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Original Article

Epidemiology and Trends of Infective Meningitis in Neonates and Infants Less than 3 Months Old in Hong Kong

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ABSTRACT

Objectives: Meningitis in neonates and young infants leads to significant morbidity and mortality worldwide. This study aimed to investigate pathogens, antibiotic resistance and secular change of incidence in Hong Kong.

Methods: A retrospective search was performed on meningitis in neonates and infants aged <3 months in three Hong Kong public hospitals from 2004 to 2019. Medical charts were reviewed, with focus on the identification and antibiotic resistance of the pathogens.

Results: A total of 200 cases of meningitis were identified (67% were bacterial). Group B *Streptococcus* (GBS) and *Escherichia coli* (*E. coli*) were the commonest bacterial pathogens. The annual rates of early-onset GBS meningitis decreased after the implementation of universal GBS screening and intrapartum antibiotic prophylaxis (IAP) in 2012, while that of late-onset GBS meningitis remained similar. A significant portion of *E. coli* isolates were resistant to ampicillin and/or gentamicin.

Conclusion: GBS and *E. coli* were the most common bacteria for meningitis in this age group. The annual rate of bacterial meningitis in Hong Kong has declined in recent years, which has been attributed to the decline in early-onset GBS meningitis due to universal GBS screening and IAP. Antimicrobial-resistant bacterial strains that cause meningitis require further clinical and public health attention.

Introduction

Meningitis remains a significant burden on healthcare systems at a global level, especially in children. The number of meningitis cases was over 5,000,000 in all ages in 2017 (James et al, 2018). Despite antimicrobial treatment, up to 23% of survivors may still suffer from long-term neurological sequelae at the age of 5 years (de Louvois, Halket, & Harvey, 2005). Neonates and infants aged <3 months are particularly prone to suffer from meningitis because of their exposure to potential pathogens in

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the birth canal, immaturity of both cellular and humoral immunity, and a developing blood-brain barrier (Barichello et al, 2013; Chandran, Herbert, Misurski, & Santosham, 2011; de Louvois et al, 2005; Libster et al, 2012; Okike et al, 2014a; Thigpen et al, 2011).

According to data from the United Kingdom (UK) in 2014 and France in 2011, Group B *Streptococcus* (GBS) and *Escherichia coli* (*E. coli*) are the most common pathogens that cause neonatal meningitis, with meningococcal and pneumococcal meningitis together contributing 8% and 5% in these two studies, respectively (Gaschignard et al, 2011; Okike et al, 2014b). In contrast, a meta-analysis showed that *E. coli* and *Streptococcus pneumoniae* were the most common pathogens of neonatal meningitis in the African region (Oordt-Speets, Bolijn, Van Hoorn, Bhavsar, & Kyaw, 2018). These highlight the differences in pathogens causing neonatal meningitis across different regions of the world.

A study in 2019 conducted on childhood meningitis in Shenzhen, a city with a 12.5 million population adjacent to Hong Kong (HK), found that GBS and *E. coli* were the most common pathogens in neonatal meningitis (Shen et al, 2019). However, an up-to-date aetiological study in HK investigating this potentially lethal and disabling disease is lacking. The latest study from HK was published in 1997, which was a single-centre retrospective study describing the aetiology of paediatric meningitis between 1984-1993 (Sung, Senok, Ho, Oppenheimer, & Davies, 1997).

Many changes in the past 20 years have likely made the past published information about neonatal meningitis less reflective of the current situation. The HK government started the pneumococcal vaccination program for infants and the elderly in 2007 (*Hong Kong Reference Framework for Preventive Care for Children in Primary Care Settings Module on Immunisation*, 2019). Furthermore, a universal GBS screening program and use of intrapartum antibiotic prophylaxis (IAP) commenced in HK in 2012, which was similar to the revised guideline on *Prevention of Perinatal Group B Streptococcal Disease* by Centers of Disease Control and Prevention in 2010 (Ma et al, 2018; Verani, McGee, & Schrag, 2010). The current strategy of GBS screening in HK is a culture-based approach to detect maternal GBS colonisation by rectovaginal swabs at the gestational ages of 35-37 weeks. IAP is given to mothers with: GBS colonisation (except caesarean deliveries performed before the onset of labour on women with intact amniotic membranes); known GBS bacteriuria; a definite history of a previous infant who was affected by GBS disease; or unknown GBS status at the onset of labour with no available GBS screening results in the presence of risk factors, including gestational age <37 weeks, maternal fever or prolonged rupture of amniotic membrane (>18 hours). This screening program detected a colonisation rate of 21.8%, according to a study conducted from 2012-2014 (Ma et al, 2018).

