

Invasive *Streptococcus agalactiae* ST283 in Hong Kong

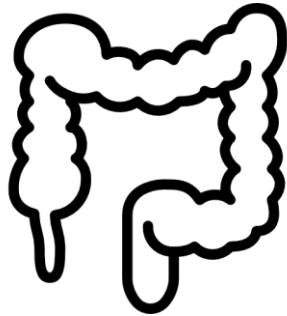
David Lung

Department of Pathology

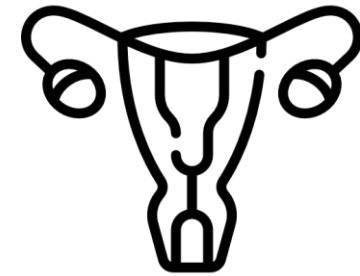
Queen Elizabeth Hospital / Hong Kong Children's Hospital

Common colonizer in human

Young healthy adults
20-40%

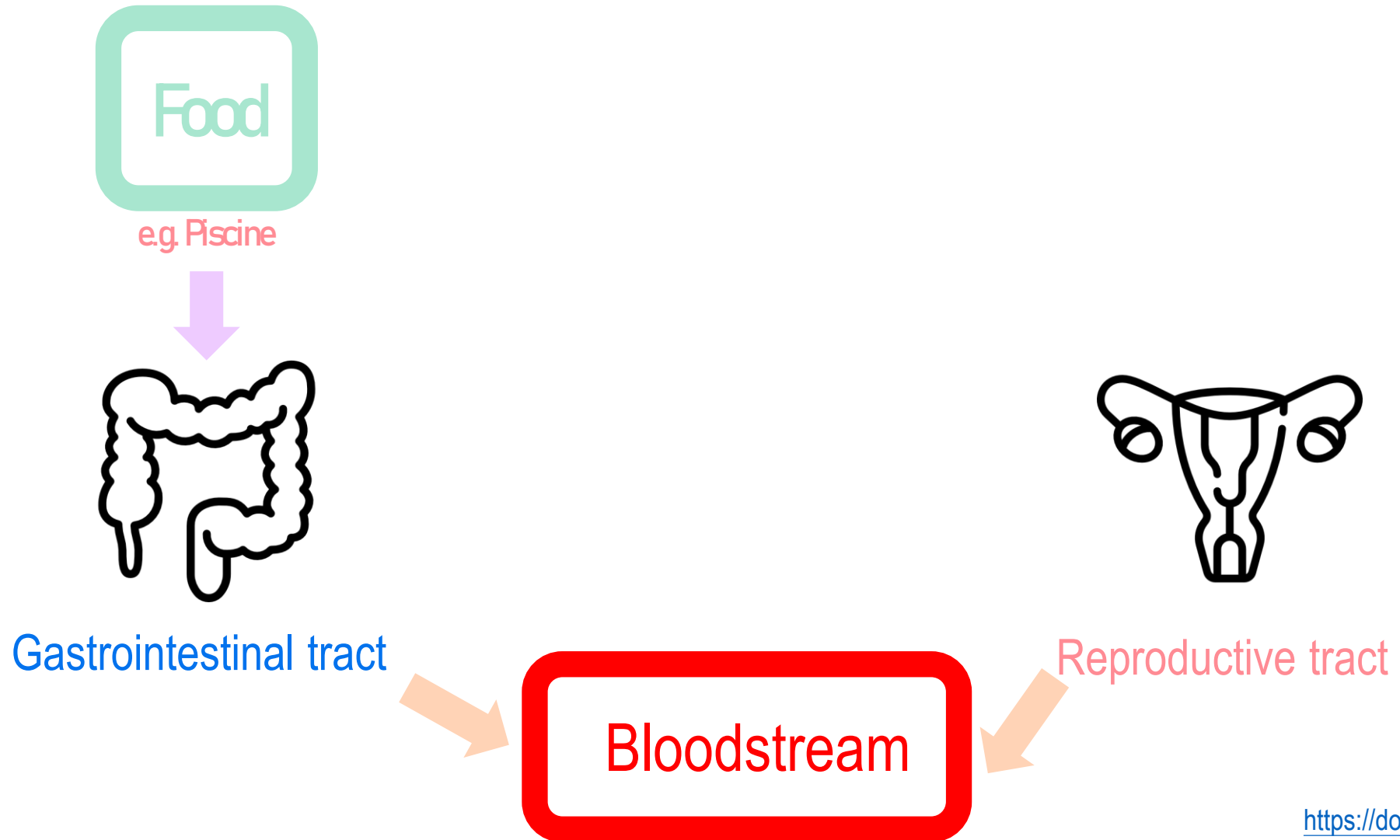


Gastrointestinal tract



Reproductive tract

Portal of entry of GBS



GBS infection: Food stalls told to stop selling Chinese-style raw fish dishes unless fish is from safe suppliers



1 of 4 Many hawkers have stopped selling porridge with raw fish slices. ST PHOTO: ALPHONSUS CHERN



