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Hospital clusters of invasive Group B Streptococcal disease: A systematic review

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SUMMARY

Objectives: To characterize outbreaks of invasive Group B Streptococcal (iGBS) disease in hospitals.
Methods: Systematic review using electronic databases to identify studies describing iGBS outbreaks/clusters or cross-infection/acquisition in healthcare settings where 'cluster' was defined as ≥2 linked cases. PROSPERO CRD42018096297.
Results: Twenty-five references were included describing 30 hospital clusters (26 neonatal, 4 adult) in 11 countries from 1966 to 2019. Cross-infection between unrelated neonates was reported in 19 clusters involving an early-onset (<7 days of life; $n=3$), late-onset (7–90 days; $n=13$) index case or colonized infant ($n=3$) followed by one or more late-onset cases (median serial interval 9 days (IQR 3–17, range 0–50 days, $n=45$)); linkage was determined by phage typing in 3 clusters, PFGE/MLST/PCR in 8, WGS in 4, non-molecular methods in 4. Postulated routes of transmission in neonatal clusters were via clinical personnel and equipment, particularly during periods of crowding and high patient-to-nurse ratio. Of 4 adult clusters, one was attributed to droplet spread between respiratory cases, one to handling of haemodialysis catheters and two unspecified.
Conclusions: Long intervals between cases were identified in most of the clusters, a characteristic which potentially hinders detection of GBS hospital outbreaks without enhanced surveillance supported by genomics.

Introduction

Streptococcus agalactiae (group B *Streptococcus*, GBS) is a leading cause of neonatal sepsis, and of growing public health concern as a cause of sepsis in adults, particularly the elderly.[1–3] Infant invasive GBS disease is classified as early-onset disease (EOD) if it occurs during the first 6 days of life or late-onset disease (LOD) if it develops 7 or more days after birth. The worldwide burden of infant and maternal GBS disease is substantial,[4–13] and efforts are underway to develop vaccines as a preventive measure to replace or supplement antenatal screening and intrapartum antibiotics effective against early but not late-onset disease.[14–17] EOD arises from vertical transmission from a GBS colonized mother to her baby during or just before birth, with clinical signs occurring within 48 h in more than 90% of cases.[18,19] Transmission routes for LOD are poorly understood,[20] the presumption being that late-onset GBS infection is acquired postnatally from the mother, a community source or hospital environment.[18,21] Sources and transmission of GBS infection in adult cases, including nosocomial events, have not been well characterized.

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Published reports of healthcare-associated GBS clusters typically describe such events as rare. Our objectives in the present study were to characterize reported GBS clusters in detail by systematic review, including patients of all ages without date or language restrictions. Our underlying aim was to improve understanding of nosocomial transmission as a route of infection in late-onset infant and adult invasive GBS disease, with a view to identifying opportunities for preventive measures in healthcare settings.

Methods

Review protocol and searches

The protocol for this systematic review and meta-analysis was defined in advance and registered with PROSPERO (CRD42018096297). We searched MEDLINE, EMBASE, EMCARE, COCHRANE, TRIP, SCOPUS, and CINAHL on 24th May 2019 without date or language restrictions. Full search terms are provided in a supplementary file (Supplementary Appendices). Where the search identified relevant systematic reviews, we performed forward and backward citation searches. Citations were imported into EndNote (EndNote X8; Clarivate Analytics, Boston, MA 02210, USA) for de-duplication, and then imported into to EPPI-Reviewer (EPPI-Reviewer 4; EPPI-Centre Software; Social Science Research Unit, UCL Institute of Education, London, UK).

Screening, quality assessment and data extraction

Screening and quality assessment were conducted independently in parallel by two reviewers. References were included if they described a cluster occurring in a healthcare setting (≥2 cases of invasive GBS described/reported as a 'cluster'/'outbreak' or due to horizontal transmission, regardless of microbiological confirmation, or familial relatedness). The methodological quality of included studies was rated by two reviewers using a 10-item quality assessment tool adapted from the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Supplementary Appendices).[22] Data extraction was by one reviewer, checked by a second reviewer.

