

Rapid pneumococcal evolution in response to co-trimoxazole prophylaxis in a high-HIV burden population

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Background

- Disease caused by *Streptococcus pneumoniae* represents a major problem in South Africa, where ~17% (~6 million) of the adult population were HIV positive in 2011 according to the 2012 UNAIDS report.
- In 2000, co-trimoxazole chemoprophylaxis was implemented for HIV-infected individuals in South Africa.
- Prior to PCV introductions, 23F was the forth serotypes causing disease in all ages groups in South Africa, and were associated with resistance to penicillin, tetracycline, and chloramphenicol.
- A sample of 132 serotype 23F invasive isolates between 1989 and 2007 throughout South Africa, revealing two different 23F lineages, PMEN1 and PMEN15, in which PMEN15 was in an increasing trend.
- This study aimed to reconstruct the phylogeny of PMEN15 in South Africa and its rapid response to the widespread use of co-trimoxazole chemoprophylaxis in South Africa.

Methods

Recombination-removed phylogeny with **GUBBINS** using RAxML, detection of antibiotic resistance determinants with **ARIBA**. Visualisations with **Phandango**

Results

A total of 242 serotype 23F invasive isolates between 1989 and 2014 throughout South Africa, revealing PMEN1 was common in the 1990s, but MDR PMEN15 lineage rose in the early 2000s (Mann-Kendall test, $p = 2.9 \times 10^{-9}$), as PMEN1 disappeared (Fig. 1). There were two major PMEN15 sub-lineages, PMEN15A and PMEN15B (Fig. 2A). Fig. 1 showed the dynamics of PMEN1 and two PMEN15 sub-lineages within South Africa.

