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Scarlet fever changes its spots

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Historically, the human pathogen *Streptococcus pyogenes* (group A streptococcus) was a major cause of death as a result of sepsis and fatal epidemics of scarlet fever.[1] Despite a decline in the incidence and severity of these toxin-mediated diseases over the past century in high-income countries, group A streptococcus is still among the top ten infectious causes of human mortality, with more than 500 000 deaths annually.[2] In addition to the persistently high disease burden in low-resource nations, an unprecedented global resurgence of scarlet fever and severe invasive group A streptococcal infections has been seen in the past few decades. However, there is continuing scientific uncertainty surrounding specific factors that might have led to the re-emergence of these diseases.

Group A streptococcus is classified into more than 200 *emm* types.[3] Since the mid-1980s, a hypervirulent serotype *emm*1 group A streptococcus clone has been frequently isolated from severe forms of invasive group A streptococcal disease.[4] The ongoing outbreak of scarlet fever in the UK, first reported in 2014, is polyclonal in nature and not caused by a single epidemic strain of group A streptococcus.[5,6] This scarlet fever outbreak is associated with multiple distinct *emm* types, with *emm3, emm12*, *emm1*, and *emm4* being the most prevalent. In *The Lancet Infectious Diseases*, Nicola Lynskey and colleagues[7] report on the rapid emergence of a new dominant group A streptococcus *emm1* lineage in the UK ($M1_{UK}$) during the 2014–16 scarlet fever seasonal surges, accounting for a synchronous rise in the incidence of invasive infections. Comparative genomic and phylogenetic analysis of upper respiratory tract (isolates from 2009–16) and invasive (2013–16) *emm1* group A streptococcus isolates from the UK showed that the $M1_{UK}$ lineage—which appears to have evolved in the UK as early as 2010—is genotypically distinct from other pandemic *emm1* isolates and is characterised by 27 lineage-defining mutations in regulatory and metabolic genes. These conserved and lineage-specific mutations are associated with significantly increased expression of streptococcal pyrogenic exotoxin A (SpeA)—a phage-encoded superantigen that is crucial for the establishment of nasopharyngeal infection[8] and has played an important role in the epidemic spread of *emm1* strains since the 1980s.[4] Lynskey and colleagues' findings, therefore, provide a plausible explanation for the increased capacity of $M1_{UK}$ to cause toxin-mediated scarlet fever and invasive infections in the UK. Given that intermediate members of the $M1_{UK}$ lineage were also identified in countries outside the UK, there is major concern as to whether similar pathogenic changes might occur elsewhere.

Public Health England reported an alarming rise in scarlet fever notifications across the UK in 2018, with a doubling in numbers of reported cases compared with the start of the outbreak in 2014. Mainland China and Hong Kong also have an ongoing outbreak of scarlet fever, with about 500 000 reported cases since 2011.[9] Similar to the UK, case numbers have been increasing in east Asia in the past 2 years; however, the driving force responsible for the enhanced pathogenicity of group A streptococcus in this region is yet to be understood. In contrast to the UK, acquisition of novel prophages harbouring new combinations of toxin genes (encoding the superantigens streptococcal superantigen A and streptococcal pyrogenic exotoxin C, and the DNase Spd1) and antimicrobial resistance genes were closely associated with the emergence and expansion of scarlet fever-associated *emm12* and *emm1* lineages in mainland China and Hong Kong.[9,10]

Comparative population analyses of scarlet fever *emm1* genomes from east Asia and the UK support

the conclusions made by Lynskey and colleagues that these lineages have different evolutionary histories (appendix). None of the scarlet fever genomes from east Asia carry the $M1_{UK}$ defining polymorphisms, including *rofA* mutations. Variable carriage of scarlet fever associated virulence genes (*ssa*, *speA*, and *speC*) and the DNase *spd1* is also evident within the global scarlet fever *emm1* population, providing further support that scarlet fever *emm1* lineages from different geographical regions are evolving independently and are associated with different virulence characteristics. These data show that multiple mechanisms related to toxin carriage and expression characteristics probably play a key role in global disease outcomes.

The continuing increase in scarlet fever and invasive disease notifications in the UK exemplifies the essential need to install global surveillance systems and address the increased group A streptococcus disease activity as a public health priority. The report by Lynskey and colleagues sends out an important warning for the global public health community: recently emerging scarlet fever group A streptococcus strains have enhanced invasive potential, which might have profound implications for the future global health burden.

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Essential metrics for high-quality reporting of neonatal sepsis research in low-resource settings

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Although mortality in children younger than 5 years in sub-Saharan Africa has declined by 58% since 1990, neonatal deaths (in infants younger than 28 days) represent an increasing proportion, currently at 37%.[1–3] Infection remains the third most important cause overall, and the leading cause of late neonatal deaths is hospital-acquired sepsis.[1,4] It is within this context that, in *The Lancet Infectious Diseases*, Uduak Okomo and colleagues reviewed the causes of severe bacterial infections (bloodstream infection and meningitis) and the antimicrobial resistance profile of the causative pathogens among neonates in sub-Saharan Africa.[5] The authors also assessed the quality of neonatal infection reporting by use of the Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) checklist.[6] This review is timely, in the leadup to the Sustainable Development Goal of ending preventable neonatal deaths by 2030. Annual cost estimates for neonatal sepsis in sub-Saharan Africa range from US$10 billion to 469 billion, with an associated loss of 5·3–8·7 million disability-adjusted life years.[7,8] Current and regionally-representative data on neonatal pathogens and their antibiotic susceptibility patterns in sub-Saharan Africa are essential to guide