Linette Lai
Political Correspondent

UPDATED JAN 21, 2016, 08:10 AM

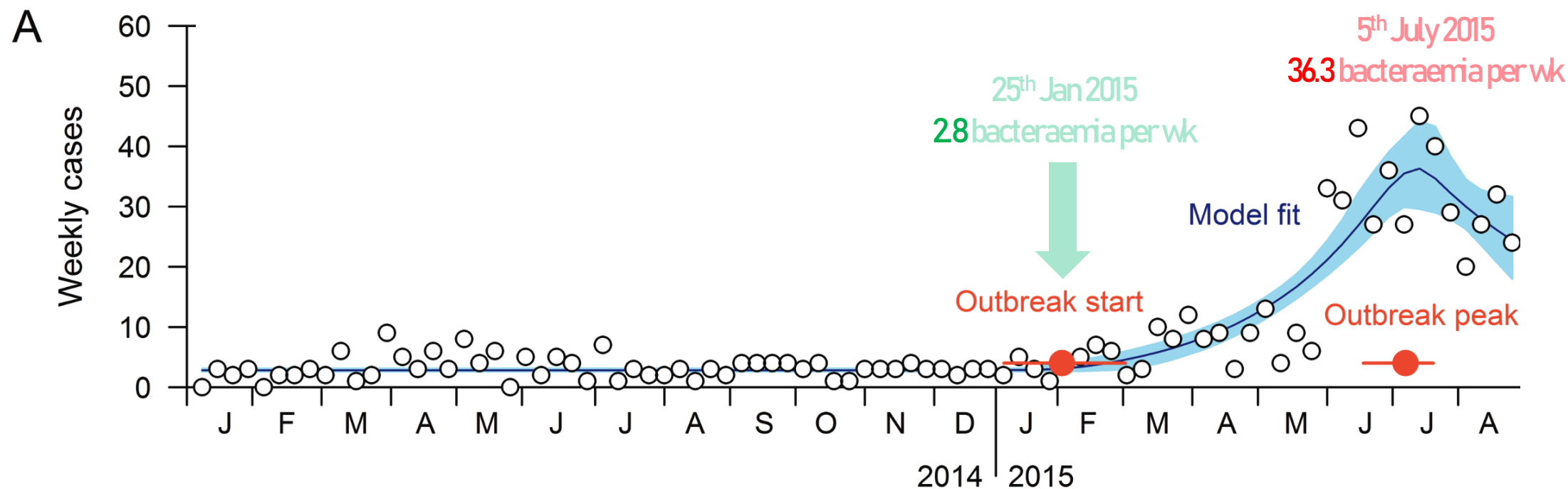
160

GBS Cases

ST283

	TTSH EID 2016 Vol 22, No. 11 Pg 1974-1977	Singapore MoH EID 2016 Vol 22, No. 11, Pg 1970-1973
Number of subjects	22 (9 ST283, 13 non-ST283)	40 (19 ST283)
Period	21 June – 21 Nov 2015 Epidemiologic week 25-46	1 June -14 July 2015
Risk factors	<ol style="list-style-type: none">1. Younger (59.4 yrs 74yr vs 77.5yr)2. Less likely to have preexisting medical condition (33% vs 84.6% vs 90.8%)3. Consumed raw or undercooked fish 2 weeks prior before admission	<ol style="list-style-type: none">1. Younger than non-ST283 (57.4 vs 68.6%)2. Lower proportion ST283 had underlying medical condition vs non-ST2833. Consumed fresh water fish before onset (mean 3.7 d, median 4 d)
Study type	Case-control study 1:3.5	Case-control 1:1.45
Control	<ol style="list-style-type: none">1. TTSH inpatient with negative culture2. Non-ST283 GBS	<ol style="list-style-type: none">1. Household members or colleagues of case patient2. Non-ST283 GBS

2015 Epidemic of Severe *Streptococcus agalactiae* Sequence Type 283 Infections in Singapore Associated With the Consumption of Raw Freshwater Fish: A Detailed Analysis of Clinical, Epidemiological, and Bacterial Sequencing Data

408
Study subjects35.8%
ST283

ST283 GBS infection



Native joint septic arthritis
30.1% vs 5.0%, $p < 0.001$



Spinal infection
8.2% vs 1.9%, $p < 0.005$



Meningitis/meningoencephalitis
19.9% vs 0, $p < 0.001$

Non-ST283 GBS infection



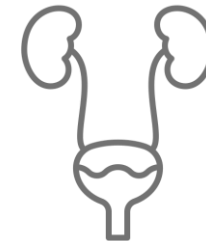
Bacteraemia without focus
22.3% vs 23.5%, $p = 0.903$



