharyngeal carriership . In some patients invasive disease with a mild course develops, while some cases have a lethal outcome . The reasons of this wide variation range are not clear . The objective of the present work was to assess whether the development of invasive meningococcal disease or its prognosis are associated with HLA class I . METHODS AND RESULTS: The group of patients was formed by 40 patients (29 females, 11 males, mean age 16 years, range 8 months to 52 years) . In 28 patients the disease was caused by N . meningitidis group C, in 9 cases group B, in three cases the serotype was not assessed . The etiology was confirmed by cultivation or latex

agglutination . Twenty-three patients had a mild course of the disease, 8 a medium severe one, 9 patients a severe clinical course (score according to Stiehme, Damrosch and Rosenblat) . The patients were compared with 227 non-related blood donors (114 women, 113 men, 18 to 50 years old) . In patients and controls 24 lymphocytic HLA antigens class I were identified as to type . Typing was done using the standard microlymphocytotoxic test in the NIH modification . The results were processed by statistical methods using Fisher's exact test and the 2 x 2 test with Yates correction . In patients with a mild course HLA antigens B7 and B12 predominate ($p = 0.03$; $p = 0.02$), in medium severe cases antigen A11 ($p = 0.03$), in patients with the most severe course antigen A9 ($p = 0.04$) . In invasive infections caused by N . meningitidis serotype B antigen B17 predominates ($p = 0.05$) . CONCLUSIONS: The severity of meningococcal invasive infections is associated with HLA class I . Invasive disease caused by N . meningitidis serotype B are more likely to occur in carriers of HLA B17 . No relationship was found between HLA class I and invasive disease caused by N . meningitidis regardless of serotype and with serotype C.

J Clin Microbiol, 1998 Dec, 36(12), 3680 - 2
Heterogeneity of the PorB protein in serotype 22 Neisseria meningitidis; Urwin R et al.; The genetic diversity of porB genes from meningococcal isolates characterized as serotype 22 was investigated by gene sequencing . This procedure identified seven distinct porB sequences, demonstrating variation in the PorB protein recognized by the serotype 22 monoclonal antibody . This is consistent with the genetic heterogeneity of serotype 22 meningococci reported previously.

J Travel Med, 1994 Jun 1, 1(2), 72 - 78
Inadequacies in Health Recommendations Provided for International Travelers by North American Travel Health Advisors; Keystone JS et al.; The rise of international travel has increased the need for more, improved travel advice from physicians and public health facilities . The quality of the health information given has not been examined on a large-scale basis by many studies, however . Surveys in Canada, Switzerland, and the United States, for example, report that only 20% to 50% of practitioners could give accurate information regarding immunization and prophylaxis about travel-related disease . Anonymous surveys were sent to 1165 American and 96 Canadian public health units and travel clinics . Using five scenarios on travel to developing countries, each source was asked to complete a standardized form giving their recommendations for immunization, antimalarials, travelers' diarrhea, and other travel issues . Of the American respondents, 60% were physicians equally distributed among private practice, university, and corporate clinics; nurses comprised 75% of the Canadian respondents, primarily from public health clinics . The number of travelers counseled per year ranged from 3 to 40,000 (American mean, 448; Canadian mean, 2180) . Depending on the scenario, 20 to 75% of the immunization groups recommended were inadequate or inappropriate: most frequently, lack of tetanus/polio boosters; indiscriminant use of yellow fever/cholera vaccines; haphazard advice about meningococcal, rabies, and typhoid vaccines; and a lack of consideration of measles in young adults . Of the antimalarial recommendations given, 20 to 60% were incorrect, including prescribing medication for nonrisk areas, failure to recognize chloroquine-resistant areas, and failure to understand the use of, or contraindications to, mefloquine . Frequently, acclimatization, altitude sickness, sunscreens, and safe-sex issues were omitted . The prevention and treatment of travelers' diarrhea were adequately covered, however . Pre-travel advice given by North American health advisors shows a considerable variability in the accuracy and extent necessary for effective travel disease prevention and treatment . Despite the growing efforts to further educate those responsible, higher quality of health advice needs to become a priority.

J Travel Med, 1994 Mar 1, 1(1), 4 - 7
Meningococcal Disease in Travelers: Vaccination Recommendations; Koch S et al.; 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.

Intensive Crit Care Nurs, 1998 Apr, 14(2), 91 - 5
Nursing perspectives in meningococcal disease; Moore E et al.; Meningococcal sepsis is a potentially life threatening disease . Recent advances have led towards increased emphasis being placed on early identification and prompt aggressive management of these patients . This article outlines the disease pathology, describing a case study to illustrate the management and nursing care of a child with meningococcal sepsis . Current therapies are also discussed.

J Bacteriol, 1998 Nov, 180(22), 6043 - 7
Transport of intact porphyrin by HpuAB, the hemoglobin-haptoglobin utilization system of Neisseria meningitidis; Lewis LA et al.; The meningococcal hemA gene was cloned and used to construct a porphyrin biosynthesis mutant . An analysis of the hemA mutant indicated that meningococci can transport intact porphyrin from heme (Hm), hemoglobin (Hb), and Hb-haptoglobin (Hp) . By constructing a HemA- HpuAB- double mutant, we demonstrated that HpuAB is required for the transport of porphyrin from Hb and Hb-Hp.

