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Major Article

Screening asymptomatic households for *Streptococcus pyogenes* pharyngeal carriage as a part of in-hospital investigation of puerperal sepsis

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Background: Invasive group A streptococcal (iGAS) infection in the peripartum setting is a rare but devastating disease occasionally occurring as a health care–associated infection (HAI). Current guidelines suggest enhanced surveillance and streptococcal isolate storage after a single case of iGAS, as well as a full epidemiological investigation that includes screening health care workers (HCWs) from several sites after 2 cases. Current guidelines do not recommend routine screening of household members of a patient with iGAS.

Methods: We conducted studies of 3 patients with iGAS puerperal sepsis and related epidemiologic and molecular investigations.

Results: Identical GAS *emm* gene types were found in pharyngeal cultures of 3 asymptomatic spouses of patients with iGAS puerperal sepsis. HCWs screened negative for GAS, and *emm* typing indicated that other iGAS cases from this hospital were sporadic and not related to the puerperal cases.

Conclusions: The concurrent presence of the same *emm* type in a household member practically excludes the option of an inadvertent HAI or facility outbreak. Hence, we suggest that screening close family members for asymptomatic GAS carriage should be performed early as a part of infection prevention measures, as doing so would have significant utility in saving time and resources related to a full epidemiological inquiry.

BACKGROUND

Invasive group A streptococcal (iGAS) infection in the peripartum setting is a rare but devastating disease resulting in morbidity and mortality.[1] The Centers for Disease Control and Prevention (CDC),[2] as well as other authorities,[3,4] have issued guidelines to prevent iGAS among household contacts of severe iGAS cases and to limit hospital outbreaks. Because health care workers (HCWs) are occasionally implicated as triggers for hospital-acquired outbreaks,[5-11] HCWs previously in contact with a patient with iGAS should be considered as possible sources. The guidelines suggest enhanced surveillance and streptococcal isolate storage after a single case of iGAS, as well as a full epidemiological investigation that includes culturing HCWs from several sites and, as necessary, the environment after 2 cases. This investigation is time and resource consuming. On the other hand, because invasive disease among family members is exceedingly rare and chemoprophylactic regimens have limitations, current guidelines do not recommend routine screening or treatment of household members of a patient with iGAS as a preventive measure.

The CDC guidelines do not address the issue of screening household members as part of hospital-related epidemiological investigations.

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A more recent set of practice guidelines from the United Kingdom[12] suggests ascertaining whether or not the iGAS is health care associated before embarking on enhanced surveillance or epidemiological investigations of HCWs. This should be determined based on the presence or absence of symptoms or signs of infection already present on admission of the patient or obvious signs of infection among close household contacts. The authors of this paper observed that identification of a close personal contact with symptoms or signs of group A *Streptococcus* (GAS) infection reduced the likelihood that the infection was acquired from a health care source. Alas, the close household contact source may not always be as obvious as a spouse with an open wound or symptomatic pharyngitis and instead can be an asymptomatic carrier of the culprit strain of GAS causing puerperal sepsis.

In this paper, we suggest, relying on our experience and the limited existing literature, that screening asymptomatic households for GAS carriage may have an influence on the hospital-related epidemiological investigation of puerperal iGAS infection. We describe here a case series of 3 patients with iGAS puerperal sepsis and their related epidemiological investigations.

Case reports

The cases were admitted to Sanz Medical Center, a 400-bed regional hospital in Netanya, Israel. The hospital has 2 obstetrics wards with approximately 9000 labors per year. Puerperal iGAS is a rare occurrence, documented in only 0 to 5 cases per year over the last 5 years. Each case is investigated to rule out health care–associated infection (HAI), and to this date no case of iGAS-related HAI or a HCW-related outbreak has been documented. All iGAS isolates are routinely sent to the reference laboratory for *emm* typing. During the first 7 months of 2018, we encountered 3 sequential cases of puerperal iGAS cases and describe them here.