Analysis

Key characteristics of each included study were summarized, including setting, numbers of clusters and cases, intervals between cases, evidence or microbiological method for linkage (time and place, serotype, phage type, pulsed-field gel electrophoresis (PFGE) profile, multilocus sequence typing (MLST), whole genome sequencing (WGS)), case characteristics, epidemiological investigations undertaken, and putative routes of transmission. For neonatal clusters involving late-onset cases, we calculated summary measures of the serial interval between cases, gestational age, birthweight, and age at onset. The serial interval excluded colonized infants unless reported to be the index 'case' in a cluster, because colonization was not reported consistently across studies and its detection is dependent on active screening.

Results

Database searches identified 1356 references and bibliographic searches identified a further 8 references (Fig. 1). Citation searches were performed on 6 systematic reviews. Of 192 full text references, 25 were included. Quality assessment rated 13 (52%) as 'good', 11 (44%) as 'fair' and one (a conference abstract) as 'poor' quality. Of the 25 references, 22 described hospital clusters of early or late-onset neonatal GBS and 3 reported adult patient clusters. The 22 neonatal cluster references were categorized as: sibling-only cases (twins and triplets); EOD only; LOD only; and mixed EOD and LOD. Summary characteristics and a full textual data synthesis for all included studies are provided in supplementary files (Supplementary Full Data Synthesis and Table S1).

Neonatal GBS disease clusters

Of the 22 studies describing neonatal GBS disease clusters, 9 were in the USA,[23–31] 9 in Europe (United Kingdom 3, Italy 2, Denmark 1, Germany 1, Norway 1, Sweden 1),[32–40] 2 in Canada,[41,42] and one each in Japan[43] and South Korea (Table 1).[44] Most of the studies (17/22) reported clusters occurring in neonatal intensive care units (NICUs) or special care nurseries; the remainder described clusters occurring in or originating from maternity units in regional, district or community hospitals. There were two reports of LOD in twins[35] and triplets[38] and two references describing clusters only of EOD[23,34] (see supplementary files). The other reported clusters involved LOD ($n = 12$) or a mix of early and LOD ($n = 6$) as described below.

Late-onset disease clusters

There were 16 clusters of LOD cases in 12 references (Table 1), comprising 10 reports of single clusters (of 2–5 cases),[25–29,39,40,42–44] one report of 2 clusters (2 and 5 cases),[33] and one 4-cluster report (4, 2, 2, and 3 cases).[37] Colonization was reported in 5/12 references.[25,28,33,37,39] In one of the clusters reported by Berardi et al.[33] and in the single cluster described by Morinis et al.[42] index cases were postulated to have arisen from consumption of mothers' breast milk, although the authors of both studies emphasized that this was unproven. Inadequate disinfection of equipment or surfaces as a mechanism of transmission was suggested in 5 references,[26,33,37,39,42] including shared breast pumps.[33,37]

Five references suggested transmission via healthcare workers,[25,27,29,33,39,42] Boyer et al. found that overall GBS carriage among nursery staff at the time of the cluster was 34% (18/53), comprising rectal (16/18), vaginal (13/18) and throat (3/18) carriage.[25] Whilst none of the staff isolates matched the phage type identified in the two cluster cases, a culture survey conducted one month later found 4/15 infants colonized with a phage type carried by 3 staff at the time of the cluster. Steere et al. reported that 41% (11/27) of staff who had direct contact with cluster cases were GBS-positive (throat, vaginal or urethral, and rectal swabs), of whom 4 had the cluster serotype.[29]

Poor infection control was mentioned by Kim et al.[44] and MacFarquhar et al., the latter specifying deficient cot spacing, inadequate staff and family hand hygiene, formula preparation, and equipment disinfection (including medication pumps and laryngoscope blades).[26] Periods of crowding and high patient-to-nurse ratio were mentioned in relation to two clusters.[27,28] Environmental samples, when taken, were negative for GBS in two studies[29,37] but positive from multiple surfaces in a room where 3/5 cases were located in one study.[39] The latter study identified factors potentially facilitating transmission including staff and infants rotating between rooms within the NICU and responsibility for cleaning being shared between neonatal and hospital service staff.