Rev Esp Salud Publica, 1998 Jul-Aug, 72(4), 365 - 74
{Seroprevalence of bactericidal anti-meningococcal antibodies in Cantabria 10 months following a vaccination campaign}; Gonzalez de Aledo Linos A et al.; BACKGROUND: The Self Governing Region of Cantabria within the state of Spain has a population of 541,885, of which 107,787 individuals are aged from 18 months to 19 years . A vaccination campaign against meningitis was conducted in this Region in February and March, 1997 . It was directed at children from the age of 18 months up to 19 years old, and included all municipal areas, achieving a coverage of more than 95% . In the following 12 months the efficacy achieved by the vaccination was 95.68% for all age groups . To help decide on the need for re-vaccination, a study of the prevalence in serum of bactericide antibodies in the vaccinated population was carried out . METHODS: In December 1997 blood samples from 414 vaccinated children were analysed, obtained at random in opportunist sampling in First-Aid Centres and Public Hospitals within this Region, as well as from children in public kindergartens run by the General Board of Social Well-Being in Cantabria . The number of bactericide antibodies was analysed in the National Centre for Microbiology, and the level of "vaccination effect" was set at a dilution of 1/8 . RESULTS: The following percentages of titres > or = 1/8 were obtained (the age groups of school pupils are shown in brackets): 0% (18-24 months old), 4% (1.5-4 years old), 7.1% (1.5 to 6 years old), 51.3% (6 to 12 years old) . Due to the fact that the definition of the "vaccine effect" was artificially set at a dilution of 1/8, while other studies set it at a dilution of 1/4, in 287 serum samples with a result of < 1/8 the bactericide assay was repeated with a dilution of 1/4, with the result that 286 (99.6%) were negative . I.e., the final result does not vary if we set the cut-off point at 1/4 instead of 1/8 . No significant differences were found due to whether or not the samples came from children in municipalities where there had been cases of meningitis C . CONCLUSIONS: Bactericide activity is very low in those children aged less than 4-6 years old, and is less than has been published, although it is greater above this age . This contrasts with the excellent clinical-epidemiological results, as there was no case amongst the least serologically "protected" population, in spite of the fact that meningococcus C remains in circulation in

Cantabria, within the population that was not targeted by the campaign.

Rev Cubana Med Trop, 1995, 47(2), 108 - 12
{The seasonality of meningococcal disease in infants less than 1 year old . Cuba, 1983-1990}; Rico Cordeiro O et al.; Children less than one year old behave as the group with the highest incidence of meningococcal disease during all the epidemic period in the past '80s decade in Cuba . There were used chronological series of monthly incidence rates between 1983 and 1990, in order to identify the behavior of seasonality, taking into account the clinical form and the insert of years 1989 and 1990 in the series: in both of them a massive antimeningococcal vaccination campaign took place . It is evident that seasonality has a different behavior in accordance with the clinical form: it is like the countries from the northern hemisphere with a moderate climate for the meningoencephalitis, and like the countries of the southern hemisphere with a warm climate for the meningococcal syndrome . Months of the rainy period have the lowest seasonal index . Modifications of these seasonal patterns are not found after executing the vaccination.

Rev Cubana Med Trop, 1995, 47(1), 59 - 64
{The post-licensing efficacy of VA-MENGOC-BC in children under 6 in HolguÃn, Cuba . The first year of observation}; Rico Cordeiro O et al.; The assessment of the after-licensing efficacy of the Cuban vaccine VA-MENGOC-BC was performed one year after the mass immunization campaign was completed in children under 6 years of age in the Province of Holguin which had the second highest incidence rate of meningococcal disease during 1988 in Cuba . In the design of the study the following aspects were taking into account: case definition; case detection, determination of the state of vaccination, and comparability of exposure . The utilization of 2 case definitions with different sensitivity and specificity is introduced within the methodology, as well as 2 estimation methods . Incidence rates from exposed and nonexposed subjects, as well as the ratio of cases and of the vaccinated population are used . The impact of this prophylactic intervention was determined by the estimation of the percentual preventive population fraction . Among outstanding results, the high efficacy of more than 98% found in both variants of case definition is to be mentioned . It is evidenced that the effect of the vaccine accounts for more than 80% of the observed case reduction . Such reduction in the number of cases was obtained without changing diagnostic criteria since the isolation of the agents was hept at levels similar to the ones from previous years.

Commun Dis Intell, 1998 Oct 1, 22(10), 205 - 11
Annual report of the Australian Meningococcal Surveillance Programme, 1997; Age-related immunogenicity of meningococcal polysaccharide vaccine in aboriginal children and adolescents living in a Northern Manitoba reserve community; Department of Medical Microbiology, University of Manitoba, Canada . blaw@ms.umanitoba.ca

OBJECTIVE: To determine the total and functional serogroup C antibody response to a quadrivalent meningococcal polysaccharide vaccine in a group of aboriginal infants, children and adolescents . A secondary objective was to determine their prevalence of meningococcal carriage . DESIGN: Open prospective, before and after intervention study . SUBJECTS: Aboriginal children ages 0.5 to 19.9 years, living in a single Northern community and eligible for a public health immunization campaign conducted in all Manitoba native reserve communities to control a meningococcal serogroup C, electrophoretic type (ET) 15 outbreak . No outbreak cases had occurred in the community at the time of the study . METHODS: Total serogroup C capsular polysaccharide antibody (CPA) and functional bactericidal antibody (BA) responses were measured by enzyme-linked immunosorbent assay and bactericidal assay, respectively . RESULTS: Neisseria meningitidis was recovered from the oropharynx of 13 (5.2%) of 249 aboriginal children including 4 (1.6%) serogroup C isolates, all with the designation C:2a:P1.2,5 ET15 . Paired sera from 152 children were available for assay . For CPA the geometric mean concentrations and proportions with > or =2 microg/ml before and after immunization were 0.69, 18% and 12.3, 96%, respectively . A significant increase in serum

CPA was achieved by children of all ages, with the greatest response occurring after age 11 years . Among infants < lyear old 89% achieved concentrations of > or =2 microg/ml . For BA the pre- and post-vaccine geometric mean titers were 1.02 and 45.9 . The response was significantly associated with age . BA titers > or =1:8 were present, before and after immunization, respectively, in 0 and 0% of infants <1 year old, 0 and 20% of 1- to 1.4-year-olds, 0 and 50% of 1.5- to 1.9-year-olds and 1 and 100% of > or =2-year-olds . CONCLUSION: The age-related total and functional group C meningococcal antibody response after quadrivalent polysaccharide vaccine among aboriginals is similar to that reported for Caucasian children . After age 2 all children made excellent CPA and BA responses . In the younger age groups the BA response was blunted but 82 to 95% achieved CPA titers of > or =2 microg/ml.