Case 1

A 25-year old-female, 39 weeks pregnant, was admitted in labor at midnight of January 30, 2018. She gave birth vaginally within an hour without epidural anesthesia. She was married with 3 children, her pregnancy follow-up was normal, and she was not previously screened for group B *Streptococcus* carriage. She had iron-deficiency anemia (hemoglobin, 10.3 g/dL). After an uneventful 24 hours, she complained of abdominal pain and dizziness without fever. Low blood pressures (60/30 mmHg) and tachycardia (150 beats per minute) were noted. A vaginal ultrasound study did not show signs of hemorrhage, and electrocardiography was suspected to present supraventricular tachyarrhythmia. She was transferred to the cardiac intensive care unit (ICU) and continued to complain of weakness, abdominal pain, and diarrhea. Her blood count showed anemia (8.9 g/dL) and mild neutrophilia (8,100 cells/mcL). A single measurement of temperature of 37.8°C was documented, and the tachycardia was ameliorated. On February 2, a blood count showed leukopenia (600 cells/mcL), neutropenia (500 cells/mcL), and thrombocytopenia (93,000 cells/mcL), and hematological and infectious diseases consultations were ordered. Because severe puerperal sepsis and toxic shock syndrome were suspected, fluid resuscitation, cathecholamines, and high-dose penicillin G and clindamycin were administered, as well as intravenous immunoglobulins. Blood, throat, vagina, and urine cultures were taken. A computerized tomography raised suspicion of uterine tear, and an emergency abdominal exploration was performed. The uterus was found to be necrotic, and a subtotal hysterectomy was performed. During the operation the patient developed disseminated intravascular coagulation so the operation was terminated early. Her abdomen was closed 2 days later after stabilization in the surgical-medical ICU. GAS was cultured from the blood, abdominal fluid, abdominal wound, and vagina. During 3 weeks of ICU stay she suffered from septic shock, adult respiratory distress syndrome, necrotizing pneumonia, and superficial venous thrombosis of the cephalic vein. She was discharged home on February 25. A thorough epidemiological investigation was undertaken (described in details below). *emm* typing of the GAS isolates of both the patient and her husband found them to be *emm* 75.0.

METHODS

Lancefield grouping was performed by the agar precipitation method using streptococcal group antisera (Statens Serum Institut; København, Denmark). *emm* gene typing was performed according to the CDC protocol.[13]

RESULTS

Epidemiological investigation of Case 1

Case 1 was our second iGAS case in January 2018 and accordingly a full epidemiology investigation was commenced. The investigation included screening of positive GAS cultures in the previous 6 months, analyzing the suspected hospital-acquired iGAS cases, investigation and screening of potentially related HCWs, investigation of close contacts and household members, post-exposure chemoprophylaxis considerations, and neonatal and environmental considerations, in addition to reporting and transferring GAS isolates to the central national laboratory for streptococci.

Screening GAS isolated in the hospital laboratory during the previous 6 months yielded 211 isolates. After excluding non-gynecological-related pharyngeal isolates, we found the following:

- The 17 iGAS isolates, all of which were community acquired, identified upon admission included 8 bloodstream infections, 7 wound cultures, 1 placental culture, and 1 sputum culture.
- Five cases of non-invasive GAS were identified from the gynecology ward (2 vaginal and 3 throat cultures).
- Three cases were suspected to be HAIs:
  1. GAS bacteremia that occurred in January 2018 was cultivated 72 hours after admission in an internal medicine ward. The same blood culture was also positive for *Salmonella* spp. The patient had a proven influenza infection and died after a few hours in the ICU.
  2. In July 2017, GAS was identified on vaginal culture 72 hours after admission.
  3. Also in July 2017, GAS was identified from the wound culture of a child who had earlier been stitched in the emergency room.

Investigation of suspected HAIs

There were no obvious links between previous cultures and this present case. The strain from the bacteremic patient was sent for typing to the central laboratory for streptococci. Although the vaginal culture did not represent an invasive GAS disease, the treating HCWs in this case were identified, and a nurse (N#5, Table 1) who was found to have also participated in the treatment of this case was screened for GAS carriage.