Native valve endocarditis
10.3% vs 5%, $p = 0.064$

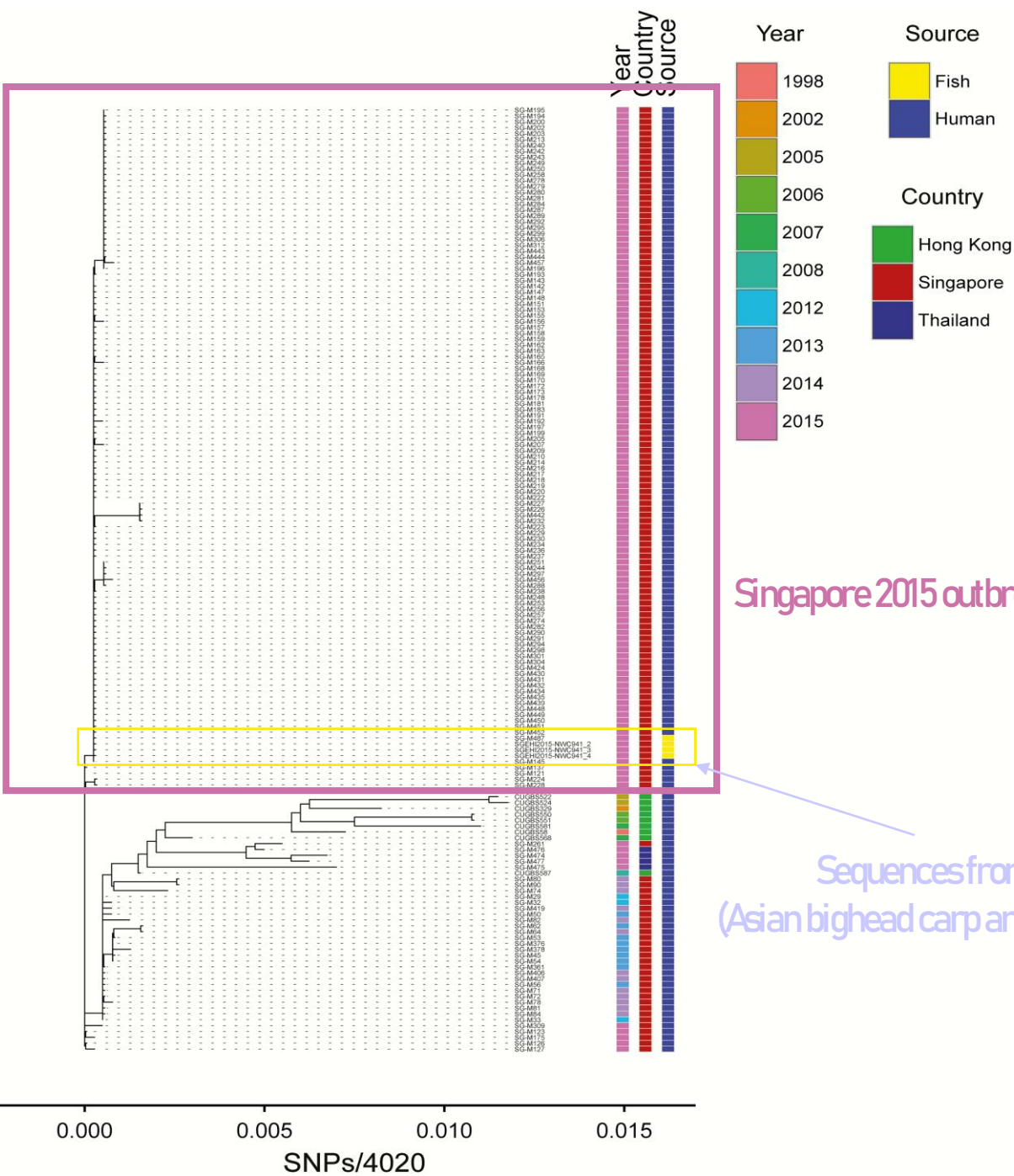


Skin and soft tissue infection
18.5% vs 42%, $p < 0.001$



Lower urinary tract infection
3.4% vs 11.8%, $p = 0.007$

Phylogenetic tree analysis based on core genome SNP



14 SNP

2015 human isolate differed by maximum (except 1 isolate SGM261)

27
SNP/Mbp/yr

Substitution rate

Singapore NEA and MoH issuing notice to ban freshwater fish in ALL RTE raw fish dish



MEDIA RELEASE FOR IMMEDIATE RELEASE

FRESHWATER FISH BANNED FROM READY-TO-EAT RAW FISH DISHES

Retail food establishments are to use only saltwater fish intended for raw consumption

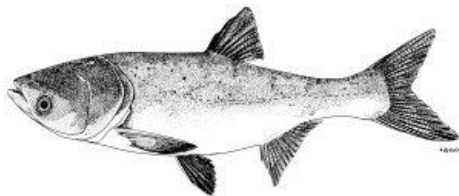
Singapore 5 December 2015 – As a further step to protect consumers from public health risks, the National Environment Agency (NEA) will ban with immediate effect the use of freshwater fish in all ready-to-eat (RTE) raw fish dishes sold by retail food establishments. Tests conducted by Agri-Food & Veterinary Authority of Singapore (AVA) and NEA have found such fish to have significantly higher bacterial

Hong Kong



Prohibition of sales of Chinese yusang

	Singapore		Hong Kong	Worldwide
Species of fish	大頭魚 Bighead carp (Hypophthalmichthys nobilis)	生魚 Snakehead (Channa argus)	鯪魚 Grass carp (Ctenopharyngodon idella)	福壽魚 Tilapia Oreochromis ssp 非洲鯽/羅非魚
Freshwater / seawater	Fresh water	Fresh water	Fresh water	Fresh water /brackish water
Type of delicacy	Yusheng (魚生) Served with hot porridge at the side		Congee Steamed with preserved vegetables Hotpot	Baked, steamed, pan fry