Pediatr Infect Dis J, 1998 Oct, 17(10), 855 - 9
Cerebrospinal fluid pleocytosis and prognosis in invasive meningococcal disease in children; Malley R et al.; BACKGROUND: The absence of cerebrospinal fluid (CSF) pleocytosis in invasive meningococcal disease (IMD) has been associated with an increased risk of death . It is unknown whether patients who lack a cellular response to central nervous system (CNS) infection are at the same risk of adverse outcome as patients who lack CNS infection . OBJECTIVES: To determine the frequency of presentation and outcome of three groups of children with IMD: Group 1, children with CSF pleocytosis; Group 2, children without CSF pleocytosis and with negative CSF cultures (bacteremia alone); and Group 3, children without CSF pleocytosis but with positive CSF cultures (CNS infection without CSF pleocytosis) . METHODS: We reviewed the medical records of children with IMD at four pediatric referral hospitals between 1985 and 1996 . Clinical and laboratory indices and severe adverse outcomes (defined as death or limb loss) were compared in the three groups . Multivariable logistic regression analysis was performed to determine whether CNS infection without CSF pleocytosis was independently associated with adverse outcome in IMD . RESULTS: Three hundred seventy-seven children with IMD were identified . Eighty-six patients were excluded because their CSF analysis either was not done or was unevaluable; of these patients 22 (25.6%) had an adverse outcome . Of the 291 evaluable patients 204 (70.1%) had CSF pleocytosis, 52 (17.9%) had bacteremia alone and 35 (12.0%) had CNS infection without CSF pleocytosis . Patients with CNS infection without CSF pleocytosis had significantly lower white blood cell and platelet counts and more coagulopathy than patients with bacteremia alone (P < or = 0.05) or patients with CSF pleocytosis (P < or = 0.01) . The frequency of adverse outcome was 40% for patients with CNS infection without CSF pleocytosis compared with 9.6% for patients with bacteremia alone (P = 0.001) and 3.4% for patients with CSF pleocytosis (P < 0.001) . CNS infection without CSF pleocytosis was independently associated with adverse outcome by multivariable logistic regression analysis (P = 0.003) . CONCLUSIONS: Approximately 30% of all children with IMD present without CSF pleocytosis . Of these patients those with CNS infection without pleocytosis are at higher risk of adverse outcome than either patients with CSF pleocytosis or patients with bacteremia alone.

Clin Infect Dis, 1998 Oct, 27(4), 746 - 50
Association of human Fc gamma RIIa (CD32) polymorphism with susceptibility to and severity of meningococcal disease; Platonov AE et al.; Phagocytosis of bacteria constitutes an important defense mechanism against invasive bacterial diseases . Efficacy of phagocytosis by polymorphonuclear neutrophils is known to vary between allotypes of Fc gamma RIIa (a class of Fc receptors for immunoglobulins that is constitutively expressed on neutrophils) . We compared the distribution of Fc gamma RIIa-R131 and Fc gamma RIIa-H131 allotypes in 98 Slavic complement-sufficient patients with meningococcal disease with that of the allotypes in 107 healthy controls . A strong association was found between the IIa-R/R131 allotype and the development of meningococcal disease after the age of 5 years, compared with IIa-R/H131 and IIa-H/H131 allotypes (P < .03; odds ratio {OR}, 2.9) . A severe course of meningococcal disease was observed in 21 (68%) of 31 episodes in patients with IIa-R/R131 genotype and in 22 (54%) of 41 episodes in patients with IIa-R/H131 genotype, in contrast to eight (31%) of 26 episodes in patients with IIa-H/H131 genotype (P < .02; OR, 4.7) . Our data show that individuals older than 5 years of age who have the IIa-

H/H131 allotype are less susceptible to severe meningococcal disease than are individuals with the IIa-R/R131 or IIa-R/H131 genotype.

Ann Emerg Med, 1998 Nov, 32(5), 620 - 3
Meningococcal meningitis presenting as stroke in an afebrile adult; Hsu SS et al.; We describe a healthy, afebrile 26-year-old man who presented to the emergency department with left hemiparesis and cranial nerve deficits caused by meningococcal meningitis . The results of the computed tomographic scan of the head were negative . Magnetic resonance imaging showed lesions in the basal ganglia and caudate consistent with ischemic infarcts . The neurologic deficits initially progressed but improved to near-resolution after 1 month . This case was unusual in that the patient was afebrile despite a high bacterial load and significant neurologic deficits . His presentation thus mimicked a straightforward stroke . Close attention to the physical examination findings led to a comprehensive evaluation that yielded the correct diagnosis.