Investigation of HCWs related to Case 1

The sepsis developed 27 hours after admission, a relatively short period of time, suggesting endogenous infection, and the patient delivered an hour after her admission, which left very few opportunities for HCWs to infect her before the labor. HCWs that were in contact with the patient up to 24 hours before the first signs of sepsis were screened. They included nurses and midwives (tagged N#1-5, Table 1), 1 gynecologist (D#1, Table 1), and close contacts sharing the hospital room. They were screened and underwent questioning and a

Table 1
Persons exposed to Case 1 in the 24 hours before sepsis onset

	Occupation	Tag	Nature (exposure date)	Known GAS carriage	Respiratory, wound, throat symptoms	Antimicrobial therapy in the last week	Wounds on examination	GAS screening/results	PEP administration	Handed an education and instruction sheet
Health care workers										
1	Nurse	N#1	Examination for bleeding and uterine contraction (1/30/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
2	Midwife	N#2	Participating in labor, with significant exposure to secretions (1/30/2018)	GAS in throat culture a month earlier, Antibiotic therapy	None	No	No	Yes (3 sites*)/negative	Yes	Yes
3	Midwife	N#3	Participation in labor (1/30/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
4	Nurse	N#4	Physical examination (2/1/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
5	Nurse	N#5	Casual exposure but was exposed to a previous invasive GAS case 6 mo earlier (1/30/2018)	Unknown	None	No	No	Yes (pharynx)/negative	No	Yes
6	Gynecologist	D#1	Prolonged exposure during pregnancy monitoring (1/30/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	No
Households										
7	Patient's sister		Prolonged exposure including during labor	Unknown	None	No	No	Yes (pharynx)/negative	No	Yes
8	Patient's husband		Prolonged exposure including during labor	Unknown	Wound in hand and paronychia	No	Yes	Yes (pharynx, finger, rectum)/positive only from throat	Advised to take antibiotics for GAS eradication	Yes and thorough explanation by an ID expert
9	Patient's close friend		Prolonged exposure including during labor	NA	NA	NA	NA	NA	NA	NA
10	Patient's roommate		Sharing room for 24 hr (1/31/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	No

GAS, group A *Streptococcus*; *ID*, infectious diseases; *NA*, not accessible; *PEP*, post-exposure prophylaxis.
*The 3 sites were pharynx, rectum, and vagina.

physical examination for open wounds by an epidemiological nurse, and they were handed an information sheet regarding development of iGAS infection signs. These data are shown in Table 1.

Household investigation

The patient's spouse and sister were regarded as close contacts and were screened. Neither had any recollection of pharyngitis or other signs of infection, but the husband had paronychia, which was also cultured using a moist cotton swab.

Potential secondary contacts

A search for other pregnant patients and HCWs who were exposed to the patient after the appearance of the sepsis signs (February 1) and before precaution measures were implemented was conducted. Eight nurses, tagged N#6-13, and 5 physicians (D#2-6) were exposed, and their related investigation are shown in Table 2. They were given information sheets, and several were screened, although this was unintentional.

Post-exposure prophylaxis

One HCW, the midwife (N#2) who delivered the baby and had significant exposure to vaginal excretions, was given post-exposure prophylaxis (PEP) with amoxicillin 1500 mg/day for 3 days. The neonate underwent a full sepsis workup, received antibiotic treatment, and was put under contact isolation. Antibiotic therapy with the intention of eradication was suggested only to the patient's husband.

Environmental cleaning

The rooms in which the patient stayed underwent meticulous cleaning, and we searched for patients who had entered these rooms before this cleaning took place (none was found).

Communications

The investigation was reported to the hospital administration, the regional health ministry office, and the national infection control unit.

Screening results

Altogether, 20 HCWs were approached, and 13 of them were screened from the pharynx, anus, and vagina. All cultures were negative. Five family members were approached, and 2 were screened (husband and sister). The husband was found to have GAS from the throat culture.

