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A MONKEY MODEL TO STUDY MEASLES VACCINATION STRATEGIES

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In humans measles is believed to confer lifelong immune protection against re-exposure to measles virus (MV), which appears largely based on persistence of MV neutralizing (VN) antibodies and the presence of MV specific cytotoxic T lymphocytes (CTL). Apart from humans several non human primate species can be infected with MV. However, the pathogenesis of this infection and the basis of immune protection in these animals is largely unknown. Here we show that cynomolgus monkeys (Macaca fascicularis) can be experimentally infected with a wild-type strain of measles virus (MV-BIL), that has recently been isolated from an outbreak of measles in school children in The Netherlands. Following intratracheal inoculation with different infectious doses, the virus could be isolated from peripheral blood mononuclear cells (PBMC), lung lavage cells and pharyngeal cells. Specific serum IgM, IgG and neutralizing antibody responses as well as MV-specific T cell mediated immunity were induced, quite similar to responses observed in infected children. Monkeys vaccinated with attenuated measles vaccine (MV-Schwartz) also showed a PBMC associated viraemia and specific IgM responses. They proved to be protected from intratracheal infection with MV-BIL 9 months after immunization. This model is currently used for the evaluation of new generations of vaccines and vaccination strategies in the framework of a WHO vaccine evaluation program.

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MEASLES IN VACCINATED HIGHSCHOOL CHILDREN AS EVIDENCED BY SPECIFIC CYTOTOXIC T CELL (CTL) AND IgA RESPONSES

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Recently, we observed an outbreak of measles among highschool children in The Netherlands, where 23 out of 949 children developed clinical measles. The virus was isolated, which, on the basis of nucleotide sequence analysis, appeared to be closely related to the wild-type MV strains that had circulated in Europe and the USA in 1989. Blood samples were collected from 10 cases with clinical measles and from 37 children who exhibited only part of the symptoms (n=33) or were clinically healthy (n=4). The simultaneous evaluation of antibody and T cell mediated measles virus (MV) specific immune responses allowed a more accurate identification of individuals with MV infection than the evaluation of specific antibody responses alone (IgM or IgG or both). On basis of the presence of MV specific IgA and of CD8+ CTL, it was concluded that 29 of the 47 children investigated had recently been infected with MV. Of these 29 children, 24 had a documented history of live MV vaccination. The replication of MV in individuals vaccinated with live attenuated measles vaccine may thus have implications for future MV eradication strategies.

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Maternally Derived Antibodies Against RSV.

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RSV-bronchiolitis is the predominant cause of severe respiratory tract infection in the first year of live, especially in the first 6 months when maternally derived antibodies are present.
In this study we analyzed the decay of maternally derived antibodies to RSV.
Sera of 44 children, taken at 0, 3 and 6 months of age, born in the period of march to june, were tested.
In a western blot antibodies of IgG subclasses (IgG1, 2, 3 and 4) against structural proteins of RSV (fusionprotein (F), glycoprotein (G), Nucleocapsid (N) and phosphoprotein (P) were tested. Direct neutralizing antibodies were tested in a microneutralisation assay.
All Children had antibodies of the IgG class at birth. In the western blot IgG1 antibodies showed the same pattern as IgG total. IgG2 was less often detectable. IgG3 and for were only detectable in one serum each, both sera taken at 0 months. This is in good agreement with the usual ratios of IgG subclasses in blood. Probably the western blot is not sensitive enough to detect IgG3 and 4 because of competition with abundant IgG1.
Direct neutralizing antibodies diminished quickly in the first 3 months; GMT at 0 months 1:300, At 3 months 1:35, at 6 months 1:18. calculated plasma half live of neutralizing titers 26 days. This finding correlates well with normal plasma half-lives of IgG antibodies. Prince et al. (J. Virology; 1985:517-520) find in a mouse model That neutralizing titers of >1:100 are necessary for protection against lower respiratory tract infection and a titer of >1:380 for complete protection. The rapid fall of neutralizing titers in the first 3 months could be responsible for the fact that children are not protected against severe RSV infection.

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CEREBROSPINAL FLUID (CSF) δ INTERFERON (INF) TUMOUR NECROSIS FACTOR-α (TNF) AND INTERLEUKIN-1ß (1L-1ß) CONCENTRATIONS IN CHILDREN WITH TUBERCULOUS MENINGITIS (TBM).

