**Supplementary material**

**Methods**

**Study population and study design**

Cases were identified as part of the Group for Enteric, Respiratory and Meningeal disease Surveillance-South Africa (GERMS-SA) national, laboratory-based, active surveillance programme. Included hospitals were mid-level, academic or referral hospitals in each province. Patients eligible to receive at least one dose of PCV through the Expanded Programme on Immunisation (EPI) were born after 15 February 2009; except the Western Cape and Free State where date of birth used was 15 May 2009 and 15 September 2009 respectively. Cases were identified through laboratory visits, record review and electronic laboratory alerts. Quarterly audits were performed to detect missed cases.

Controls were matched to the case by date of birth within one calendar month for children ≤12 and within two months for children >12 months of age. Lists of potential controls were systematically compiled daily from hospital registers. We attempted to enroll controls as soon as possible after the case-admission date. Hospitalized controls were only eligible for enrollment if identified within 72 hours of their admission. Information collected on cases and controls included household characteristics, presence of chronic medical conditions, and other potential risk factors for IPD. Parents or guardians of cases and controls were approached for consent. Case patients who died or were discharged before enrolment and for whom caregivers could not be reached despite repeated attempts were included in the study using available data from hospital records (n=4 included in final analysis).

Pneumococcal isolates were sent to the National Institute for Communicable Diseases (NICD) for serotyping and antimicrobial susceptibility testing. Culture-negative specimens (n=18) were forwarded to the reference laboratory on clinical or laboratory suspicion of pneumococcal disease and confirmed with real-time *lytA* polymerase chain reaction (PCR).[1] For the latter specimens, and when isolates became non-viable on subculture (n=19), a PCR serotyping assay consisting of 11 duplex reactions, with an additional primer/probe set for serotype 6C/D, was used.[2]Isolates were screened for resistance to penicillin (using oxacillin), erythromycin, clindamycin, chloramphenicol, tetracycline, rifampin and trimethoprim-sulfamethoxazole (Mast Diagnostics Ltd, Bootle, Merseyside, United Kingdom) by disc diffusion. Minimum inhibitory concentrations were determined for resistant isolates using broth microdilution. Results were interpreted as susceptible or non-susceptible (intermediately resistant and resistant). Penicillin non-susceptibility was defined using the lower Clinical and Laboratory Standards Institute (CLSI) meningeal breakpoints.[2]

**Statistical analysis**

Data were double-entered at NICD. Analyses were done with Stata statistical software (version 12.1). For each univariable analysis, we used all available case information. In the multivariable model, patients with missing data for included variables were dropped. We checked for colinearity and two-way interactions in all final models.

**Results**

Specimen types differed between enrolled and non-enrolled cases (110/361, 30% vs 4/27, 15% from CSF; 241/361, 67% vs 19/27, 70% from blood; 10/361, 3% vs 4/27, 15% from another site for enrolled vs non-enrolled cases respectively, p=0.002). Non-enrolled cases were more likely than enrolled cases to come from KwaZulu-Natal province (11/27, 41% vs. 52/361, 14%, p=0.04); the only province for which electronic laboratory alerts were unavailable.

Additional diagnoses with a frequency of more than 10 individuals amongst 177 HIV-uninfected controls with an “other” diagnosis included upper respiratory tract infection (n=36), toxin ingestion (n=25), congenital conditions (n=23), rash (n=16) and urinary tract infection (n=16).

Reference List

(1) Ruoff KL, Whiley R.A., Beighton D. Streptococcus. In: Murray PR, Baron E.J., Jorgensen J.H, Yolken R.H., eds. Manual of Clinical Microbiology.Washington D.C.: ASM Press, **2006**:405-21.

(2) CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement. Clinical and Laboratory Standards Institute (CLSI)(Formerly NCCLS) **2012**; Wayne, Pennsylvania:CLSI.