Ampicillin and gentamicin are the two most common mainstay empirical antibiotics used in presumed neonatal bacterial infection. The use of third-generation cephalosporins and meropenem as empirical antibiotics varies between physicians and the patient's presenting clinical picture. A potential reason for this variability is that there have been no universally accepted treatment guidelines or updated local information on the pathogens that cause neonatal meningitis and the antibiotic resistance patterns.

In view of these important changes in the past few decades, this study was performed to assess the secular change of meningitis, particularly focusing on antibacterial resistance patterns. It aimed to help ascertain whether these patients are still receiving the essential and appropriate empirical antimicrobial coverage while waiting for their final culture results.

Methods

Study Setting

This was a retrospective, multi-centre study conducted at three public hospitals (Pamela Youde Nethersole Eastern Hospital, Princess Margaret Hospital and Queen Mary Hospital) across three different districts in the HK Special Administrative Region of China, which provide approximately 30% of hospital beds for the whole paediatric and neonatal service in HK, including the paediatric and neonatal intensive care units. The number of live births in the three studied hospitals was 168,275, which was 17% of the live births across the whole HK territory during the studied period. All of these hospitals included obstetric services and received transfers from private hospitals. Approval from the Institutional Review Board of each of the three hospitals was obtained prior to the collection of data.

Patient Selection and Definitions

All inpatient admissions to the Department of the Paediatric and Adolescent Medicine of the three hospitals during the period 1 September 2004 to 31 August 2019 were filtered by the Clinical Data Analysis and Reporting System with the following criteria: 1) admission age <90 days of life, and 2) all meningitis-related International Classification of Diseases (ICD)-9 codes and/or spinal tap as the procedure code. The study included newborns delivered in the three hospitals, patients admitted via the emergency department and patients referred from other private hospitals. Discharge summaries and all laboratory results during that hospitalisation and follow-up clinic notes in their electronic medical charts were reviewed by a paediatric doctor.

Cases of microbiologically-proven meningitis were defined by a patient who exhibited symptoms, diagnosed and clinically treated as such, with cerebrospinal fluid positive for either 1) bacterial, fungal, acid-fast bacilli or viral culture; 2) latex agglutination test; or 3) viral polymerase chain reaction (PCR). Relapse was defined as meningitis due to the same organism within three weeks of completion of antimicrobial therapy from the initial episode (Durand et al, 1993). Preterm was defined as patients born at a gestational age of <37 weeks and 0 days. Meningitis was considered as early-onset if either 1) the infection occurred in the first 6 days of life (Okike et al, 2014b) or 2) the lumbar puncture was performed in the first 6 days of life if the date of presentation was not clearly documented. Mortality was defined as death during the same hospitalisation. Subjects were excluded if 1) their CSF samples were drawn beyond 89 days of life or 2) the organisms yielded in the report were considered by the patient's physicians to be due to environmental contamination and the final diagnosis of the index case was not meningitis. Live birth data were obtained from HK's Hospital Authority annual statistics report.

References for the breakpoint for resistance to antibiotics were based on the updated Clinical and Laboratory Standards Institute (CLSI) recommendation (Clinical and Laboratory Standards Institute, 2019). The presence of extended-spectrum beta-lactamases (ESBL) was tested by the combined-disk test for isolates of *Klebsiella pneumoniae, Klebsiella oxytoca, E. coli,* and *Proteus mirabilis*. The technique of 16s rRNA and MALDI-TOF-MS were not employed in the laboratory during the study.

Statistical Analysis

Data were entered and stored in an encrypted Microsoft Excel file, which was analysed by JMP version 14.2.0. Non-parametric numerical data were presented by medians and 95% inter-percentile ranges (IPR). The Wilcoxon test was employed for the analyses.

Table 1
Demographics of the cases.