Jauneikaite et al. were the only authors to use WGS.[37] They reported an initial cluster of 4 cases followed by 3 distinct clusters over a 24-month period. The clustered cases represented all but one of the LOD cases on the NICU over this period. The authors concluded that without enhanced surveillance (instituted after the first cluster, including weekly rectal swabs from all neonates) supported by WGS, subsequent clusters would not have been recognized. The first cluster was recognized mainly because the last

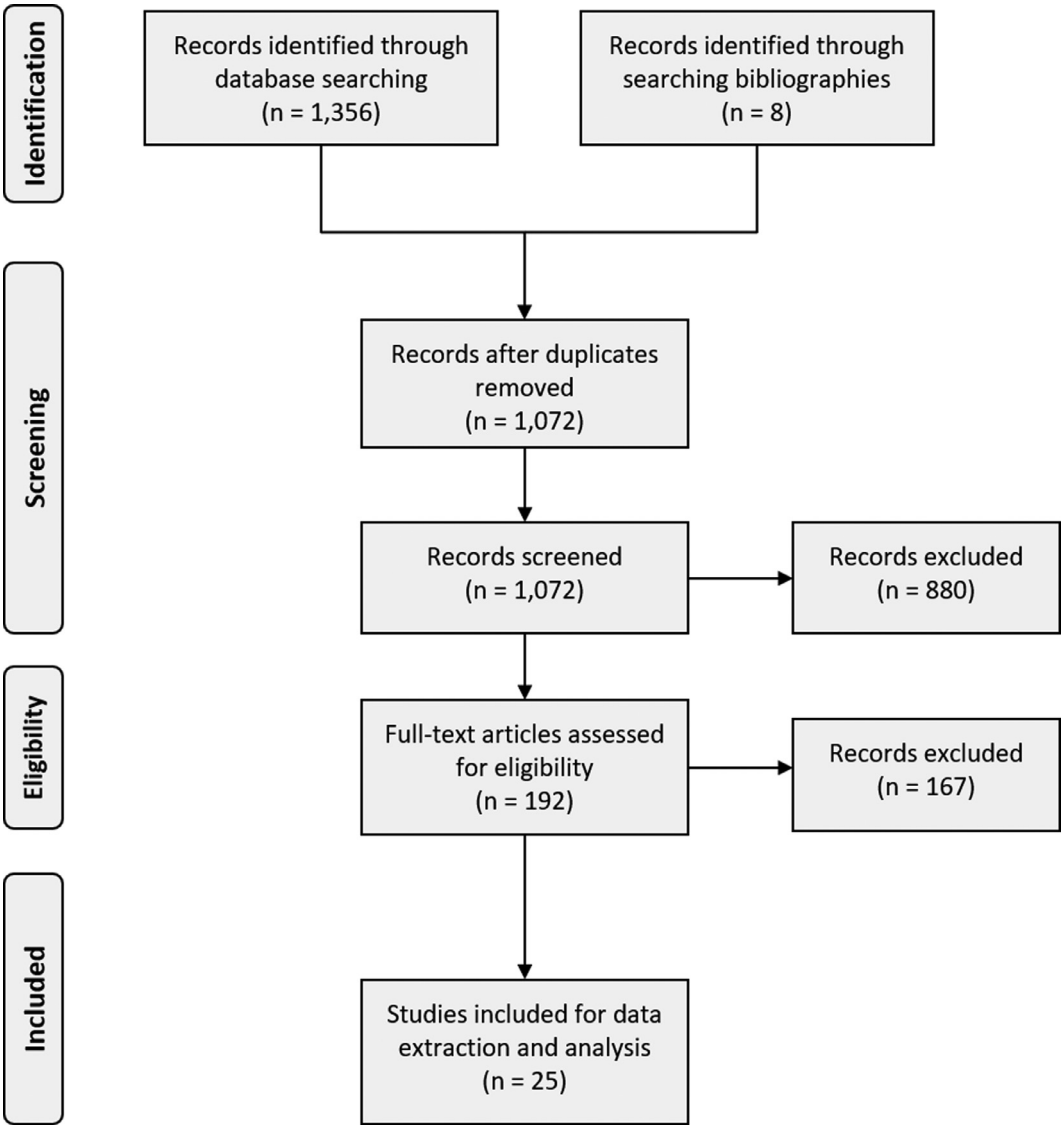

Fig. 1. Study selection (PRISMA flow diagram).

2 of the 4 cases presented on the same day and had the same antimicrobial susceptibility profile. The three clinical cases in the fourth cluster were separated by intervals of 50 and 36 days. They noted that GBS carriage was rarely detected by rectal screening (in 10/518 admissions in 1 year, of which one was a LOD case). Similarly, Berardi et al. showed that, among all neonates admitted to a NICU who underwent weekly cultures (throat and rectum) over the cluster period, 2 infants were not colonized with GBS for periods of 8 and 12 weeks until onset of LOD, whilst a third infant was colonized at 40d with LOD onset at 44d.[33] Phylogenetic analysis by Jauneikaite et al. indicated intermixing of adult and neonatal GBS isolates, showing that adult and neonatal strains originated from the same genetic pool; these authors recommended that a single LOD case in a NICU should be considered sentinel of a future cluster, prompting enhanced retrospective and prospective surveillance.[37]

Mixed early and late-onset disease clusters