Mol Gen Genet, 1998 Sep, 259(4), 363 - 71
Identification of a hotspot for transformation of Neisseria meningitidis by shuttle mutagenesis using signature-tagged transposons; Claus H et al.; Shuttle mutagenesis using signature-tagged transposons was employed to generate a library of individually tagged mutants of the Neisseria meningitidis strain B1940, which belongs to serogroup B . The use of tagged transposons allowed us to monitor for enrichment for single mutants during the process of shuttle mutagenesis, by amplification of the tags and subsequent sequence determination . Enrichment of a single clone occurred during the transformation of the meningococci with transposon-containing plasmid DNA . Sequence determination around the site of transposon insertion revealed that the transposon had mutagenized a previously unknown locus, which was designated hrtA (high rate of transformation) . hrtA-mediated transformation was independent of TnMax5 and tag sequences, and it most probably involved recombination events . The hrtA locus is restricted to meningococci and gonococci and is present in few apathogenic neisserial species . Chromosomal mapping of hrtA and six further hrt sites revealed a random distribution of highly transforming DNA fragments on the meningococcal chromosome . In conclusion, our data demonstrate that shuttle mutagenesis of naturally competent bacteria using signature-tagged transposons allows the isolation of chromosomal DNA fragments, which exhibit a high transformation efficiency, and which, therefore, are likely to be involved in horizontal gene transfer.

Scand J Infect Dis, 1998, 30(3), 263 - 4
Meningococcal polysaccharide vaccination of military recruits in Israel: preliminary assessment of vaccine effect; Mimouni D et al.; Meningococcal disease in the Israel Defense Force is caused mainly by serogroups C and Y . Immunization of recruits with quadrivalent polysaccharide vaccine was introduced in November 1994 . The person-time incidence rate dropped from 1.33 cases per 100,000 person-years for the preceding decade to 0 for the 32 months following immunization ($p = 0.025$).

Cent Eur J Public Health, 1998 Aug, 6(3), 219 - 24
Active surveillance of meningococcal meningitis in Poland; Tyski S et al.; Starting from 1970, the notification of N . meningitidis cases in Poland was compulsory and separated from other cases of meningitis purulenta . Based on the experience of European Monitoring Group on Meningococci, the active surveillance of meningococcal meningitis in Poland was initiated in April 1995 . It was the first time that such study was conducted to recognise the actual situation of meningococcal meningitis infections in our country . Ninety seven N . meningitidis strains were isolated (31 in 1995 and 66 in 1996) from cerebrospinal fluid (CSF) of meningitis patients hospitalized in 54 hospitals located in 33 out of 49 provinces of Poland . Most patients were below 2 years of age and 43% belonged to infant group . Meningococcal strains were phenotypically characterized as follow: identification of N . meningitidis was performed by Gram staining, oxidase and

catalase tests as well as latex or diagnostic sera agglutination assays . Meningococcal serotypes and subtypes were determined by whole-cell ELISA with monoclonal antibodies . The predominant meningococcal serogroup during 1995 and 1996 was B (80% of all isolates tested), the serogroup C (12.6%) and W-135 (3.5%) . Only two non-groupable and two serogroup A strains were isolated in Poland . Active surveillance allowed to determine B:22:P1.14 to be the most prevalent N . meningitidis phenotype in Poland . Two isolates of N . meningitidis phenotype C:2a:P1.2,5, which caused emergency situation in Czech Republic since 1993, were isolated from CSF of patients in October 1996 in southern Poland . All strains were susceptible to cefotaxime, chloramphenicol, ciprofloxacin, rifampin and tetracycline; some strains were resistant to sulphonamides (60.6% - MIC = 32 mg/l and 14.8% - MIC = 128 mg/l) . Only one of the tested strains in two years surveillance study in Poland was resistant to penicillin (MIC = 2 mg/l).

J Antimicrob Chemother, 1998 Sep, 42(3), 303 - 7
The detection of penicillin insensitivity in Neisseria meningitidis by polymerase chain reaction; Maggs AF et al.; Strains of penicillin-sensitive and -insensitive Neisseria meningitidis were examined using a range of polymerase chain reaction (PCR) primers directed at the meningococcal penicillin-binding protein 2 gene . DNA from isolates whose penicillin MIC was <0.2 mg/L yielded a product of the expected size with all the primers, but many amplification patterns were seen with DNA from isolates whose MIC was above this level . All strains whose MIC was >0.25 mg/L failed to produce a product of the expected size with at least one of the primers used . The changes seen in penicillin-insensitive strains were consistent with horizontal gene transfer from Neisseria flavescens in some isolates, although the source for others remains unknown . PCR-based methods for the detection of antibiotic resistance are becoming increasingly important with the expanding use of molecular techniques for bacteriological diagnosis.

J Accid Emerg Med, 1998 Sep, 15(5), 298 - 303
Avoidable deficiencies in the delivery of health care to children with meningococcal disease; Nadel S et al.; OBJECTIVES: It is apparent that delays and inadequate or inappropriate management occur frequently and may contribute to the continued high mortality seen in meningococcal disease . An attempt has been made to define the major sources of delay or inappropriate treatment . METHODS: A prospective, descriptive study of children with meningococcal disease referred to a tertiary centre paediatric intensive care and infectious disease unit . Definitions of optimal care were established at three stages: parental; general practitioner (GP)/accident and emergency (A&E) department; and hospital . Duration of symptoms and management were recorded from direct questioning of parents and carers, and from hospital records . RESULTS: 54 consecutive children with meningococcal disease were recruited to the study . Delayed parental recognition occurred in 16 children . GPs correctly diagnosed 19 of 35 children . Delay of 2.5-21 hours occurred in those who were incorrectly diagnosed . Two of 15 children who presented to the A&E department with specific features were incorrectly diagnosed . Hospital treatment was suboptimal in 71% . Shock was not recognised or treated in 50%, 20% of children had unnecessary lumbar punctures . Time from illness onset to treatment was longer in fatal disease (median 18.3, range 8-24 hours), compared with survivors (median 12, range 2-48 hours; $p < 0.01$, Mann-Whitney U test) . CONCLUSION: Suboptimal treatment in meningococcal disease is due to failure of parents, GPs, and hospital doctors to recognise specific features of the illness . Improvement by public education and better training of clinicians in recognition, resuscitation, and stabilisation of seriously ill children.