		Subgroup	n in subgroup	N	%
Gender	Male			108	54.0%
	Female			92	46.0%
Gestation	Term			143	71.5%
	Preterm			51	25.5%
		<34 weeks	28 (54.9%)		
		34-36 week and 6 days	23 (45.1%)		
	Uncertain			6	3.0%
Hospital	PMH			80	40.0%
	PYNEH			51	25.5%
	QMH			69	34.5%
CNS device in situ	Yes			7	3.5%
Bacterial meningitis				139	69.5%
		Early-onset	53 (38%)		
		Late-onset	86 (62%)		
Viral meningitis				61	30.5%
Death				4	2.0%

Abbreviations: PMH, Princess Margret Hospital; PYNEH, Pamela Youde Nethersole Eastern Hospital; QMH, Queen Mary Hospital; CNS, central nervous system

Table 2
Categorisation of pathogens involved in bacterial meningitis, according to gestational age at birth.

Category of the bacterial organism	Genus and species	Total number of case (%)	Term		Preterm (% of all preterm bacterial meningitis)	Gestation uncertain
			28 days or younger(%)	beyond 28 days (%)		
Gram positive	*Streptococcus agalactiae*	67 (48.2)	46 (67.6)	10 (52.6)	7 (14.9)	4 (80)
	Bacillus species	6 (4.3)	0	1 (5.3)	5 (10.6)	0
	Coagulase negative staphylococci	6 (4.3)	0	2 (20.5)	4 (8.5)	0
	Staphylococcus aureus	5 (3.6)	2 (2.9)	0	3 (6.4)	0
	Streptococcus bovis I/II	4 (2.9)	2 (2.9)	0	2 (4.3)	0
	Enterococcus	2 (1.4)	1 (1.5)	0	1 (2.1)	0
	Listeria monocytogenes	2 (1.4)	1 (1.5)	0	1 (2.1)	0
	Streptococcus pneumoniae	1 (0.7)	0	1 (5.3)	0	0
Total number of Gram positive		93 (66.9)	52 (76.5)	14 (73.7)	23 (48.9)	4 (80)
Gram negative	*Escherichia coli*	35 (25.3)	12 (17.6)	3 (15.8)	19 (40.4)	1 (20)
	Klebsiella pneumoniae	4 (2.9)	2 (2.9)	0	2 (4.3)	0
	Elizabethkingia species	3 (2.2)	2 (2.9)	0	1 (2.1)	0
	Morganella morganii	1 (0.7)	0	0	1 (2.1)	0
	Neisseria menignitidis	2 (1.4)	0	2 (10.5)	0	0
Total number of Gram negative		45 (32.4)	16 (23.5)	5 (26.3)	23 (48.9)	1 (20)
Other	*Mycoplasma hominis*	1 (0.7)	0	0	1 (2.1)	0
Total number of bacterial organism		139 (100)	68 (100)	19 (100)	47 (100)	5 (100)

Categorical data were compared using the Chi-square test. Differences were considered to be significant with *P*-values <0.05.

Results

During the study period, 200 records with episodes of microbiologically-proven meningitis were retrieved (Table 1): 143 (71.5%) were born at term, while 51 (25.5%) were preterm at gestational ages ranging from 25 weeks and 3 days to 36 weeks and 6 days. The gestational age was not recorded for the remaining six patients (3%). A bacterial pathogen was identified for 139 subjects (69.5%), while 61 (30.5%) cases were due to viruses. The overall proportion of late-onset meningitis cases was 70.5% (n=141); 61.8% of bacterial meningitis was late onset.

Gram-positive and Gram-negative organisms consisted of 67% and 32% of all bacterial meningitis, respectively (Table 2). GBS and *E. coli* were the two most common pathogens in bacterial meningitis in both term and preterm infants. Together, they accounted for more than 50% of the cases. GBS was the predominant pathogen in both early-onset and late-onset term meningitis. The median age for late-onset GBS meningitis was 22.5 days (95% IPR: 8-87 days). All cases of preterm GBS meningitis were late-onset (n=7), and their gestational ages at birth ranged 27-36 weeks and 5 days; *E. coli* was the predominant pathogen in preterm bacterial meningitis (19/45, 42.2%). Two cases were due to *Neisseria meningitidis* (n=2, 1%), including one imported case from outside the region, in which the patient initially presented in Hainan, China. After the patient was found to have meningitis, he was transferred to HK for further management. There was one patient who had meningitis due to *Streptococcus pneumoniae* (n=1, 0.5%). *Haemophilus influenzae* was not found in this study. There was one case of relapsed *E. coli* meningitis in a 32-week preterm infant who presented on day 4 of life; the *E. coli* isolate was sensitive to cefotaxime. The relapse episode occurred 8 days after completion of a 3-week course of cefotaxime at a higher dose indicated for treatment of meningitis.