Of the 6 references with mixed early/late-onset disease clusters,[24,30–32,36,41] 3 implicated a single EOD case as the probable index case based on proximity,[24] PFGE profile[32] or shared healthcare workers.[31] Of the other references, the probable index case in one was an infant transferred into the unit with pneumonia,[41] whilst two references either did not report the timing and spacing of the cases[36] or investigated only the LOD cases.[30]

Band described 3 late-onset cases with identical phage type over 2 weeks, 10 days after an early-onset case (whose mother also had GBS septicaemia).[24] The EOD case did not have an isolate available for typing, but all the cases had overlapping hospitalization and the authors proposed horizontal transmission during a period of high patient-to-nurse ratio. Similarly, Barbadoro et al. reported a cluster comprising 3 cases (1 EOD, 2 LOD) over 15 days where the EOD case had a similar PFGE profile to the 2 LOD cases.[32] The LOD infants were already in the NICU when the EOD case was admitted, and the authors suggested horizontal transmission via personnel. In a binary cluster described by Winterbauer et al., the EOD index case was isolated promptly and overlapped with the subsequent LOD case by only 1 h, but the same clinician and nurse cared for the index case whilst overseeing the delivery of the second infant.[31]

Al-Maani et al. described a NICU cluster which was flagged by the hospital microbiology laboratory after GBS was isolated from 5

Table 1
Epidemiological features of hospital clusters of invasive group B streptococcal disease.

