Towards evidence based medicine for paediatricians

Edited by Bob Phillips

QUESTION 1
Are household contacts of patients with invasive group A streptococcal disease at higher risk of secondary infection?

SCENARIO

You are caring for a 7-year-old boy with group A streptococcal (GAS) toxic shock syndrome (TSS). You wonder whether his parents and siblings are at increased risk for invasive GAS disease and whether chemoprophylaxis should be considered.

STRUCTURED CLINICAL QUESTION

Are close household contacts (population) of a patient with community-acquired invasive GAS disease at higher risk of invasive GAS disease (outcome) than the general population (comparator)?

SEARCH STRATEGY AND OUTCOME

PubMed, Medline (OVID, 1946–present) and EMBASE (OVID, 1974–present) databases were searched using the following structure: (group A streptococc* OR streptococcus pyogenes OR beta haemolytic streptococc* OR beta hemolytic streptococc*) AND (sepsis OR bacteraemia OR bacteremia OR septicaemia OR septicemia OR invasive OR necroti* OR toxic shock) AND (*prophylaxis OR prophylactic OR prevent* OR contact OR household OR family OR secondary OR subsequent). Limits set: human, English language. This produced 860 matches. After excluding studies related to outbreaks in nosocomial or institutional settings, and community clusters, we identified four prospective population-based studies that investigated the risk of secondary invasive GAS disease in household contacts (table 1).[1–4] Additional data from surveillance by Davies *et al* were available in a secondary publication.[5] The references of these manuscripts were hand-searched and no further relevant publications were identified.

COMMENTARY

Invasive GAS disease is defined by the isolation of *Streptococcus pyogenes* from a sterile site and comprises TSS, necrotising fasciitis, bacteraemia and focal infections such as osteomyelitis.[6 7] It causes significant morbidity, with overall mortality between 8% and 16% and up to 36% and 24% for TSS and necrotising fasciitis, respectively.[6 8] Secondary cases of invasive GAS disease in the contacts of index cases are reported in the peripartum period, nosocomial or institutional settings, households and in community clusters, such as schools.[6 9] Close household contacts are generally defined as persons that have spent at least 24 h with the index case or have spent 50% of nights in the house during the week preceding the onset of invasive GAS disease.[2 5 10] The risk of invasive GAS disease in close household contacts is highest in the first 30 days after the onset in the index case, with most secondary cases occurring in the first week and few cases beyond 1 month.[1–3 5 9]

In the four identified studies, all in industrialised countries, the background incidence of invasive GAS disease in the general population was relatively similar ranging from 2.4 to 3.5 cases per 100 000 person-years, consistent with rates reported in other industrialised countries.[6] In comparison, the annual

Table 1 Prospective population-based surveillance studies investigating the attack rate of invasive group A streptococcal (GAS) disease in household contacts of community-acquired index cases

				Key results						
Citation	Study group	Study type (level of evidence)	Outcome	No. of cases*	Background population incidence†	No. of secondary cases/total no. of household contacts of community-acquired index cases	Attack rate in household contacts†	Incidence risk ratio (95% CI)	No. of contacts per additional case	Comments
Davies *et al*[1‡]	Canada 10.7 million people over 3.5 years	Prospective population-based surveillance (I)	Attack rate of invasive GAS disease in household contacts	732	2.4[§]	4/1360	294 (80–750)	150 (41 to 387)	340	Survey of households of index cases to determine number of household contacts
Robinson *et al*[2]	USA 12.1 million people over 2.4 years	Prospective population-based surveillance (I)	Attack rate of invasive GAS disease in household contacts	1063	3.5 (3.3–3.9)	1[¶]/1514	66[¶] (2–367)	18 (0.5 to 101)	1514	Surveillance of household contacts of index cases for secondary cases (525 of 680 eligible households)
Carapetis *et al*[3]	Australia 4.9 million people over 2.5 years	Prospective population-based surveillance (I)	Attack rate of invasive GAS disease in household contacts	333	2.7 (2.4–3.0)	3/668	449 (93–1307)	165 (34 to 487)	223	Survey of households of index cases to determine number of household contacts (95 of 117 eligible households)
Lamagni *et al*[4]	UK 57 million people over 1-year	Prospective population-based surveillance (I)	Attack rate of invasive GAS disease in household contacts	1995	3.5 (3.4–3.7)	5/2316**	216** (70–503)	62 (20 to 144)	463	Secondary cases identified through geo-temporal clusters of invasive GAS