Seven infants had a ventricular device *in situ* (two external ventricular devices and five ventriculoperitoneal shunts) for underlying diseases during the episode of meningitis and all were due to Gram-positive organisms (two *Bacillus* species, four coagulase-negative *Staphylococcus* and one *Staphylococcus aureus*). The duration of the ventricular device *in situ* before the infection ranged 15-84 days (median: 35 days). None of the cases was documented with a structural defect of meninges with external communication, spinal bifida or CSF leak.

There were four deaths (2% mortality) and all of them were preterm infants (gestational ages at birth from 31 weeks and 1 day to 35 weeks and 6 days). The causative organisms were *Bacillus* species for two cases, *Klebsiella pneumoniae* and *E. coli*.

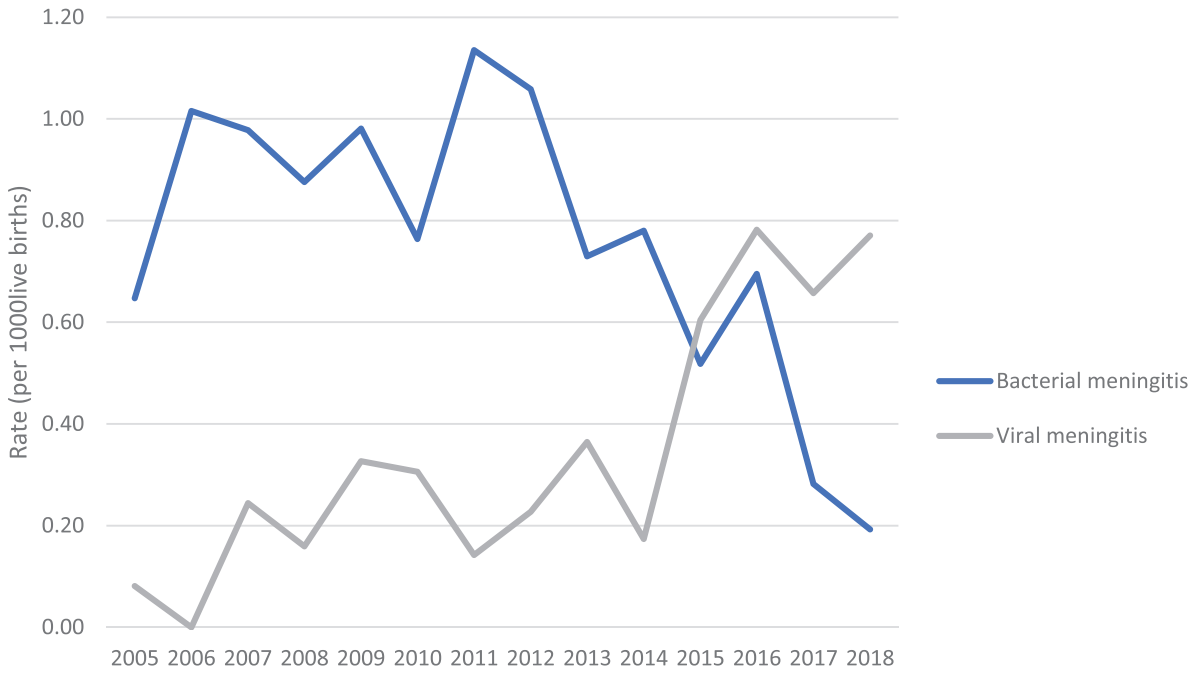


Figure 1. The rates of bacterial meningitis (blue line) and viral meningitis (grey line) across the years from 2005 to 2018. The citywide, universal GBS screening and intrapartum antibiotic prophylaxis program in the public hospital system commenced in 2012.