	Author	Year	Country	Ref	Duration	Cases	Description[a]	Serotype[a]	Microbiological method[a]
Neonatal									
Siblings	Elling	2014	Germany	35	27d	2	Twins, each with 2 LOD episodes	III (ST17)	Serotype
	Olver	2000	England	38	23d	3	Triplets, 2 with single LOD episode, one with 2 episodes	III	Serotype
Early onset only	Adams	1993	USA	23	8m	23	23 EOD cases (15 in final 3 months)	Mixed	Serotype
	Cowen	1978	England	34	8m	6	6 EOD cases (3 cases in final month)	–	None
Late onset only	Åberg	2019	Sweden	39	13w	5	5 LOD + 9 COL (5 LOD in first 9 weeks)	Ia (ST23)	PFGE + MLST
	Berardi	2018	Italy	33	25d	2	LOD from colonized index case	III (ST17)	MLST + PCR
					60d	5	3 LOD from index twins (both LOD)	III (ST17)	MLST + PCR
	Boyer	1980	USA	25	1d	2	2 LOD within 24 hrs (colonized triplets probable index)	III	PT
	Holter	2019	Norway	40	60d	4	4 LOD + 6 COL (4 LOD in first 30 days)	Ib (ST12)	MLST + PCR
	Jauneikaite	2018	England	37	28d	4	4 LOD + 2 COL	V (ST1)	WGS
					13d	2	2 LOD	III (ST17)	WGS
					21d	2	2 LOD	Ib (ST139)	WGS
					86d	3	3 LOD + 2 COL	Ia (ST23)	WGS
	Kim	2006	S Korea	44	28d	4	4 LOD cases	–	antibiogram
	MacFarquhar	2010	USA	26	14d	5	5 LOD cases	Ia (ST23)	PFGE + MLST
	Morinis	2011	Canada	42	42d	3	3 LOD cases	–	PFGE
	Noya	1987	USA	27	38d	5	5 LOD cases	Ib	PT
	Snider	2016	USA	28	5d	3	3 LOD cases + 1 COL	–	n/r
	Steere	1975	USA	29	5d	3	3 LOD cases	III	Serotype
	Takayanagi	1994	Japan	43	24d	3	3 LOD cases	III	Serotype
Early and late onset	Al-Maani	2014	Canada	41	53d	6	1 EOD + 5 LOD	–	PFGE
	Band	1981	USA	24	20d	4	1 EOD + 3 LOD	III	PT
	Barbadoro	2011	Italy	32	15d	3	1 EOD + 2 LOD	–	PFGE
	Friis-Møller	1984	Denmark	36	9m	7	5 EOD + 2 LOD + (3 pneumonia, 2 pharyngitis, 3 omphalitis)	–	None
	Weems	1986	USA	30	11w	10	3 EOD + 7 LOD (3 LOD in 14 days)	III	Serotype
	Winterbauer	1966	USA	31	7d	2	1 EOD + 1 LOD	–	None
Adult									
	Baraboutis	2010	Greece	45	1d	2	Haemodialysis patients (2 bacteraemia cases in one day)	–	None
	Denton	1993	England	46	9d	3	Patients in oncology unit (3 cases in 9 days); all pneumonia	–	None
	Nagano	2012	Japan	47	43d	5	General medical ward; 1 pus, 4 pharyngeal, 2 tracheal	VI	PFGE
					97d	2	General medical ward; 1 pharyngeal, 1 tracheal	VI	PFGE

[a] COL = colonized; EOD = early onset disease; LOD = late onset disease; HCW = health care worker; ICP = infection prevention & control; MLST = multilocus sequence type; PFGE = pulsed-field gel electrophoresis; PT = phage type; ST = sequence type; WGS = whole genome sequencing (Note: Noya et al. reported GBS as serotype Ib/c).

infants in a 2-month period, compared with one case in the past year.[41] Three of the 5 cases were linked: the probable index case (age 7mo) was transferred into the unit from a peripheral hospital with pneumonia, and GBS was cultured from endotracheal and tracheostomy tubes; two LOD cases shared a room with the transferred case, and the GBS strain infecting these 3 infants was cultured from an environmental sample taken from an alarm silence button. The cluster coincided with a period of high admissions and maximum daily census and was attributed to horizontal transmission facilitated by inadequate hand hygiene and disinfection of electronic equipment.

Weems et al. reported an apparent cluster comprising 7 late-onset GBS cases in a NICU over an 11-week period.[30] Of the 4/7 LOD cases with isolates, 3 were serotype III from infants cared for in the same NICU room by a nurse who had been assigned mainly to these infants during a period of higher-than-average patient-to-nurse ratio, all of whom had LOD in a 14-day period. However, the authors concluded from phage typing that horizontal transmission was unlikely.