*Includes community-acquired and institution-associated infections. Community-acquired cases: Canada—unknown; USA—920; Australia—251; UK—1676 (estimated).
†Per 100 000 person-years (95% CI).
‡Includes additional data not reported in original paper sourced from reference.[5]
§Number reported in article—our calculation indicates an incidence of 2.0 per 100 000 (95% CI 1.8 to 2.1).
¶One confirmed case, one probable case; when probable case included attack rate is 132 per 100 000 person-years (95% CI 16 to 476).
**Number of household contacts estimated using census data with average of 1.4 people per household.

incidence of invasive GAS disease in household contacts was considerably higher and ranged from 66 to 449 per 100 000 person-years, equating to an incidence rate ratio (IRR) for household contacts compared with the general population of between 18 and 165. This equates to an additional case of invasive GAS disease in every 223 to 1514 household contacts. Combining the data from all the studies, the annual risk of invasive GAS disease was 151 times greater in household contacts compared with the general population (IRR 151, 95% CI 79 to 264). Investigators in Australia presented their data as an IRR for the first 30 days following onset of disease in the index case under the premise that the majority of secondary cases occur in this period. Using this method, the IRR for this 30-day risk period was 2011 (95% CIs 413 to 5929).[3]

The limitations of this review include the small number of studies, the variation in definitions of invasive GAS disease and of close household contacts, and the method of ascertainment of index and secondary cases. The definition of invasive GAS disease was largely consistent between studies,[7] although some studies added caveats such as the inclusion of parapharyngeal abscess without the need for GAS isolation from a sterile site.[3] Definition of a close household contact was only explicitly defined in one of the four studies.[2] Community transmission of invasive GAS disease outside household contacts (eg, in homeless people using the same shelter) was excluded, which may have underestimated the burden of community transmission.[1] Surveillance for secondary cases was based on regional microbiological surveillance,[3] follow-up of a proportion of households of index cases[2] or a combination of these.[1] One of the studies estimated the number of household contacts using average census data.[4] None of the studies stated whether any household contacts had received GAS chemoprophylaxis, although in one study, approximately 12% of the household contacts received antibiotics in the 30-day follow-up period.[2]

Invasive GAS disease is rare, and the estimated risks of secondary transmission are based on a total of only 13 cases of secondary cases of invasive GAS disease from surveillance in a combined population of approximately 84 million people over several years. The uncertainty of the true incidence of secondary invasive GAS disease is reflected by wide CIs and underscores the questionable feasibility of a study of sufficient size to refine this risk estimate.[2]

Even acknowledging the differences between the four studies and their limitations, the overall risk of invasive GAS disease in close household contacts of an index case is considerably greater than the general population and is comparable to that estimated for invasive meningococcal disease.[11] In contrast to meningococcal disease, no studies address whether this increased risk to household contacts can be reduced by chemoprophylaxis. Plausibility of this approach is supported by the effectiveness of antibiotics in eradicating nasopharyngeal carriage in 80–95% of patients with symptomatic GAS pharyngitis.[5 12–16] Additionally, one study demonstrated that prophylaxis reduces GAS pharyngitis in siblings of index cases.[17] Effectiveness is dependent on antibiotic choice and duration.

In the absence of studies evaluating chemoprophylaxis for the prevention of secondary cases in household contacts of invasive GAS disease, consensus recommendations vary between countries. Importantly, these recommendations are based on risk estimates prior to the more recent studies of Carapetis *et al*[3] and Lamagni *et al*.[4 5 18–20] All guidelines recommend a heightened index of suspicion for subsequent GAS disease among close contacts. Chemoprophylaxis for an undefined benefit must be considered in the context of adverse drug reactions, cost and the development of antibiotic resistance. However, the number of people that would receive antibiotic prophylaxis, if recommended, is small as the disease is rare. A decision to recommend chemoprophylaxis should be an adjunct to adequate patient and family education about the need for vigilance for symptoms of invasive GAS disease during the at-risk period. Concerns have been raised that using prophylaxis may lead to a false reassurance and delayed presentation of secondary cases, particularly as the efficacy of this strategy is unknown.[21] Further studies of the effectiveness of contact chemoprophylaxis are needed, although these will be challenging in light of the sample size required.[2 22] There is also a need to establish the risk to household contacts in settings associated with a high burden of GAS disease.[23] Overcrowding and poor sanitation may lead to increased transmission and an even greater risk of secondary cases of invasive GAS disease than in the population-based studies included in this review.

Clinical bottom line

- Close household contacts have an increased risk of invasive group A streptococcal (GAS) disease, commensurate to that in meningococcal disease. (Grade A)
- Antibiotic chemoprophylaxis to reduce this risk has not been investigated.
- Educate household contacts about their increased risk of invasive GAS disease in the month following the index case, regardless of whether or not chemoprophylaxis is given. (Grade D)

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