Case 2

A 39-year-old female in the 41+5 weeks of her seventh pregnancy was admitted in May 2018 to the hospital, and she gave birth vaginally the next day. Immediately after the labor she had postpartum vaginal hemorrhage because of retained placenta, and she underwent revision in the delivery room. During the procedure, she received cefazolin. A day later she became febrile, and after cultures were taken she received ceftriaxone and metronidazole. She had leukocytosis of 13,000 cells/mcL with 80% polymorphonuclears and C-reactive protein of 345 mg/L (normal range, 0-5). Vaginal culture grew GAS, but blood and throat cultures were negative. Her fever subsided rapidly, the antibiotic therapy was replaced with oral amoxicillin after 4 days of hospitalization, and she was discharged home. Her husband recalled pharyngeal pain 2 weeks earlier that was neither diagnosed nor treated. His throat culture was also GAS positive. Both their strains were identified as *emm* 44.0. Four HCWs were screened (throat and rectal cultures) and were found negative.

Case 3

A 33-year-old female 38 weeks pregnant was admitted in July 2018 to the delivery room and gave birth vaginally after an hour. She was healthy and had had 2 previous uneventful deliveries; the current pregnancy follow-up was normal. Twelve hours later she developed fever, chills, abdominal pain, and severe weakness. She had no symptoms of pharyngitis, but her husband reported throat pain 3 weeks earlier that had been neither investigated nor treated. She had leukocytosis of 22,000 cells/mcL and borderline thrombocytopenia (150,000 cells/mcL). After blood, vaginal, and throat cultures, antibiotic therapy with ceftriaxone and metronidazole was commenced. The next day, blood cultures were reported positive with streptococci that were eventually identified as GAS. Treatment was narrowed to include penicillin G and clindamycin. The patient did not develop signs of shock. GAS was also found on vaginal culture. The clinical signs improved rapidly, and she was discharged home after a week of antibiotic treatment. A throat culture from her now asymptomatic husband was found positive to GAS. The neonate underwent sepsis workup that was negative. The 2 isolates were sent for typing and both were identified as *emm* 14.3. A full epidemiological investigation was not carried out in this case, given the typing results.

emm typing

The results of *emm* typing of the 3 cases are summarized in Table 3, along with the typing results of another 7 iGAS cases that were sent for typing during the 6 months previous to our investigation of Case 1. As can be seen, in all 3 cases the *emm* types were identical for the index patients and their spouses, but there was a considerable diversity of *emm* types among other cases (with only 1 *emm* type shared between unrelated cases).

DISCUSSION

The main conclusion from this study is that household screening for GAS can contribute considerably to in-hospital epidemiological investigations of puerperal iGAS infection. In the 3 cases described here, the spouses carried the same *emm* strain as the index patients, and epidemiological investigations of the HCWs were unproductive. The current concept is that the first consideration when assessing a case of iGAS should be the time frame of the symptoms appearance, in order to decide whether the case is HAI or community acquired. We suggest also considering screening asymptomatic households, at least as a complementary measure. Asymptomatic genital or upper airway GAS carriage in pregnant women has been reported to predate the onset of sepsis by weeks, and the sepsis onset may occur more than 72 hours after an uneventful delivery, originating from the predated GAS colonization.[14] On the other hand, asymptomatic carriage by spouses, or any other family members, diagnosed concurrently with the diagnosis of iGAS infection practically rules out cross-infection by a HCW.

A newly acquired puerperal GAS infection, if transmitted by a HCW during the days of hospitalization or delivery, cannot be transmitted within this time frame to family or other close contacts of the patient. *emm* typing to identity the strains can confirm that there was no hospital cross-infection and should bring at least part of the epidemiological investigation to a halt. Although direct studies have not been conducted to confirm this notion, supporting evidence can be drawn from circumferential data. Mearkle et al[1] estimated the risk for secondary household contacts of iGAS cases in England. They found that 17 out of 24 pairs with iGAS (71%) were household members (8 partners or spouses and 9 siblings or parent-child pairs), and the same *emm* type was shared in 12 pairs. In another study of

Table 2
Health care personnel exposed to Case 1 after the appearance of sepsis and before implementation of barrier precautions