Characteristics of neonatal unit clusters

Data on serial intervals were available for meta-analysis from 15 references describing 19 clusters whose characteristics were consistent with horizontal transmission, namely an index case or colonized infant followed by one or more late-onset cases without a discordant microbiological profile (Supplementary Table S2).[24–27,29,31–33,37,39–44] Of the index cases for these 19 clusters, 3 were colonized, 3 were early-onset and 13 were LOD; there were 45 subsequent LOD cases. Linkage was determined by phage typing in 3 clusters, PFGE/MLST/PCR in 8, WGS in 4, non-molecular methods in 4. Median cluster size was 2 (range 1–5) cases, with 16/19 involving more than 2 cases; median duration was 24 (range 5–86) days. Most clusters (12/19) were comprised entirely of neonates who had overlapping hospital stays; overlap could not be discerned in 6/19 clusters, and 1 cluster comprised 4 non-overlapping infants born at a district hospital and subsequently admitted to the same NICU.[44]

LOD cases in the clusters (including LOD index cases) had a median gestational age of 27 weeks (IQR 26–32 weeks, $n = 31$), birth weight 853 g (IQR 720–1140 g, $n = 34$) and GBS onset at 44 days of life (IQR 24–51, range 7–127 days, $n = 23$). Serotype was reported for 14 clusters: 7 were serotype III, 3 were serotype Ia, 3 were Ib, and one was serotype V. The median serial transmission interval was 9 days (IQR 3–17, range 0–50 days, $n = 45$) (Fig. 2). Of the 19 clusters, 11 (58%) had at least one serial interval of ≥14 days.

Adult GBS disease clusters

The 4 reported GBS clusters among adult patients occurred in Athens,[45] London,[46] and Tokyo.[47] Baraboutis et al. reported a cluster involving two catheter-associated bacteraemia cases occurring on the same day among outpatients at a haemodialysis unit.[45] The authors concluded that GBS was probably transmitted from one