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CSF INF concentrations were determined on 76 occasions in 30 children (mean age 27.4 months) with TBM at varying intervals during the first month of treatment. The mean concentration during the 1st week of therapy was 780 pg/ml falling to 554 pg/ml in the 2nd week, 529 pg/ml in the 3rd week and 269 pg/ml in the 4th week. TNFα and 1L-1ß concentrations were determined in 23 of these children on 56 occasions. TNFα was present in low, but detectable, concentration throughout the first month of therapy with mean concentrations of 17.15 pg/ml, 11.39 pg/ml, 11.08 pg/ml and 11.19 pg/ml in the 1st, 2nd, 3rd and 4th weeks respectively. 1L-1ß concentrations fell from a mean of 51.56 pg/ml to 43.1 pg/ml, 41.7 pg/ml and 17.62 pg/ml in the 2nd, 3rd and 4th weeks of therapy. The persistence of these cytokines in the CSF for a prolonged period after starting therapy indicates an immune response fundamentally different from that in bacterial meningitis. Evaluation of these cytokines and others could provide insights into the molecular pathogenesis and antiinflammatory treatment of TBM.

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RSV illness is associated with the prescence of autoreactive antibodies (ab)

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Background: Studying RSV ab formation by western blot sera exhibited also ab against Hep2-cells.
Aim of the study: Determination of prevalence, incidence and clinical relevance of Hep2-ab in infants hospitalized for RSV infection.
Patients and methods: 49 RSV-antigen(ag) positive infantes (median age 4 mo) and 30 rotavirus(RV)-ag positive infants as controls. IgG and IgA western blot with RSV-infected and non-infected Hep2-cells as ag.
Results: RSV ab formation was age dependent. Hep2-ab prevalence was higher in RSV (36/49) than in RV-ag positive (5/30) infants (p=0.001). Hep2-ab were mostly directed against 65, 47, 46, 33, 30 kD ag. Seroconversion occured only in 3/49 of the RSV group. A **multiple regression** analysis revealed the following correlations: 33 kD **Hep2-ab** with airway disease (OR 12, p=0.012), 30 kd ab with underlying cardiac disease (OR 20, p=0.011); 42 kD **RSV-ab** with pneumonia (OR 7.5, p=0.017), 94 kD ab negatively with bronchilitis (OR 0.064, p=0.006)
Conclusion: The study proved to be internally validated by demonstrating the expected effect of RSV-ab. The data on Hep2-ab point on a role for these pre-existing autoreactive ab in the pathogenesis of RSV infection.

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Epidemiology and microbiology of congenital bacterial infections in VLBW-infants with respiratory failure.

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Background: Bacterial infections are considered to be a main factor for preterm birth. We analyzed the epidemiology of congenital bacterial infections on basis of data from three multicenter trials in VLBW-infants. **Patients and Methods:** Congenital bacterial infections were defined as clinical illness with positive blood culture (sepsis) or respiratory failure with positive bacteriological culture of the tracheal aspirate (congenital bacterial pneumonia), both samples taken within hour one following birth. VLBW-infants were enrolled in different trials of bovine surfactant (SF-RI1, Alveofact®) investigating efficacy, modifying factors, and dosing of the particular surfactant preparation. **Results:** A total of 453 VLBW-infants were enrolled (mean gestational age 27.9 ± 1 wks, mean birthweight 1022 ± 168 g; ± SD) all infants requiring intubation and mechanical ventilation during hour one following birth. Positive bacteriological cultures were obtained in 55 infants, (septicemia 20). The microbiologic data are given in table 1:

gram-positive germs		gram-negative germs	
Group B streptococci	(n = 16)	E. coli	(n = 10)
Streptoc. vir.	(n = 4)	Pseudomonas aer.	(n =2)
Staph. aureus	(n = 2)	Enterobacter cloacae	(n = 3)
Coag. neg. staph.	(n = 3)	Serratia marc.	(n = 1)
Pneumococci	(n = 1)	Acinetobacter	(n = 2)
Enterococci	(n = 3)	Fusobact.	(n = 2)
Listeria monocyt.	(n = 2)	Bacteroides frag.	(n = 4)

Conclusion: The incidence of congenital bacterial infections was found in the range of 12%, with GBS and E. coli as the most frequently isolated germs. These findings have to be considered with respect to timing and selection of antimicrobial therapy.