	Occupation	Tag	Nature (exposure date)	Known GAS carriage	Respiratory, wound, throat symptoms	Antimicrobial therapy in the last week	Wounds on examination	GAS screening/results	PEP administration	Handed an education and instruction sheet
1	Nurse	N#6	Taking vital signs (2/2/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
2	Nurse	N#7	Taking blood samples (2/2/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
3	Nurse assistant	N#8	Taking vital signs (2/2/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
4	Nurse	N#9	Taking vital signs, physical examination (2/2/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
5	Nurse	N#10	Taking vital signs, physical examination (2/2/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
6	Nurse	N#11	Taking vital signs, physical examination (2/2/2018)	Unknown	None	No	No	Yes (3 sites*)/negative	No	Yes
7	Nurse	N#12	Taking vital signs (2/2/2018)	Unknown	None	No	No	No	No	Yes
8	Nurse	N#13	Physical examination (2/2/2018)	Unknown	None	No	No	No	No	Yes
9	Hematologist	D#2	Physical examination, taking blood samples (2/2/2018)	Unknown	None	No	No	No	No	Yes
10	Gynecologist	D#3	Vaginal examination (2/1/2018)	Unknown	None	No	No	No	No	Yes
11	Gynecologist	D#4	Vaginal examination (2/1/2018)	Unknown	None	No	No	No	No	Yes
12	Gynecologist	D#5	Vaginal examination (2/1/2018)	Unknown	None	No	No	Yes (pharynx)/positive for GAS	No	Yes
13	Intensive care doctor	D#6	Physical examination (2/2/2018)	Unknown	None	No	No	No	No	Yes

GAS, group A *Streptococcus*; *PEP*, post-exposure prophylaxis.
*The 3 sites were pharynx, rectum, and vagina.

household risks for iGAS, Robinson et al[15] found that, among the 127 household contacts of iGAS cases who visited a physician, 50% to 65% had confirmed GAS infection or confirmed asymptomatic GAS throat colonization.

These 2 studies, as well as others,[16] found increased risk (229- to 2011-fold) for secondary household infection with GAS, even though the absolute risk remained low. The higher rate of GAS colonization found in these community-based studies may not be enough to warrant post-exposure prophylaxis but could indeed have an impact on hospital investigations of suspected outbreaks. Furthermore, in their molecular investigation of a lethal iGAS postpartum outbreak, Turner et al[17] found that 50% (3 out of 6) of household members of 2 iGAS puerperal cases were carriers of the same *emm* type; pharyngeal cultures from their 2 partners were also included, although both of them were symptomatic. Cantwell et al,[18] in their review of maternal mortality, reported that all mothers who died from iGAS either worked with or had young children. Several mothers had a history of recent sore throat or respiratory infection, and some had family members with sore throat, suggesting that spread from family members is a risk factor for developing life-threatening iGAS infection. Also, GAS contamination of the perineum was more likely when the woman or someone in the household had a sore throat or upper respiratory tract infection.

Because GAS colonization of the genital tract is extremely rare,[19] the upper airways are a significant source of puerperal iGAS, and spouses and children serve as important sources of GAS infection. In their review of pregnancy-related GAS infections, Hamilton et al[20] concluded that only 13.9% of GAS postpartum infections are nosocomially acquired, suggesting that acquisition of GAS in the home environment is increasingly important and could be a target for intervention or prevention.

The international guidelines focus on 2 areas of iGAS prevention: the institution[2,12] and household contacts.[2,21] The former concerns identifying possibly asymptomatic HCWs who may infect susceptible women with specific invasive GAS strains, and the latter deals with the possibility of household members sharing the same invasive strain and calculating the odds of another invasive manifestation caused by this strain. Five population-based studies[1,15,16,22,23] that estimated the risk of secondary household transmission all found higher than baseline risks for a secondary iGAS infection. But, because the number needed to treat was still high, there is still debate regarding how to approach household preventive measures in a single case of iGAS. Several authorities recommend PEP for some high-risk patients (such as neonates and elderly patients),[2-4,21] and others recommend PEP only when the index case is fatal or severely sick.[24] Either way, these recommendations do not include household screening for GAS. Screening of households should probably not be a guide to prophylaxis administration, but it does serve a role in institution inquiries, because identifying an asymptomatic carrier of the same *emm* strain among close household contacts practically excludes the chances for an institutional outbreak.