There was an uptrend in the annual rates of bacterial meningitis from 2006 to 2010, peaking in 2011 (Figure 1). However, there has been a decline in the annual rates of bacterial meningitis since 2012, with a 5.5-fold reduction in 2018 compared to 2011. The overall annual rates of early-onset and late-onset GBS meningitis across the studied period were 0.009 and 0.019 cases per 1,000 live birth per year, respectively. Since the introduction of universal GBS screening in HK in 2012, the median of the rate of early-onset GBS meningitis (adjusted by the live birth rate of the three hospitals) decreased from 0.17 (95% IPR: 0.08-0.306) between 2005 and 2011 to 0 (95% IPR: 0-0.173) between 2012 and 2018 per 1,000 live births per year (P=0.02) (Figure 2). In contrast, the median rate of late-onset GBS meningitis showed no statistically significant difference before and after 2012, from 0.28 (95% IPR: 0.081-0.407) to 0.26 (95% IPR 0-0.547) per 1,000 live births per year (P=0.8). Meanwhile, the median rate of non-GBS meningitis was of no statistical difference before and after 2012 (non-GBS meningitis: 0.478 (95% IPR: 0.153- 0.638) vs 0.193 (95% IPR: 0.173-0.605); P=0.307). The annual rate of viral cases steadily increased over the years, which was mostly contributed by enteroviral meningitis (Figure 1).

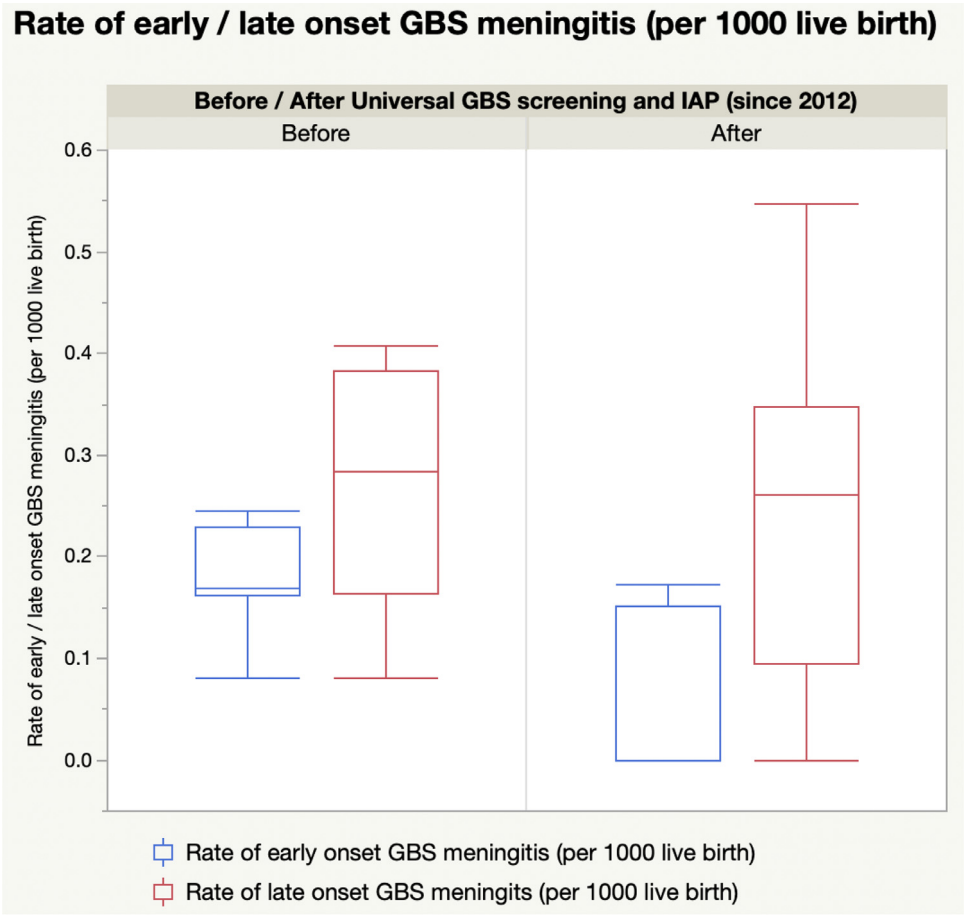
Antimicrobial susceptibility test results were available for 31 of 35 isolates of *E. coli* meningitis (the rest were diagnosed by latex agglutination with no culture available for antibiotic sensitivity tests). Resistance to ampicillin and gentamicin was 74% and 32%, respectively, in all tested isolates (Table 4). There was gentamicin resistance in 60% and 33% of isolates from preterm infants (n=6) and term infants (n=4), respectively. Five of the 31 *E. coli* isolates (16%) showed resistance to a third-generation cephalosporin (cefotaxime or ceftriaxone or both), including four of them (three preterm and one term infant) that were extended-spectrum beta-lactamase (ESBL)-producing strains. Of those *E. coli* isolates tested with susceptibility to meropenem (n=6) and amikacin (n=5), no resistance was found.