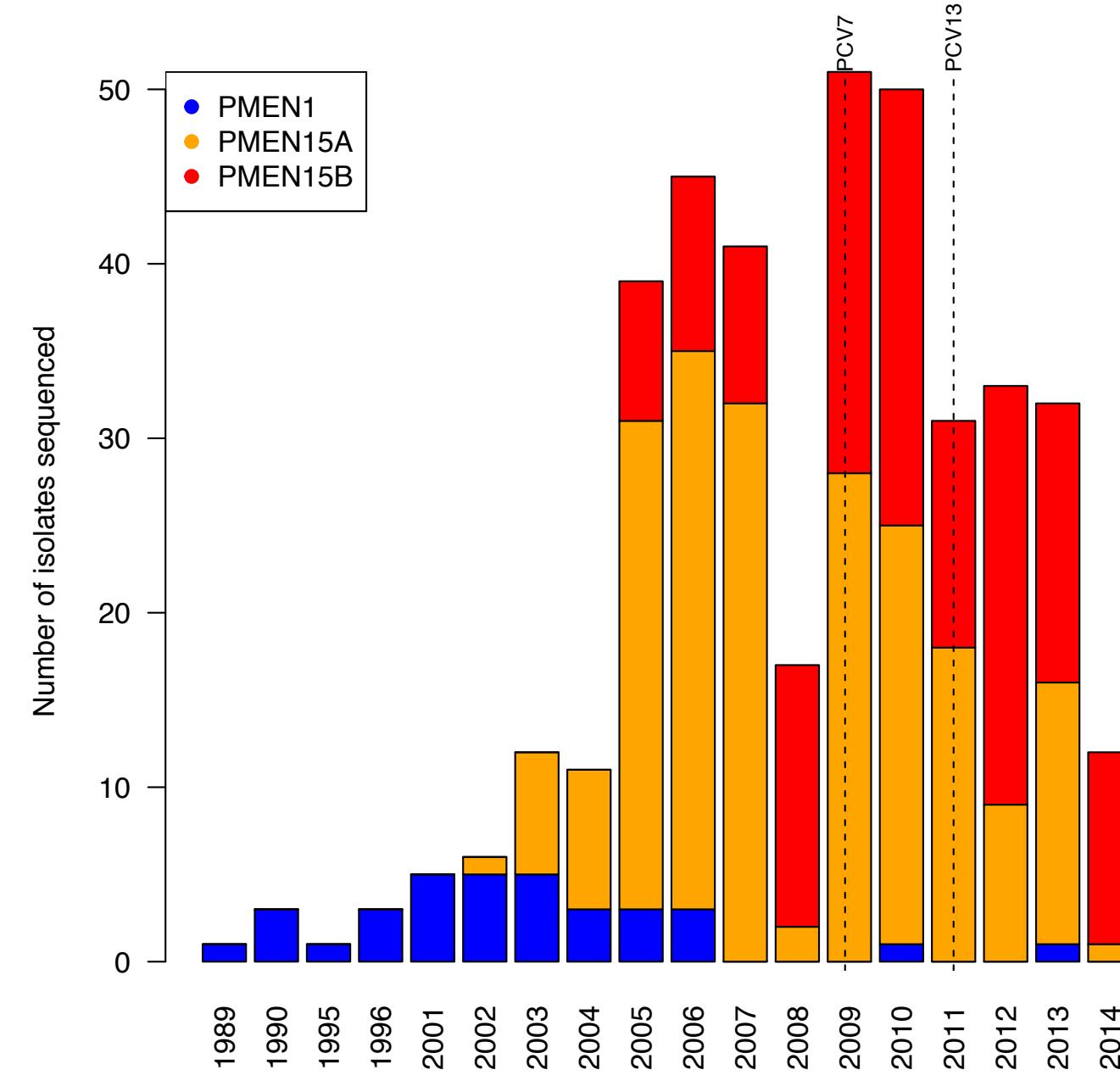


Fig.1 Prevalence of PMEN1 and two major PMEN15 sub-lineages over time

The evolution of this emerging lineage was characterised with a global collection of PMEN15 ($n=489$), which included South African isolates ($n=369$) and isolates from other fifteen countries ($n=120$) for comparison. Among them, 356 and 133 were invasive and carriage isolates, respectively.

Conclusions

This study showed a parallel expansion of two sub-lineages that independently acquired co-trimoxazole resistance in South Africa. The rapid evolutionary response of PMEN15 to HIV-associated chemoprophylaxis may contribute to its success.

This lineage exhibited strong phylogeographic structure (Fig. 2A) and it had entered South Africa twice. High recombination frequency was observed in two resistance determinants, *folA* and *folP*, which are associated with co-trimoxazole resistance (Fig. 2C).