Infect Immun, 1998 Nov, 66(11), 5350 - 6
Complement activation in relation to capillary leakage in children with septic shock and purpura; Hazelzet JA et al.; To assess the relationship between capillary leakage and inflammatory mediators during sepsis, blood samples were taken on hospital admission, as well as 24 and 72 h later, from 52 children (median age, 3.3 years) with severe meningococcal sepsis, of whom 38 survived and 14 died . Parameters related to cytokines (interleukin 6 {IL-6} IL-8, plasma phospholipase A2, and C-reactive protein {CRP}), to neutrophil

degranulation (elastase and lactoferrin), to complement activation (C3a, C3b/c, C4b/c, and C3- and C4-CRP complexes), and to complement regulation (functional and inactivated C1 inhibitor and C4BP) were determined . The degree of capillary leakage was derived from the amount of plasma infused and the severity of disease by assessing the pediatric risk of mortality (PRISM) score . Levels of IL-6, IL-8, C3b/c, C3-CRP complexes, and C4BP on admission, adjusted for the duration of skin lesions, were significantly different in survivors and nonsurvivors (C3b/c levels were on average 2.2 times higher in nonsurvivors, and C3-CRP levels were 1.9 times higher in survivors) . Mortality was independently related to the levels of C3b/c and C3-CRP complexes . In agreement with this, levels of complement activation products correlated well with the PRISM score or capillary leakage . Thus, these data show that complement activation in patients with severe meningococcal sepsis is associated with a poor outcome and a more severe disease course . Further studies should reveal whether complement activation may be a target for therapeutical intervention in this disease.

Pediatr Infect Dis J, 1998 Sep, 17(9), 816 - 9
Azithromycin compared with rifampin for eradication of nasopharyngeal colonization by Neisseria meningitidis; Girgis N et al.; OBJECTIVES: To evaluate the efficacy and safety of azithromycin compared with rifampin for eradication of nasopharyngeal carriage of Neisseria meningitidis METHODS: Pharyngeal swabs were obtained from 500 students attending nursing school in Cairo, Egypt, to determine the colonization rate with N . meningitidis . Colonized individuals were randomized to receive azithromycin (500 mg once) or rifampin (600 mg twice daily for four doses) . Subjects were then recultured 1 and 2 weeks posttreatment to determine the effectiveness of the antibiotic therapy for eradication of meningococcal nasopharyngeal colonization . RESULTS: Individuals treated with azithromycin had a 93% eradication rate at 1 and 2 weeks posttreatment comparable with 95 and 91%, respectively, for rifampin . No significant side effects were reported by any subjects treated with either antibiotic . CONCLUSION: Azithromycin is effective in the eradication of N . meningitidis from the nasopharynx of asymptomatic colonized individuals and deserves further evaluation for use as prophylaxis against N . meningitidis.

MMWR Morb Mortal Wkly Rep, 1998 Oct 9, 47(39), 833 - 7
Outbreaks of group B meningococcal disease--Florida, 1995 and 1997; Matrix metalloproteinases contribute to the blood-brain barrier disruption during bacterial meningitis; Department of Neurology, Ludwig-Maximilians-University of Munich, Klinikum Brosshadern, GermanyIn this study, we investigated the involvement of matrix metalloproteinases (MMPs) in the pathophysiology of bacterial meningitis . By using an enzyme immunoassay, high concentrations of MMP-9 were detected in the cerebrospinal fluid (CSF) of adult patients with bacterial meningitis but not in controls, and in patients with Guillain-Barre syndrome . Moreover, we observed significantly elevated concentrations of the tissue inhibitor of metalloproteinase-1 (TIMP-1) in the CSF of patients with bacterial meningitis, compared with controls . In a rat model of meningococcal meningitis, intracisternal injection of heat-killed meningococci caused a disruption of the blood-brain barrier (BBB), an increase in intracranial pressure, and CSF pleocytosis paralleled by the occurrence of MMP-9 activity in the CSF 6 hours after meningococcal challenge . The MMP inhibitor batimastat (BB-94) significantly reduced the BBB disruption and the increase in intracranial pressure irrespective of the time of batimastat administration (15 minutes before and 3 hours after meningococcal challenge) but failed to significantly reduce CSF white blood cell counts . In conclusion, our results suggest that MMPs are involved in the alterations of BBB permeability during experimental meningococcal meningitis.

Rev Cubana Med Trop, 1996, 48(1), 34 - 9
{Meningococcal disease and VA-MENGOC BC in minors less than 1 year of age . Cuba, 1983 to 1991}; Rico Cordeiro O et al.; A study of the chronological series of mortality due to meningococcal disease in children under one year old, the group of highest incidence during the last epidemy in Cuba, was carried out . Data

were collected by doing a survey in an uniform way since 1983 throughout the country . More than 90% of the population between 3 months and 5 years old were vaccinated with VAMENGOC BC since the end of 1988 until April, 1990 . The behaviour of this disease was studied in order to identify the influence of this vaccine . It is stressed that the mortality incidence reached its epidemic achme in 1986 and begins a slow descence which is accentuated in 1990 and 1991, with an annual relative decrease of 26.1 and 34.9%, respectively . The highest mortality rate was found in 1984, with a significant reduction in 1990 (-23.8%) and 1991 (-41.8%), after the culmination of the vaccination campaign with VA-MENGOC BC . It was detected that morbimortality, which is lower in children under one month because of the probable protection provided by maternal antibodies, started to increase until the fifth month of life, when it is observed a trend towards the reduction of morbidity and mortality . According to the present immunization chronogram, overall protection in only attained after the sixth mont of life.