Surveillance of GBS in food

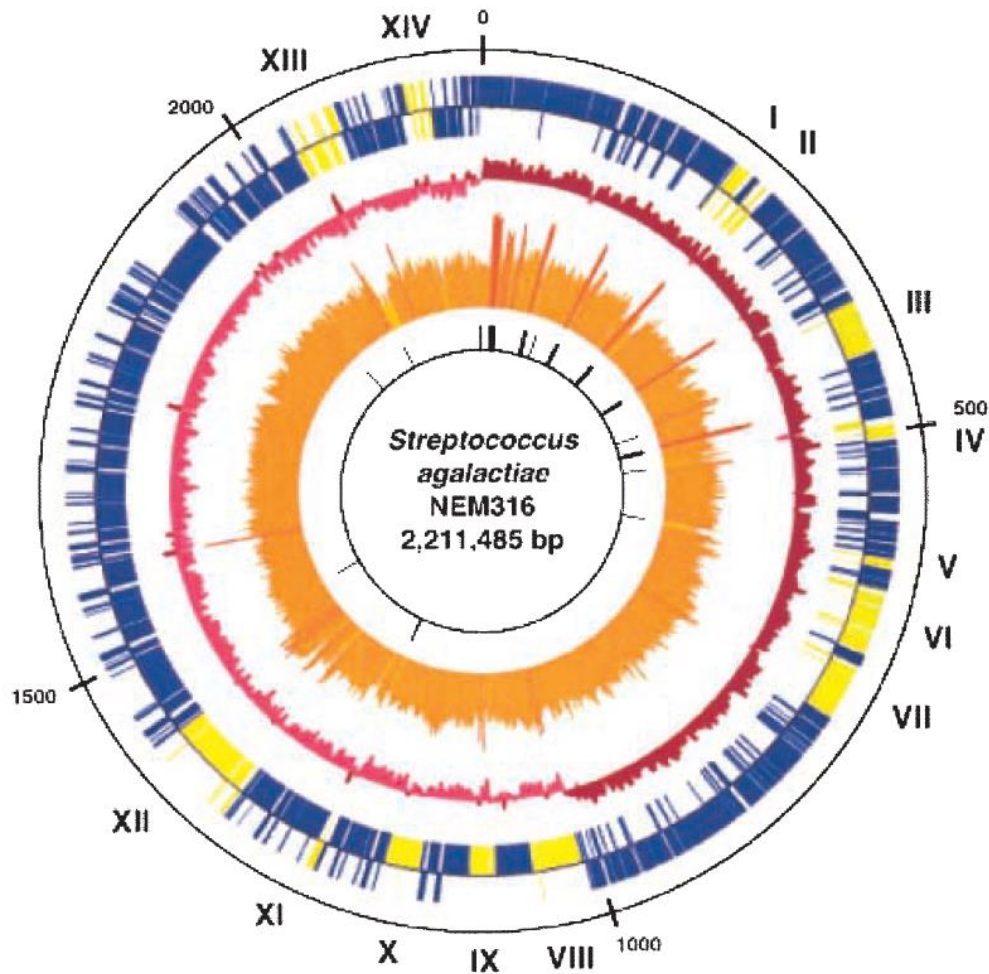
Country	ST283 GBS	Non-ST-283 GBS	Reference
Singapore	Freshwater fish (market 28.2%, RTE 14.3%, ports, 1%)	Freshwater fish Saltwater fish	EID 2017 Vol 23, No. 12 1982-1990
Singapore	Oyster	Salmon ST1 Oyster ST1, ST10, ST24, ST1647 Surf clam ST1	Food Control 133 (2022) 108625
Thailand	Talipia (13) Edible frog (1) giant sea perch (1) catfish (1)	Talipia (15 ST7 and 1 ST500), giant sea perch (2 ST7), Edible frog (1 ST7)	Pathogens 2023, 12, 525
Vietnam	Talipia (38)	Talipia (3 CC522/ST1395, 3 CC7/ST7)	
Brazil		Bullfrog (ST not specified)	J Wildlife Dis 1983 Vol 19, No. 3, 180-184
China		Talipia (ST7)	Fish Sci 2011 77:623- 632
Kuwait		Fish (5 ST7, 2 ST257, ST260, ST259, ST258, ST261) Dolphin (ST7)	Journal of Medical Microbiology (2008), 57, 1369–1376