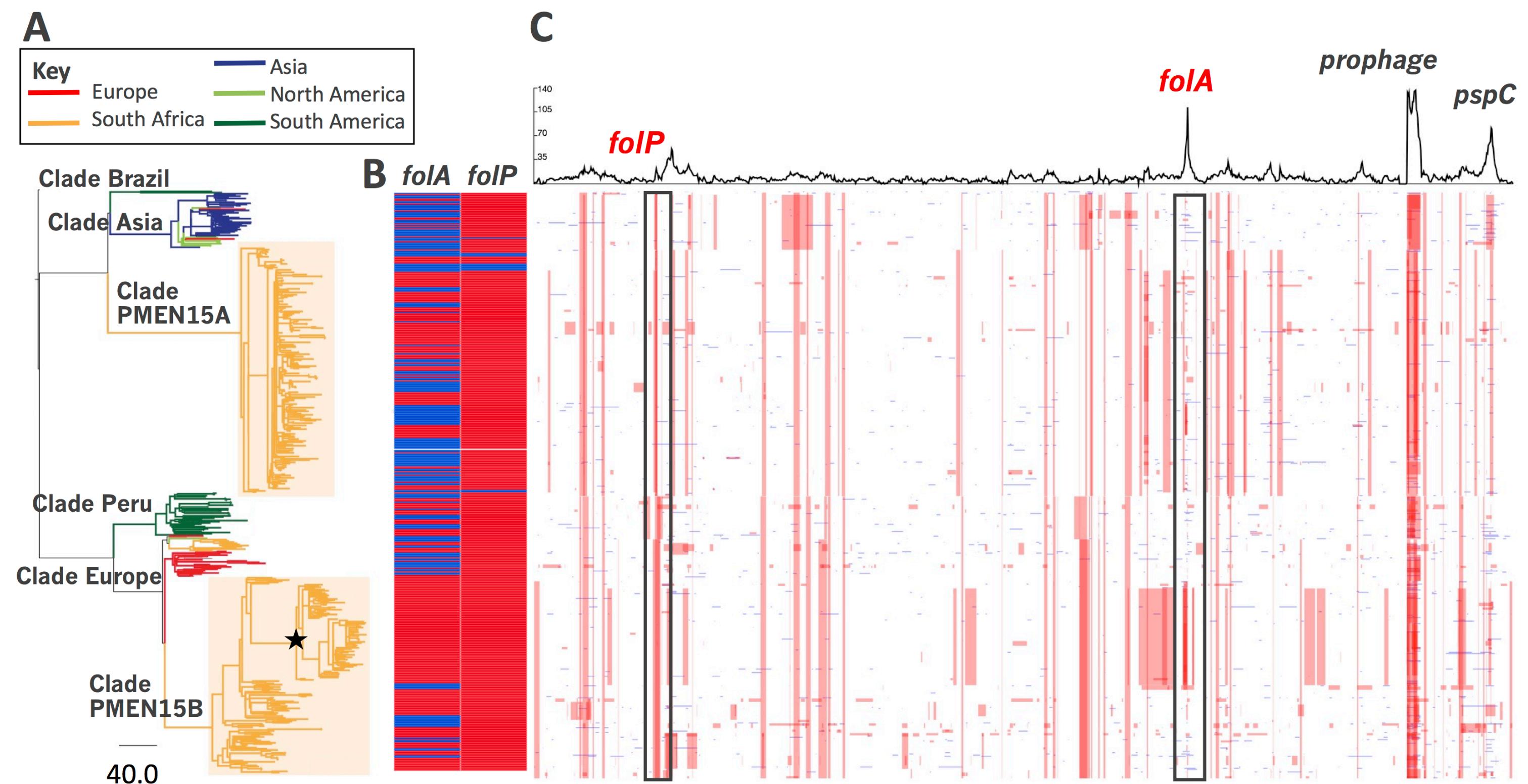


Fig. 2 Reconstruction of the evolutionary history of PMEN15. (A) Phylogeny of PMEN15 (B) The columns indicated the wildtype (blue) and mutated (red) *folA* and *folP* (C) Plot showing recombination frequency (D) position of the putative recombination events corresponding to the plot.

High-level co-trimoxazole resistance was observed in 68.3% (252/369) of the South African isolates, 60.5% (23/38) in South American isolates, 40.9% (9/22) in European isolates, 25% (12/48) in South-Asian isolates. The high prevalence of cotrimoxazole resistance in South African PMEN15 isolates is the consequence of the acquisitions of mutations in *folA* and *folP* within PMEN15A and PMEN15B.

Clade PMEN15A isolates with mutations in *folA* and *folP* had 3-fold increase in prevalence in 2005 (Fig. 3), which coincides its rise at the same year shown in Fig.1. Mutations in both genes were acquired by multiple independent recombination events (Fig.2D). Clade PMEN15B isolates were all non-susceptible to co-trimoxazole based on the *folA* and *folP* genotypes (Fig. 3). It was first detected in 2005 and had four-fold increase in prevalence by 2008 (Fig.1 and Fig.3). A clonal expansion of beta-lactam non-susceptible isolates was observed within this clade (Fig. 2A, asterisked). Unlike PMEN15A, PMEN15B was disseminated throughout the country (Fig. 4).