Discussion

GBS and *E. coli* were the most common bacterial pathogens and accounted for 48.2% and 18.1% of all bacterial meningitis cases, respectively. This finding was consistent with other large-scale population studies in developed countries (Gaschignard et al, 2011; Okike et al, 2014b; Ouchenir et al, 2017; Shen et al, 2019; Thigpen et al, 2011). Based on the current study, two patients had meningococcal and one had pneumococcal meningitis. There were no cases involving *Haemophilus influenzae*. These statistics are mostly in parallel with the studies performed in this region 30 years ago and in the latest study in Shenzhen (Shen et al, 2019; Sung et al, 1997).

The rate of bacterial meningitis was steadily high from 2005 to 2011 and has declined since 2012. It is postulated that the decreasing trend in the annual rate of bacterial meningitis after 2012 was at least partially attributed to the effectiveness of the universal GBS screening program and IAP in preventing early-onset GBS meningitis, as the annual rates of late-onset GBS meningitis and non-GBS meningitis had no statistically significant difference over time. Taken together, these findings further support the notion that IAP can effectively prevent early-onset invasive GBS infections, but not late-onset GBS infection, including meningitis (Gaschignard et al, 2011; Seale et al, 2017; Tephanie et al, 2000).

Ampicillin and gentamicin are two commonly used empirical antibiotics for presumptive neonatal bacterial infections. In this study, 74% and 32% of the 31 *E. coli* isolates were resistant to these two antibiotics, respectively. These antimicrobial resistance frequencies were similar to data reported in the recent study in Shenzhen (75% for ampicillin and 33% for gentamicin, n=12) but more prevalent than that in the Canadian study conducted in 2017 (56% for ampicillin and 13% for gentamicin) (Ouchenir et al, 2017; Shen et al, 2019). Based on these findings, empirical use of third-generation cephalosporin is recommended for presumptive invasive infectious diseases in neonates or young infants (with the addition of ampicillin in neonates within the first month of life to cover *Listeria monocytogenes*), particularly those with clinical suspicion of meningitis, known maternal or perinatal *E. coli* infection. Third-generation cephalosporins have better penetration through the blood-brain barrier than gentamicin (Bornstein, 1987). Additionally, four isolates from the current study were ESBL-producing *E. coli* and one isolate was resis-



		Before / After Universal GBS screening (median, 95% inter-percentile range)		
		Before	After	p value
Total GBS meningitis	Corrected with HK live birth (per 1000)	0.42 (0.243-0.611)	0.35 (0-0.547)	0.16
Early onset GBS meningitis		0.17 (0.080-0.245)	0 (0-0.173)	0.02
Late onset GBS meningitis		0.28 (0.081-0.407)	0.26 (0-0.547)	0.8

Figure 2. Box plots of the rates of early-onset (blue box) and late-onset (red box) GBS meningitis (per 1,000 live birth in each calendar year) comparing those before (between 2005 and 2011) and after (between 2012 and 2018) the commencement of universal GBS screening and intrapartum antibiotic prophylaxis in 2012. There were 65 cases of GBS meningitis in total, including 21 early-onset GBS meningitis and 44 late-onset GBS meningitis. There was a significant reduction in the rate of early-onset GBS meningitis (0.17 vs. 0, P=0.02), while no statistical difference was found in late-onset GBS meningitis (0.28 vs. 0.26, P=0.8).

tant to a third-generation cephalosporin (the ESBL status was not stated in the report). Therefore, in neonates or young infants who present with ill-appearance, severe complications, rapid deterioration or with known maternal colonization with ESBL-producing organisms, carbapenems may be an appropriate empirical antimicrobial choice.