Typing of GBS

Classification of *Streptococcus agalactiae* typing method

	Typing method	Scientific basis	Content	Remarks
Pre-genomic typing method	Serotyping	Rabbit immune sera against substance C	10 major serotypes Ia, Ib, II-IX	Classical phenotypic method
	Ribotyping RAPD RFLP PFGE MLEE	Obsolete		
	MLST	Sequencing of 7 house keeping gene	11 CC 1962 ST	Ease of typing Portability between labs Reasonable resolution Widely used
Post-genomic era	Next generation sequencing	SNP		High resolution Determine SNP difference

Streptococcus agalactiae genome



2Mbp

Genome size

>1900

Protein-coding genes

MLST

7

Housekeeping genes

Multilocus Sequence Typing System for Group B Streptococcus

Nicola Jones,^{1*} John F. Bohnsack,² Shinji Takahashi,³ Karen A. Oliver,¹ Man-Suen Chan,⁴
 Frank Kunst,⁵ Philippe Glaser,⁵ Christophe Rusniok,⁵ Derrick W. M. Crook,¹
 Rosalind M. Harding,⁶ Naiel Bisharat,¹ and Brian G. Spratt⁷

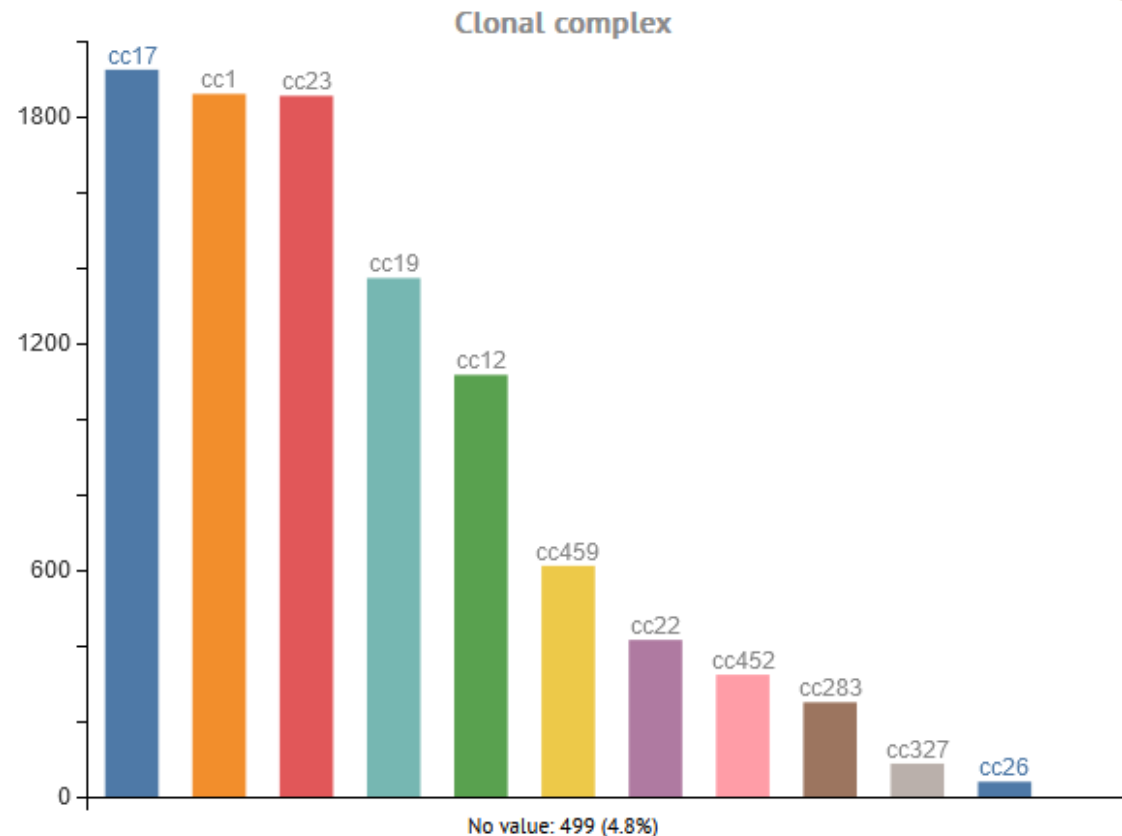
TABLE 2. Characteristics of loci included in the GBS MLST system^a