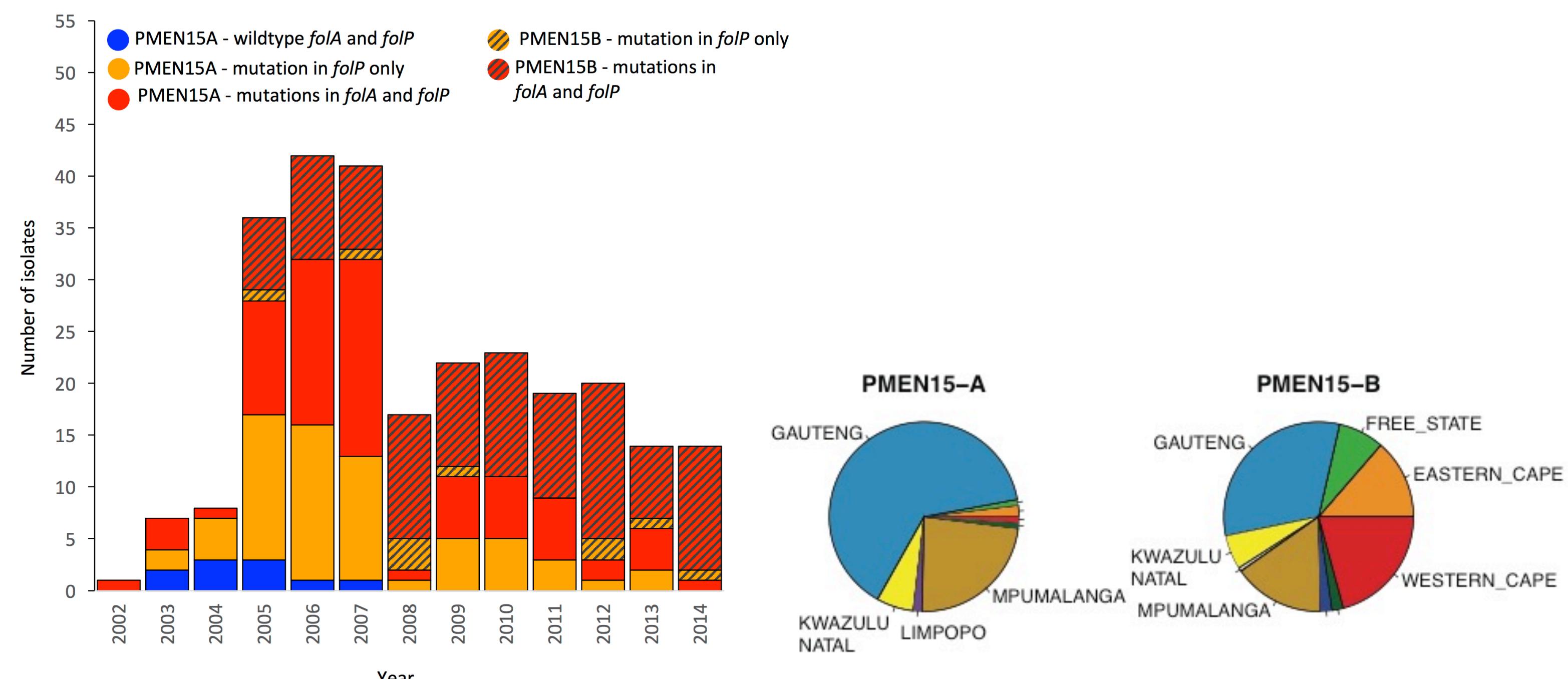
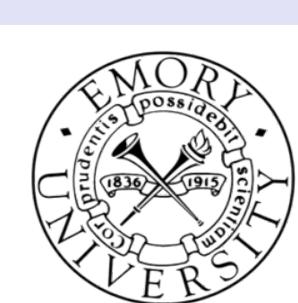


Fig. 3 Prevalence of co-trimoxazole resistant genotypes over time

Fig. 4 Geographical distribution of PMEN15 sub-lineages in South Africa



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