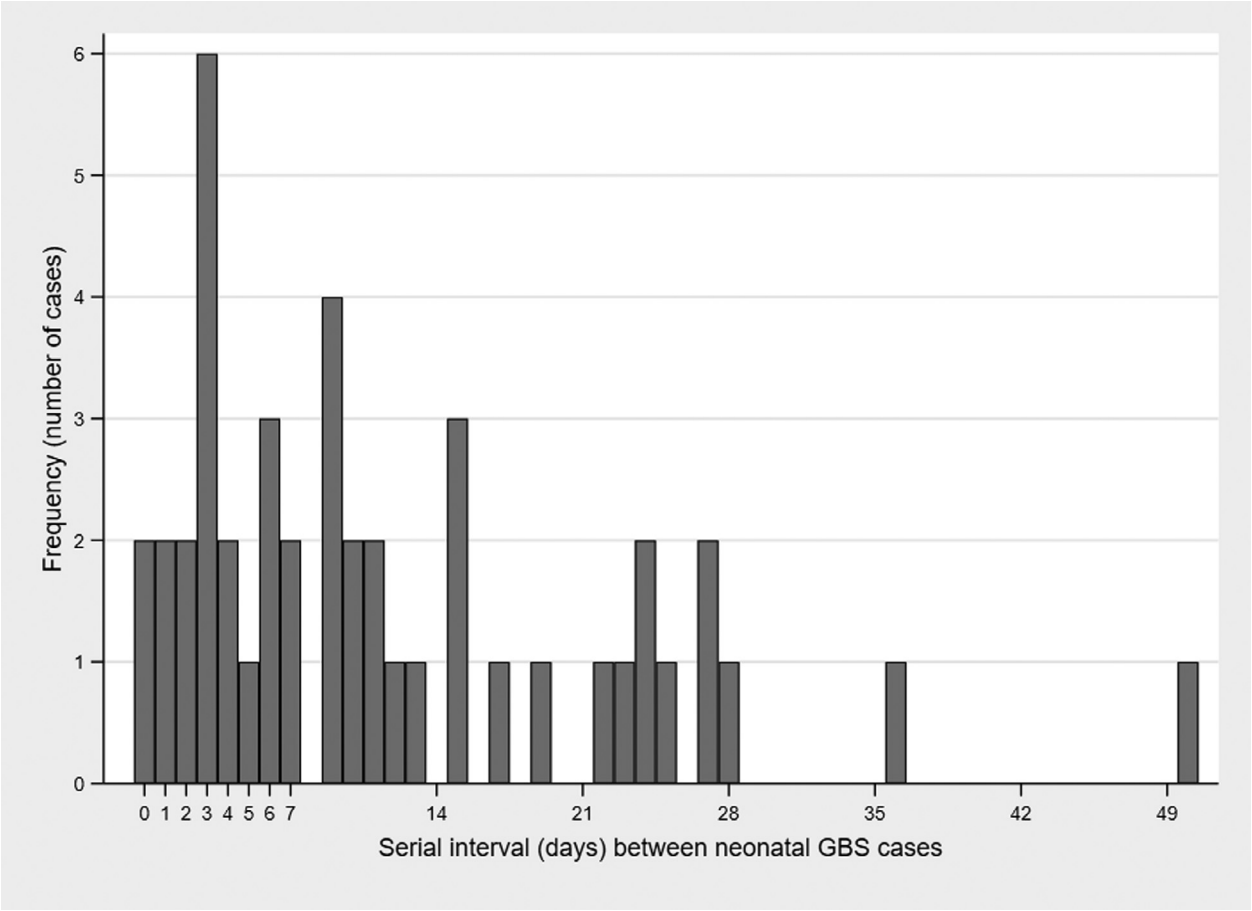

Fig. 2. Serial interval between GBS cases in neonatal clusters.[a]
[a]Clusters involving an early-onset, late-onset or colonized index case followed by one or more late-onset cases.

patient to the other via the hands of a nurse who had cared for both patients, including handling central venous catheters, at their last two dialysis sessions prior to diagnosis of invasive GBS. Denton et al. described a cluster that occurred over 11 days involving 3 out of 8 male patients receiving radiotherapy in a 34-bed oncology unit.[46] All the men had pneumonia (no bacteraemia reported); GBS was isolated from the sputa of all 3 patients (serial intervals 2 and 6 days), and one patient also had S. pneumoniae in his sputum. The cluster was attributed to droplet spread as the men were being treated in the same vicinity within the oncology unit. Nagano et al. reported a cluster involving 8 patients on 3 wards of a general hospital.[47] PFGE typing indicated one cluster of 5 patients (4 of whom were on the same ward) with serial intervals of 0, 2, 8, and 33 days, a second distinct cluster of two patients (both on the same ward, onset 97 days apart) and one unrelated case. In all cases GBS was isolated from pharyngeal swabs or tracheal aspirates and had reduced susceptibility to penicillin. The authors did not suggest a transmission route.

Discussion

This is the first systematic review of group B streptococcal (GBS) disease clusters in healthcare settings. Excluding 2 sibling and 2 early-onset only 'clusters', we found 21 studies describing 26 hospital clusters in 10 countries over a 50-year period. Most clusters occurred in neonatal intensive care units, involving preterm infants, but we also found 4 clusters in adult patients. Although it has long been known that GBS can spread within hospital nurseries,[48] outbreaks are considered to occur very rarely. Of note, half of the studies identified were reported in the past 9 years. This may reflect a genuine increase in frequency due to an expanding pool of susceptible infants, given improved survival of premature and very low-weight babies.[49] It may also reflect improved outbreak detection through use of more discriminatory microbiological methods or as result of a general increased awareness of GBS. Our findings suggest however that hospital GBS clusters are likely to be under-reported. Of the GBS clusters with evidence of horizontal transmission, intervals between consecutive cases were on occasion very long (up to 50 days) with more than half of the clusters having at least one serial interval of 2 weeks or longer. GBS clusters, particularly those affecting small numbers of patients or with long intervals between cases, might therefore go undetected, especially in the context of the prevailing assumption that such outbreaks are rare.[41] Serotype III predominated in our reviewed clusters, representing 42% of clustered late-onset cases, compared with 73% worldwide,[4] followed by serotype Ia (24% vs 14% worldwide).[4] The lower proportion of serotype III isolates in reported clusters may reflect detection bias because serial detection of cases with less common serotypes is more likely to raise suspicion of cross-infection.