Mol Microbiol, 1998 Aug, 29(4), 975 - 84
Identification of a novel gene involved in pilin glycosylation in Neisseria meningitidis; Jennings MP et al.; The pili of Neisseria meningitidis are a key virulence factor, being major adhesins of this capsulate organism that contribute to specificity for the human host . Recently it has been reported that meningococcal pili are post-translationally modified by the addition of an O-linked trisaccharide, Gal (beta1-4) Gal (alpha1-3) 2,4-diacetimido-2,4,6-trideoxyhexose . Using a set of random genomic sequences from N . meningitidis strain MC58, we have identified a novel gene homologous to a family of glycosyltransferases . A plasmid clone containing the gene was isolated from a genomic library of N . meningitidis strain MC58 and its nucleotide sequence determined . The clone contained a complete copy of the gene, here designated pglA (pilin glycosylation) . Insertional mutations were constructed in pglA in a range of meningococcal strains with well-defined lipopolysaccharide (LPS) or pilin-linked glycan structures to determine whether pglA had a role in the biosynthesis of these molecules . There was no alteration in the phenotype of LPS from pglA mutant strains as judged by gel migration and the binding of monoclonal antibodies . In contrast, decreased gel migration of the pilin subunit molecules of pglA mutants was observed, which was similar to the migration of pilins of galE mutants of same strains, supporting the notion that pglA is a glycosyltransferase involved in the biosynthesis of the pilin-linked trisaccharide structure . The pglA mutation, like the galE mutation reported previously, had no effect on pilus-mediated adhesion to human epithelial or endothelial cells . Pilin from pglA mutants were unable to bind to monospecific antisera recognizing the Gal (beta1-4) Gal structure, suggesting that PglA is a glycosyltransferase involved in the addition of galactose of the trisaccharide substituent of pilin.

Res Microbiol, 1998 Jun, 149(6), 381 - 7
Cooperation between the components of the meningococcal transferrin receptor, TbpA and TbpB, in the uptake of transferrin iron by the 37-kDa ferric-binding protein (FbpA); Gomez JA et al.; Meningococcal TbpAB complexes TbpA, TbpB and FbpA were purified and used to study their role in the uptake of iron from transferrin to FbpA . Purification was achieved by affinity chromatography techniques, yielding homogeneous, non-denatured and functional material . TbpA could not be separated from TbpB and had to be purified from a TbpB-defective mutant strain . FbpA was able to bind iron from transferrin only when TbpAB complexes, TbpA and/or TbpB, were also present during the interaction . The highest uptake efficiences were obtained with TbpAB complexes or TbpA/TbpB mixtures . We conclude that the TbpA and TbpB molecules form true functional transferrin receptors, that FbpA is able to take iron directly from transferrin when in the presence of the components of the receptor, and that both Tbps are necessary for an optimal operation of the uptake system.

Acta Crystallogr D Biol Crystallogr, 1998 Sep 1, 54 (Pt 5), 1005 - 7
Crystallization and preliminary X-ray diffraction analysis of antigen-binding fragments which are specific for antigenic conformations of sialic acid homopolymers; Patenaude SI et al.; Meningococcal meningitis is a

severe childhood disease which often results in significant disability or death . Two major etiological agents of meningitis are the group B meningococci and capsular type K1 E . coli . The virulence of these organisms is attributable to structural mimicry between their common alpha(2-8)-polysialic acid capsular polysaccharide and human tissue antigens, which allows the bacteria to evade immune surveillance . There is currently no effective vaccine to protect against this infection . It has been demonstrated that the capsular polysaccharide of the bacteria can adopt a unique 'antigenic conformation' . This antigenic conformation has formed the basis for the development of an N-propionylated polysialic acid vaccine . Immunization trials in mice with this vaccine show the production of two groups of antibodies, of which only N-propionylated polysialic acid-specific were protective . Knowledge of the structure of the antigen-binding site which recognizes the protective epitope is essential to determining the antigenic conformation of the polysaccharides, and is a critical aspect in understanding and improving the action of potential vaccines . The antigen-binding fragments (Fab) of one protective (13D9) and one non-protective (6B9) monoclonal antibody specific for the capsular polysaccharides of group B meningococci have been crystallized and have undergone preliminary X-ray diffraction analysis . Both crystals are observed to scatter X-rays to approximately 1.7 A resolution at the A1 station at the Cornell High-Energy Synchrotron Source . 13D9 has an orthorhombic unit cell with a = 41.8, b = 102.3, c = 134.7 A, with space group P212121 . Fab 6B9 has an orthorhombic unit cell with a = 89.6, b = 132.0 and c = 36.9 A, with space group P21212.

Rev Inst Med Trop Sao Paulo, 1998 Mar-Apr, 40(2), 113 - 7
The use of oligonucleotide probes for meningococcal serotype characterization; Sacchi CT et al.; In the present study we examine the potential use of oligonucleotide probes to characterize Neisseria meningitidis serotypes without the use of monoclonal antibodies (MAbs) . Antigenic diversity on PorB protein forms the bases of serotyping method . However, the current panel of MAbs underestimated, by at least 50% the PorB variability, presumably because reagents for several PorB variable regions (VRs) are lacking, or because a number of VR variants are not recognized by serotype-defining MAbs . We analyzed the use of oligonucleotide probes to characterize serotype 10 and serotype 19 of N . meningitidis . The porB gene sequence for the prototype strain of serotype 10 was determined, aligned with 7 other porB sequences from different serotypes, and analysis of individual VRs were performed . The results of DNA probes 21U (VR1-A) and 615U (VR3-B) used against 72 N . meningitidis strains confirm that VR1 type A and VR3 type B encode epitopes for serotype-defined MAbs 19 and 10, respectively . The use of probes for characterizing serotypes possible can type 100% of the PorB VR diversity . It is a simple and rapid method specially useful for analysis of large number of samples.

