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Title: MODES OF TRANSMISSION AND ATTACK RATES OF GROUP A STREPTOCOCCAL INFECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background & Aims: Group A Streptococcus (Strep A) is an important cause of mortality and morbidity globally. This bacterium is responsible for a range of infections and post-infectious sequelae which includes rheumatic heart disease. Droplet transmission is the dominant paradigm, but little is known about the relative contribution of other modes of transmission of Strep A infection. We aimed to summarise contemporary evidence of Strep A transmission in humans to inform the development of environmental prevention and control strategies to reduce the burden of Strep A diseases.

Methods: Using a comprehensive search strategy to identify Strep A transmission studies that have been published in English since 1980, full-text articles were identified and considered for inclusion against predefined criteria. Studies were subject to meta-analysis if molecular techniques were used to identify Strep A and if the same strain was identified in both clinical and environmental swabs. We used the random-effects meta-analysis model to aggregate attack rate estimates with 95% confidence intervals (CI) calculated for each transmission mechanism incorporating the Freeman-Tukey transformation to account for between-study variability. Direct transmission occurs when there is direct contact with secretions of an index case. For Strep A these include transmission through droplets and skin-to-skin contact. Indirect transmission requires an intermediate stage that has been contaminated. For Strep A these include airborne transmission, vehicles (inanimate objects), and vectors (animals). Attack rates were calculated by dividing the number of people infected by those exposed.

Results: Whilst Strep A causes an enormous global burden of disease with > 600 million estimated episodes per year, the published literature over 43 years only contains limited data on 1, 022 individuals. In this context, the results are biased towards situations in which Strep A transmission can be documented. Nonetheless, our results provide key new insights. One hundred and sixty-six transmission cohorts were included of which 36 transmission cohorts were eligible for meta-analysis. All 36 transmission cohorts were pooled to determine an overall attack rate for Strep A. For direct contact, there were 11 cohorts which comprised droplet (1) and contact (10) modes of transmission. For indirect contact, there were 23 cohorts which comprised airborne (4), vehicle (16), and vector (3) modes of transmission. Two cohorts reported multiple modes involved. The overall Strep A attack rate for both direct and indirect contact was 19.53% (95% CI, 14.05% to 25.54%). The attack rate for direct contact was 20.53% (95% CI 8.26% to 36.37%) and for indirect contact was 20.35% (95% CI 14.15% to 27.26%). There was considerable variation in pooled attack rates by modes of transmission for indirect contact. These included transmission via airborne particles, moist and dry surfaces, clothing, food, medical equipment and animals. Pooled attack rates for Strep A by geographical location was 30.38% (95% CI 20.89% to 40.75%) in non-urban settings and 7.36% (95% CI 2.60% to 14.21%) in urban settings. Droplet transmission is no longer the only nor dominant mode of Strep A transmission.

Conclusions: This review is the first to systematically synthesise transmission mechanisms of Strep A and quantify associated attack rates. Strep A attack rates were high for direct and indirect contact transmission. The dominant assumed mechanism of transmission was reported in only 1 cohort, whilst direct contact and indirect transmission via airborne particles, surfaces, food, clothing and medical equipment were common. The difference between urban and non-urban settings may also be limited by publication bias and likely higher in non-urban settings due to social determinants of health being more common. Further studies are needed before animal-associated transmission is prioritised for prevention activities.