Factors implicated in late-onset disease clusters included lapses in infection prevention and control practices (8/17 references), inadequate disinfection of equipment and surfaces (6/17, including shared breast milk equipment[33,37] and formula preparation facilities[26]) and close proximity of cots (7/17); 5/17 references mentioned crowding and/or high patient-to-nurse ratio as possible contributory factors. Although most clusters affected neonates whose hospital stays overlapped, we cannot infer that the outbreaks were propagated rather than being spread from a point source. One study reported cases in infants without overlapping stays at the

district hospital where they were born, raising suspicion of a potential point source.[44]

The role of persistent GBS carriage in neonatal unit personnel seeding clusters is a highly sensitive topic which merits further investigation. Of the studies we reviewed, staff screening was undertaken in 3 studies (anogenital and throat in 2 studies, throat in one), with evidence of staff carriage as a potential reservoir identified in both studies where anogenital and throat samples were analysed. Interpreting the significance of positive staff screens requires use of highly discriminatory methods, ideally WGS, given the commonality of carriage in men and women (18% worldwide in pregnant women).[6] The implications for staff found to be the source could be far-reaching given the potential difficulty in decolonizing gut carriage, but this putative source of infection cannot be ignored where standard precautions are failing to protect patients.

Our review identified patient and staff pharyngeal GBS carriage as a potentially important but overlooked source of infection. Culture survey results in one of the neonatal cluster studies showed that, of 7 affected infants, 5 had positive throat cultures as did 3 of 18 personnel on the unit (albeit without confirmed linkage to the cluster cases).[25] The index case in another neonatal cluster had pneumonia when transferred into the unit,[41] and one of the four adult clusters was attributed to respiratory transmission of GBS between patients.[46] Based on these findings and evidence of respiratory spread of GBS in childcare settings,[50] future investigation should consider assessing upper respiratory tract carriage as a possible means of GBS transmission.

The small number of adult clusters in our review precluded a meaningful summary. As with neonatal clusters, outbreaks in adult settings may well go undetected. Given the increasing incidence of invasive GBS disease in adults,[1,2,51] further research into clustering of adult cases based on routinely collected microbiological data is warranted.

The strengths of this systematic review are its historical scope, with references dating back to 1966, and that neonatal clusters were reasonably homogeneous therefore allowing summary measures to be calculated. The main limitations relate to the representativeness of published clusters and the generalizability of cluster characteristics to middle and low-income settings. The small median cluster size in our review (2 cases) suggests that larger clusters may not have been disproportionately represented in the literature, but we cannot infer from our review the 'true' distribution of cluster size. The frequency and characteristics of infant GBS clusters in settings with fewer resources (and fewer preterm infants surviving to be placed in intensive care) may differ. An inherent limitation of our review is that, in some clusters, evidence linking cases or suggesting transmission routes was non-molecular or was obtained by molecular methods such as phage typing or antimicrobial susceptibility profiles which are less discriminatory than methods such as PCR and WGS, therefore providing putative rather than conclusive evidence.

Our review highlights the potential for GBS to disseminate in hospital settings and suggests that outbreaks are likely to be under-recognized. Improved detection of GBS clusters and investigation using whole genome sequencing will inform future approaches to control of GBS transmission in healthcare settings, particularly within neonatal units.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.11.008.

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