The epidemiology investigation that is conducted after a single case of iGAS acquired in the hospital consumes much time and effort.[12] Determining where an infection was acquired is not always simple, as not all patients are cultured upon admission, and some patients have many opportunities to be infected during multiple encounters within the health care system (such as high-risk pregnancy clinics) before being admitted to labor. Furthermore, screening HCWs from 3 sites, including intimate locations such as the vagina and anus, may cause embarrassment, bitterness, resistance, and a lack of cooperation among the staff, as well as anxiety related to positive cultures and exclusion from work until typing is completed. In the investigation of Case 1, we approached and interviewed 20 HCWs, screened 13 HCWs and 2 household members, took 41

Table 3
emm typing of 3 iGAS case investigations and cases from the preceding 6 months

Setting	Case	Date of sample	Person sampled	Source of isolate	Patient's diagnosis	Patient's outcome	*emm* type
Puerperal cases	Case 1	January-February 2018	Index patient	Blood, vagina, abdominal fluid, wound	Puerperal sepsis, septic shock, hysterectomy	Discharge	*emm* 75.0
			Index patient's husband	Throat	Asymptomatic carriage	—	*emm* 75.0
			Another patient from the high-risk pregnancy ward	Vagina	Asymptomatic puerperal vaginal carriage	Discharge	*emm* 89.0
	Case 2	May 2018	Index patient	Vagina	Puerperal sepsis	Discharge	*emm* 44.0
			Index patient's husband	Throat	Asymptomatic carriage	—	*emm* 44.0
	Case 3	July 2018	Index patient	Blood, vagina	Puerperal sepsis	Discharge	*emm* 14.3
			Index patient's husband	Throat	Asymptomatic carriage	—	*emm* 14.3
Other iGAS isolates	Patient 1	June 2017	Index patient	Blood	Septic shock	Death	*emm* 3.1
	Patient 2	August 2017	Index patient	Blood	Cellulitis	Discharge	*emm* 1.0
	Patient 3	October 2017	Index patient	Blood	Cellulitis	Discharge	*emm* 93.0
	Patient 4	October 2017	Index patient	Blood	Strongyloides hyperinfection–related GAS bacteremia and toxic shock	Discharge	*emm* 4.5
	Patient 5	October 2017	Index patient	Blood	Primary GAS bacteremia	Discharge	*emm* 36.7
	Patient 6	November 2017	Index patient	Blood	Cellulitis	Discharge	*emm* 118.0
	Patient 7	November 2017	Index patient	Blood	Cellulitis	Discharge	*emm* 1.0
	Patient 8	January 2018	ICU patient presenting the same week as Case 1	Blood	Influenza A, concurrent *Salmonella* bacteremia	Death	*emm* 9.0

GAS, group A *Streptococcus*; iGAS, invasive group A *Streptococcus*; *ICU*, intensive care unit.

cultures, and spent hours gathering and analyzing laboratory data to determine possible connections between patients and HCWs, in addition to spending considerable time educating and reassuring staff members.

CONCLUSIONS

Invasive GAS puerperal infection is a grave disease associated with high morbidity and mortality,[25] and cross-infection within a hospital can lead to a wide range of emotions for HCWs suspected to be the culprit. The epidemiological and molecular investigations may take days before reaching a conclusion, during which the patients and staff usually feel insecure and anxious. The infection control team should investigate both the possibility of cross-infection of the index patient by HCWs and the possibility of patients and staff being cross-infected by the index patient before proper barrier measures were taken, in addition to attempting to identify common environment-related sources.[26] Such investigations can be significantly shortened by identifying asymptomatic carriers among close family members through screening. Such screening is not recommended in current guidelines but should be further explored and consideration given to including it in institution-related epidemiological investigations. Because our conclusions are based on just 3 cases, further prospective studies are necessary that are designed to screen households of patients with puerperal iGAS infection for asymptomatic carriage, in addition to including this practice during in-hospital investigations. We suggest early routine screening (of at least the pharynx) of close contacts of patients with puerperal iGAS and probably other types of iGAS infections, as well as rapid typing of positive cultures, in order to ease the workload and reduce anxiety related to the epidemiological inquiries, particularly because positive households and hospital outbreaks are probably mutually exclusive.

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