This study identified that viral meningitis became more prevalent than bacterial meningitis in this locality, as reported since 2015 in the UK (Kadambari et al, 2019). Enteroviruses accounted for 96% of viral meningitis. In the past, a conclusive diagnosis of viral meningitis in young infants was limited by the low yield from viral culture (Shukla et al, 2017; Vareil et al, 2018). With the use of PCR technology that recently became standard in all microbiology laboratories, more viral pathogens can be identified (Lyons, Mcadam, Cohn, Monuteaux, & Nigrovic, 2012; O'Brien et al., 2018). Of note, severe viral meningoencephalitis can be caused by the herpes simplex virus (HSV) (Pinninti & Kimberlin, 2018). One neonate in the current study suffered from HSV meningoencephalitis, who initially presented with a vesicular rash over the truncal area. The PICNIC study by the Canadian group found that all HSV (seven cases out of 174 episodes of CNS infection in 2 years) presented before 21 days of life, among which four of them had a seizure, and five of them had extra-CNS manifestation, including vesicular lesions, transaminitis, pneumonitis, and coagulopathy (Petel et al, 2020). Empirical coverage with acyclovir may not be warranted unless in the presence of clinical features suggestive of HSV meningoencephalitis, such as vaginal birth in the setting of active herpes labialis, the presence of vesicles on initial skin examination, extra-CNS manifestation such as hepatic transaminitis, pneumonitis and coagulopathy, and seizure.

This study had a few limitations. First, cases were filtered according to ICD-9 coding for diseases and procedures. Therefore, cases may have been missed if they were not accurately coded. Second, the reported rates were adjusted by the live birth data within the three studied hospitals; however, these studied hospitals also accepted cases referred from private hospitals, and there could have been cases born in other public hospitals that later attended the studied hospitals. Nevertheless, most of the patients born in one hospital tend to return to the same hospital when a new illness occurs, as the public health service is regionally organised. Furthermore, because of the retrospective nature of the study there was no standardised documentation of the clinical details and microbiological investigations, leading to some missing information. The three studied hospitals provided about 30% of neona-

Table 3
Categorisation of viral pathogens in viral meningitis.

Viral detection		number	%of total
Enterovirus	Coxsackievirus A	5	8%
	Coxsackievirus B	19	31%
	Echovirus	8	13%
	Enterovirus 71	3	5%
	Enterovirus- unspecified	24	39%
Other	Paroechovirus	1	2%
	HSV	1	2%
Total number of virus		61	100%

Table 4
Antibiotic resistance of *Escherichia coli* isolates.

	Term: Early-onset *Escherichia coli* meningitis				
	N	Sensitive	%	Resistant	%
Ampicillin	5	1	20%	4	80%
Gentamicin	3	1	33%	2	67%
3GCP	5	5	100%	0	0%
ESBL	0				
	Term: Late-onset *Escherichia coli* meningitis				
Ampicillin	9	3	33%	6	67%
Gentamicin	9	7	78%	2	22%
3GCP	8	7	88%	1	13%
ESBL	1				
	Preterm: *Escherichia coli* meningitis				
Ampicillin	14	2	14%	12	86%
Gentamicin	10	4	40%	6	60%
3GCP	15	11	73%	4	27%
ESBL	3				

Abbreviations; 3GCP, third-generation cephalosporin; ESBL, extended-spectrum beta-lactamase

tal, general paediatric and intensive care services in the public sector in HK, with respect to bed numbers. Therefore, it is possible that the data from this study did not fully represent the situation for the entire territory. Finally, variations in the routine practice in clinical care and microbiology laboratories among the three studied hospitals may have lead to some heterogeneity in the final dataset.

Table 3

In conclusion, GBS and *E. coli* were still the most common pathogens in neonates and infants aged <3 months. The current practice of universal GBS screening and use of IAP appears to have successfully reduced the rates of early-onset but not late-onset GBS meningitis. Frequencies of ampicillin and gentamicin resistance for *E. coli* meningitis are high, with implications for the choice of empirical antibiotics before the culture results are available. This is a major public health concern that needs to be addressed by prospective research with a prospective approach and involving all hospitals in various regions.

Conflict of interest:

The authors declared no conflicts of interest.

Funding Source:

No funding source was involved in this study.

Ethical Approval:

Ethical approvals were obtained from the research ethics committees in the three participating hospitals (PYNEH ref no.: HKECREC-2019-081; PMH ref no.: KW/EX-20-157(154-03); QMH ref no: UW19-615).

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