**Article:**
Turner, C.E. orcid.org/0000-0002-4458-9748 (2023) Can group A streptococcus infections be influenced by viruses in the respiratory tract? The Lancet Infectious Diseases, 23 (2). pp. 142-144. ISSN 1473-3099

https://doi.org/10.1016/s1473-3099(22)00865-9

**Can group A *Streptococcus* infections be influenced by viruses in the respiratory tract?**

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Infections such as tonsilitis, scarlet fever and invasive disease caused by group A *Streptococcus* (also known as *Streptococcus pyogenes* or Strep A) display strong seasonality, typically increasing in winter and peaking in spring. The 2022-23 seasonal increase in scarlet fever and invasive group A *Streptococcus* (iGAS) notifications in England (reported by the UKHSA[1]) has occurred earlier than in previous seasons but it is also unusual in that the cases of iGAS are concerningly higher in children under 10 than in the past 5 seasons.

In 2014, UKHSA reported a sudden seasonal surge in scarlet fever notifications to a 50-year high, the majority (87%) being in children under 10.[2] This scarlet fever resurgence has occurred every season since, with the exceptions of 2020-21 where notification level dropped when the COVID-19 pandemic measures were introduced, and remained low over 2021-22. Scarlet fever and iGAS have the same seasonal pattern and notifications of both decreased while the pandemic measures were in place. In some pre-pandemic seasons where scarlet fever notifications were high, so were iGAS notifications, most notably during 2017-18 where cases peaked to their highest since the resurgence.

In this current unusual season it is not yet clear as to whether we are currently observing an early return to the pre-pandemic seasonal upsurges in GAS infections or something else is happening. However, Scotland, European countries including Ireland, The Netherlands, France, and Sweden, and the CDC (USA) have also reported increases or high rates of iGAS cases in children under 10, suggesting some international factor is at play. One theory that has been proposed is the concurrent high level of circulating respiratory viruses in children. While SARS-CoV-2 continues to circulate at fairly high levels, cases of respiratory syncytial virus (RSV) recently peaked in young children and viral influenza cases are currently surging along with other respiratory viruses that typically increase during winter.

GAS and the majority of respiratory viruses share the same seasonal pattern of infection rates, and it is very likely that they influence each other and impact on infection outcome. The severity of respiratory tract infections can significantly increase when bacterial infections occur concurrently with or after viral infections, known as coinfection or superinfection respectively.

It has been known since the 1918 pandemic that bacterial infections can complicate viral influenza infections[3] and the most common causes of severe and lethal bronchopneumonia during this time were coinfections of influenza A virus (IAV) with *Streptococcus pneumoniae* (pneumococcus) or GAS .[4] Circulating IAV and influenza B virus (IBV) have both been associated with increased risk of severe GAS infections.[5,6] Vaccination against influenza has also been shown to reduce the risk of severe invasive GAS disease.[7] Although data is currently limited for GAS, there may be complex interactions between virus and bacteria that involve direct effects on the bacteria and host environment as well as modifications to the immune response that predispose the host to superinfections.

The most well characterised interactions are that of IAV and pneumococcus. Several studies have shown that pneumococcal burden, inflammation and mortality increased when mice were infected with pneumococcus after a non-lethal IAV infection. The limited work with IAV and GAS also indicates enhanced infection severity for superinfections than for mono-infections.[3] The damage and epithelial barrier disruption caused directly by IAV or by the subsequent inflammation may allow bacterial pathogens to access the host. For example, the sialic acid removal activity of IAV neuraminidase on human respiratory cells exposes targets to enhance pneumococcal adhesion, although neuraminidase activity varies between viral strains.[8] Other modifications of the host environment by IAV, such as alterations to host metabolome, also influence the behaviour and burden of bacteria within the same environment and can last beyond detectable viral infection.

Other respiratory viruses, such as rhinovirus, RSV and enteroviruses are also often associated with bacterial coinfections in children and can have enhanced infection severity.[9] Direct binding of the RSV protein G to the

pneumococcal cell wall protein PBP1a led to upregulation of pneumococcal virulence factors, influencing inflammation and disease.[10]

Indirect effects of viruses on bacterial superinfections include the localised depletion of immune cells by IAV-induced cell death and the suppression of immune cell responses through anti-viral T-cell induced IFN-gamma response and anti-inflammatory IL-10 secretion.[9] While direct and indirect effects of viruses may leave the host vulnerable to bacterial infection, research indicates this may be dependent on both viral and bacterial strain types.

Data on GAS superinfections is scarce; patients with severe GAS infections are not normally additionally tested for respiratory viruses. It is important that we do consider the potential for close interactions between viruses and bacteria as they can significantly impact on infection outcomes. We also need to know if asymptomatic or carriage state viruses can influence infections in the same way as active viral infections. There is a critical need for more research in this area as it may shed some light on the current situation and, importantly, influence future research, treatments, and other infection interventions.

**Declaration of interest**

I declare no competing interests

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