IV. ABSTRACT

The human metapneumovirus is a novel paramyxovirus associated with acute respiratory infections in children, adults, elderly and immunocompromised individuals. It has a worldwide distribution and the prevalence range between 1.5% to 25% in individuals with respiratory infections. Based on phylogenetic analysis 2 distinct genetic groups (A and B) that are sub-divided into four subgroups (A1, A2, B1 and B2) have been shown to circulate. Until recently, there was no information on the molecular epidemiology and the clinical characteristics of the hMPV in Africa, including South Africa, a region with a high prevalence of paediatric human immunodeficiency virus type-1 (HIV) infection.

The molecular epidemiology and clinical characteristics of the hMPV in South Africa was investigated over a three period (2000-2002) in children hospitalized with lower respiratory tract infection. The children were part of a cohort participating in a phase 3 clinical trial investigating the efficacy of a 9-valent-pneumococcal protein-polysaccharide conjugate vaccine (PCV).
The objectives of the study were: i. to investigate the molecular epidemiology of hMPV in South Africa; ii. characterize the burden of hMPV disease and determine the clinical features of hMPV-LRTI in children infected and not infected by HIV; iii. probe the role of *Streptococcus pneumoniae* in the pathogenesis of hMPV-LRTI.

The overall prevalence of hMPV in children hospitalized with lower respiratory tract infections (LRTI) was 7.4%. The mean age of children with hMPV

associated LRTI (hMPV-LRTI) in South Africa was 13.3 months (range 1.4-49.2 months), with HIV infected children being older than children not infected with HIV (mean [range] 17.6 [4.5-44.3] vs. 12.3 [1.4-49.2] months; P=0.007). The incidence of hMPV-LRTI was 5.0 (95%C.I.3.3-7.5) fold greater in HIV infected children (incidence rate: 2 504 [95%C.I. 1 683-3 577] per 100 000) than in HIV uninfected children (incidence rate: 505 [95%C.I. 409-618] per 100 000, P<0.0001). Human metapneumovirus was identified less frequently than RSV but more commonly than other studied respiratory viruses.

The double-blind PCV-9 vs. placebo controlled trial was used to probe the role of pneumococcal co-infections contributing to the pathogenesis of severe hMPV-LRTI. The incidence of hospitalization for hMPV-LRTI was reduced by 46% (95%, CI, 25-63; P=0.0002) in PCV-9 vaccinees compared to placebo recipients. This inferred that coinfection with *Streptococcus pneumoniae* was integral to the pathogenesis of hMPV-LRTI requiring hospitalization.

Both groups of the hMPV circulated during the three year period including concurrent circulation of multiple subtypes of the virus. There was a transition from group B to group A subtype virus as the dominant circulating virus over sequential years.

Sequence analysis of the two attachment glycoproteins (F and G), showed the F gene protein to be highly conserved, in contrast the attachment protein gene (G protein) was highly variable particularly in the extracellular domain between lineages. Repeat hMPV-LRTI by either homologous or heterologous

strains within 3 months of each other suggested that natural infection did not confer complete immunity to hMPV.

The present study demonstrated that hMPV is a leading pathogen associated with LRTI among children in Africa and indicated that occult pneumococcal co-infections' were integral in the pathogenesis of hMPV-LRTI requiring hospitalization. Additionally, this is the first study to have characterized the molecular epidemiology of hMPV in Africa and provides insight as to issues that may exist regarding the design of an hMPV vaccine.