Rev Inst Med Trop Sao Paulo, 1998 Mar-Apr, 40(2), 65 - 70
Meningococcal disease caused by Neisseria meningitidis serogroup B serotype 4 in SÃ£o Paulo, Brazil, 1990 to 1996; Sacchi CT et al.; A large epidemic of serogroup B meningococcal disease (MD), has been occurring in greater Sao Paulo, Brazil, since 1988 . A Cuban-produced vaccine, based on outer-membrane-protein (OMP) from serogroup B: serotype 4: serosubtype P1.15 (B:4:P1.15) Neisseria meningitidis, was given to about 2.4 million children aged from 3 months to 6 years during 1989 and 1990 . The administration of vaccine had little or no measurable effects on this outbreak . In order to detect clonal changes that could explain the continued increase in the incidence of disease after the vaccination, we serotyped isolates recovered between 1990 and 1996 from 834 patients with systemic disease . Strains B:4:P1.15, which was detected in the area as early as 1977, has been the most prevalent phenotype since 1988 . These strains are still prevalent in the area and were responsible for about 68% of 834 serogroup B cases in the last 7 years . We analyzed 438 (52%) of these strains by restriction fragment length polymorphism (RFLPs) of rRNA genes (ribotyping) . The most frequent pattern obtained was referred to as Rb1 (68%) . We concluded that the same clone of B:4:P1.15-Rb1 strains was the most prevalent strain and responsible for the continued increase of incidence of serogroup B MD cases in greater Sao Paulo during the last 7 years in spite of the vaccination trial.

Trop Med Int Health, 1998 Sep, 3(9), 742 - 6
Meningitis caused by a serogroup W135 clone of the ET-37 complex of Neisseria meningitidis in West Africa; Kwara A et al.; Meningococci belonging to serogroup W135 caused several cases of meningococcal meningitis in The Gambia in 1995 and were isolated during a serogroup A epidemic in Mali in 1994 . The eight isolates tested belonged to the same clone of the ET-37 complex and differed in several bands from the pulsed-field gel electrophoresis restriction pattern of serogroup C meningococci of the ET-37 complex isolated in Mali . Three of 6 patients infected in The Gambia died, indicating that this W135 clone is virulent . Vaccines that protect only against infections with meningococci belonging to serogroups A and C are usually used to control outbreaks in Africa, although vaccines containing the W135 polysaccharide are available . The findings of this study indicate that outbreaks of meningococcal meningitis in Africa can be associated with serogroup W135 infections and that serogrouping is essential before vaccination campaigns are started.

Epidemiol Infect, 1998 Aug, 121(1), 95 - 101
Molecular variation of meningococcal serotype 4 antigen genes; Urwin R et al.; Changes in the frequency of serogroup B non serotypable (B:NT) meningococci isolated in England and Wales were investigated by T-track fingerprint analysis, DNA nucleotide sequence determination, and serotyping by whole cell ELISA and dot blot assay . Seventy-three per cent of the isolates designated as B:NT by the Meningococcal Reference Unit (MRU) dot blot assay during 1993-4, expressed variants of the serotyping antigen, PorB, that were serotype 4 by whole cell ELISA . T-track fingerprint patterns of these and other 'serotype 4' isolates revealed five distinct porB alleles which were shown by nucleotide sequence determination to encode different peptide sequences . Differential binding of the 'serotype 4' mAbs MN14G21 and 5DC4C8G8 in whole cell ELISA and dot blot assays was the result, (i) of differences in the peptide sequence of predicted surface loop I and (ii) an amino acid deletion in predicted loop VI of the PorB protein.

Epidemiol Infect, 1998 Aug, 121(1), 85 - 94
Dynamics of the meningococcal carrier state and characteristics of the carrier strains: a longitudinal study within three cohorts of military recruits; Andersen J et al.; Three cohorts of Danish male military recruits (n = 1069) were studied for pharyngeal meningococcal carriage during 3 months at different seasons: 39-47% of entrants were meningococcal carriers and the carriage rate remained constant over time and season . However, individual changes in the carrier state occurred frequently, and after 3 months 34% had changed carrier state on one or more occasions . Initially, a loss of carriage predominated; on the other hand almost 20% of non-carriers had acquisition of meningococci within the first month . The serological phenotypes of the 670 carrier strains were compared with those of 261 invasive strains recovered concurrently from patients with meningococcal disease country-wide . Both carrier strains and invasive strains were phenotypically heterogeneous . Almost 60% of the invasive strains belonged to three phenotypes: B:15:P1.7, 16, C:2a:P1.2, 5 and C:2b:P1.2, 5 . In contrast, these phenotypes only amounted to 3.2% of the carrier strains, among which no phenotype was found with a prevalence above 4.9% . However, 30% of the carrier strains had serological phenotypes identical to those of 80% of the invasive strains . Our results indicated that the transmission rate of potential pathogenic carrier strains did not differ from that of other carrier strains.

Infect Immun, 1998 Oct, 66(10), 4755 - 61
Specificity of bactericidal antibody response to serogroup B meningococcal strains in Brazilian children after immunization with an outer membrane vaccine; Milagres LG et al.; Pre- and postvaccination serum samples from 77 children aged 2 to 6 years, who received the Cuban BC vaccine (B:4:P1.15), were analyzed for bactericidal antibodies against a local B:4:P1.15 strain (N44/89) . Sera from 16 individuals with bactericidal antibodies against the B:4:P1.15 strain were tested against 23 Brazilian isolates . These include B:4 strains of

distinct serosubtypes: P1.15, P1.7,1, P1.3, P1.9, P1.nt, and a B:8,19,23:P1.16 strain . A Cuban B:4:P1.15 strain (Cu385/83) was also included in the study . The specificities of bactericidal antibodies were analyzed by using mutant strains lacking a class 1 protein (PorA protein) or a class 5 protein or both . The results indicated that PorA and class 5 proteins are the main targets recognized by the bactericidal antibodies of vaccinees . Nonetheless, a complex pattern of recognition by bactericidal antibodies was found, and vaccinees were grouped according to antibody specificity . Antibodies from some individuals recognized PorA of serosubtype P1.15 . However, antibodies from these individuals could not kill all P1.15 strains tested . Antibodies from a second group recognized both PorA and class 5 proteins, and antibodies from a third group recognized an as yet unidentified target antigen . The results demonstrate the importance of determining the fine epitope specificity of bactericidal antibodies to improve the existing vaccines against B meningococci.

J Clin Microbiol, 1998 Oct, 36(10), 3103 - 4
Unreliability of disc diffusion test for screening for reduced penicillin susceptibility in Neisseria meningitidis; Block C et al.; The 2-U penicillin and microgram oxacillin discs proposed for screening meningococci for susceptibility to penicillin were evaluated by using MICs measured by the E test . The discs yielded unacceptably high frequencies of misclassification of susceptibility category and should be abandoned in favor of MIC estimations . An agreed breakpoint for reduced penicillin susceptibility in meningococci is needed for the E test.

J Clin Microbiol, 1998 Oct, 36(10), 2828 - 34
Molecular epidemiology of recent belgian isolates of Neisseria meningitidis serogroup B; Van Looveren M et al.; In Belgium an increase in the incidence of meningococcal disease has been noted since the early 1990s . Four hundred twenty clinical strains isolated during the period from 1990 to 1995, along with a set of 30 European reference strains, and 20 Dutch isolates were examined by random-primer and repetitive-motif-based PCR . A subset was investigated by multilocus enzyme electrophoresis and pulsed-field gel electrophoresis . The data were compared with results obtained by serotyping (M . Van Looveren, F . Carion, P . Vandamme, and H . Goossens, Clin . Microbiol . Infect . 4:224-228, 1998) . Both phenotypic and molecular epidemiological data suggest that the lineage III of Neisseria meningitidis, first encountered in The Netherlands in about 1980, has been introduced in Belgium . The epidemic clone, as defined by oligonucleotide D8635-primed PCR, encompasses mainly phenotypes B:4:P1.4 and B:nontypeable:P1.4, but strains with several other phenotypes were also encountered . Therefore, serotyping alone would underestimate the prevalence of the epidemic clone.

J Biol Chem, 1998 Sep 25, 273(39), 25329 - 38
Characterization of the structure, function, and conformational stability of PorB class 3 protein from Neisseria meningitidis . A porin with unusual physicochemical properties; Minetti CA et al.; PorB proteins constitute the vast majority of channels in neisserial outer membranes and can be subdivided within meningococcal strains into two distinct and mutually exclusive families that are designated as class 2 and class 3 proteins . We recently characterized the functional activity and conformational stability of a PorB class 2 protein from Neisseria meningitidis (Minetti, C . A . S . A., Tai, J . Y., Blake, M . S., Pullen, J . K., Liang, S . M., and Remeta, D . P . (1997) J . Biol . Chem . 272, 10710-10720) . To evaluate the structure-function relatedness among the PorB proteins, we have employed a combination of electrophoretic and spectroscopic techniques to assess the conformational stability of zwittergent-solubilized class 3 trimers . The functional, physicochemical, and structural properties of the meningococcal class 2 and class 3 proteins are comparable with the notable exception that the latter exhibits a significantly higher susceptibility to SDS . The SDS-induced dissociation and partial unfolding of PorB class 3 is characterized by a single two-state transition with a midpoint at 0.35% SDS . The native trimeric assembly dissociates reversibly, forming partially folded monomers that retain the characteristic beta-sheet content of the transmembrane domain

with a concomitant increase in random coil structure arising from unfolding the rigid surface loops . These results provide new insight into the elucidation of porin folding pathways and the factors that govern the overall structural stability of meningococcal proteins.

J Med Microbiol, 1998 Sep, 47(9), 757 - 60
Analysis of TbpA and TbpB functionality in defective mutants of Neisseria meningitidis; Pintor M et al.; Iron uptake analysis suggested that the Neisseria meningitidis transferrin (Tf) binding proteins, TbpA and TbpB, form only one type of receptor complex . Mutants defective in the synthesis of either TbpA or TbpB, but not defective in both proteins, can bind Tf, suggesting that both proteins are surface exposed and function in Tf binding . Also, iron uptake from Tf into the meningococci did not require the presence of both Tbps . The TbpB-defective mutant incorporated c . 37% of the iron taken up by the wild-type strain, but this was insufficient for bacterial growth . The TbpA-defective mutant incorporated c . 50% of the iron taken up by the wild-type strain and was able to grow with Tf as the only iron source . Mouse antibodies specific for TbpA were able to block c . 70% of the iron uptake from Tf in the wild-type strain, whereas they blocked only 22% of iron uptake in the TbpB-defective mutant and did not block uptake in the TbpA-defective strain . These results emphasise that TbpA should be considered in future vaccine trials in which iron-restricted proteins are to be included in the vaccine formulation.

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vedi: Bibliografia sui danni neurologici (meningite ed altro) da Vaccino