Locus	Putative function of gene	Size of sequenced fragment (bp)	No. of alleles identified	No. (%) of polymorphic nucleotide sites	% G+C	d_n/d_s	Position in GBS genome ^b (bp)
<i>adhP</i>	Alcohol dehydrogenase (gbs0054)	498	11	12 (2.4)	43.1	0.13	72286
<i>pheS</i>	Phenylalanyl tRNA synthetase	501	5	7 (1.4)	37.1	0.17	912817
<i>atr</i>	Amino acid transporter (gbs0538)	501	8	12 (2.4)	36.9	0.14	560085
<i>glnA</i>	Glutamine synthetase	498	6	6 (1.2)	35.7	0.12	1868862
<i>sdhA</i>	Serine dehydratase (gbs2105)	519	6	13 (2.5)	41.4	0.12	2179923
<i>glcK</i>	Glucose kinase (gbs0518)	459	4	7 (1.5)	42.6	0.13	538770
<i>tkt</i>	Transketolase (gbs0268)	480	5	8 (1.7)	38.9	0.42	287111

^a Genes: *adhP*, alcohol dehydrogenase (gbs0054); *pheS*, phenylalanyl tRNA synthetase; *atr*, amino acid transporter (gbs0538); *glnA*, glutamine synthetase; *sdhA*, serine dehydratase (gbs2105); *glcK*, glucose kinase (gbs0518); *tkt*, transketolase (gbs2105). Alleles of the seven housekeeping loci can be obtained at <http://sagalactiae.mlst.net>.

^b From reference 11.

Streptococcus agalactiae



Multilocus sequence typing (MLST) scheme

Based on 7 house keeping genes

≥ 4 alleles match: same **Clonal Complex (CC)**

7 Alleles match: same **Sequence type (ST)**

Multilocus Sequencing Typing Scheme

CC	Number of ST	Examples
CC1	450	ST 1, ST7
CC12	274	ST8, ST9, ST15
CC17	309	ST17, ST108
CC19	346	ST19, ST110
CC22	86	ST22, ST37
CC23	305	ST23
CC26	20	ST26, ST127, ST2001
CC283	19	ST11, ST283 , ST491, ST1311
CC327	12	ST327, ST328, ST1711
CC452	49	ST452, ST24, ST322, ST1010
CC459	92	ST66, ST459, ST944
Total: 11 Clonal complex	1962 Sequence Type	

Identification of a *Streptococcus agalactiae* Serotype III Subtype 4 Clone in Association with Adult Invasive Disease in Hong Kong[▽]

Margaret Ip,^{1*} Edmund S. C. Cheuk,¹ Michelle H. Y. Tsui,² Fanrong Kong,³
 T. N. Leung,² and Gwendolyn L. Gilbert³

Department of Microbiology¹ and Department of Obstetrics and Gynaecology,² Chinese University of Hong Kong, Shatin, Hong Kong, and Centre for Infectious Diseases and Microbiology Laboratory Services, Institute of Clinical Pathology and Medical Research, Westmead, NSW, Australia³

TABLE 2. Protein gene and IS profiles and MLSTs for representative isolates of GBS serotype III subtypes 1 to 4^a

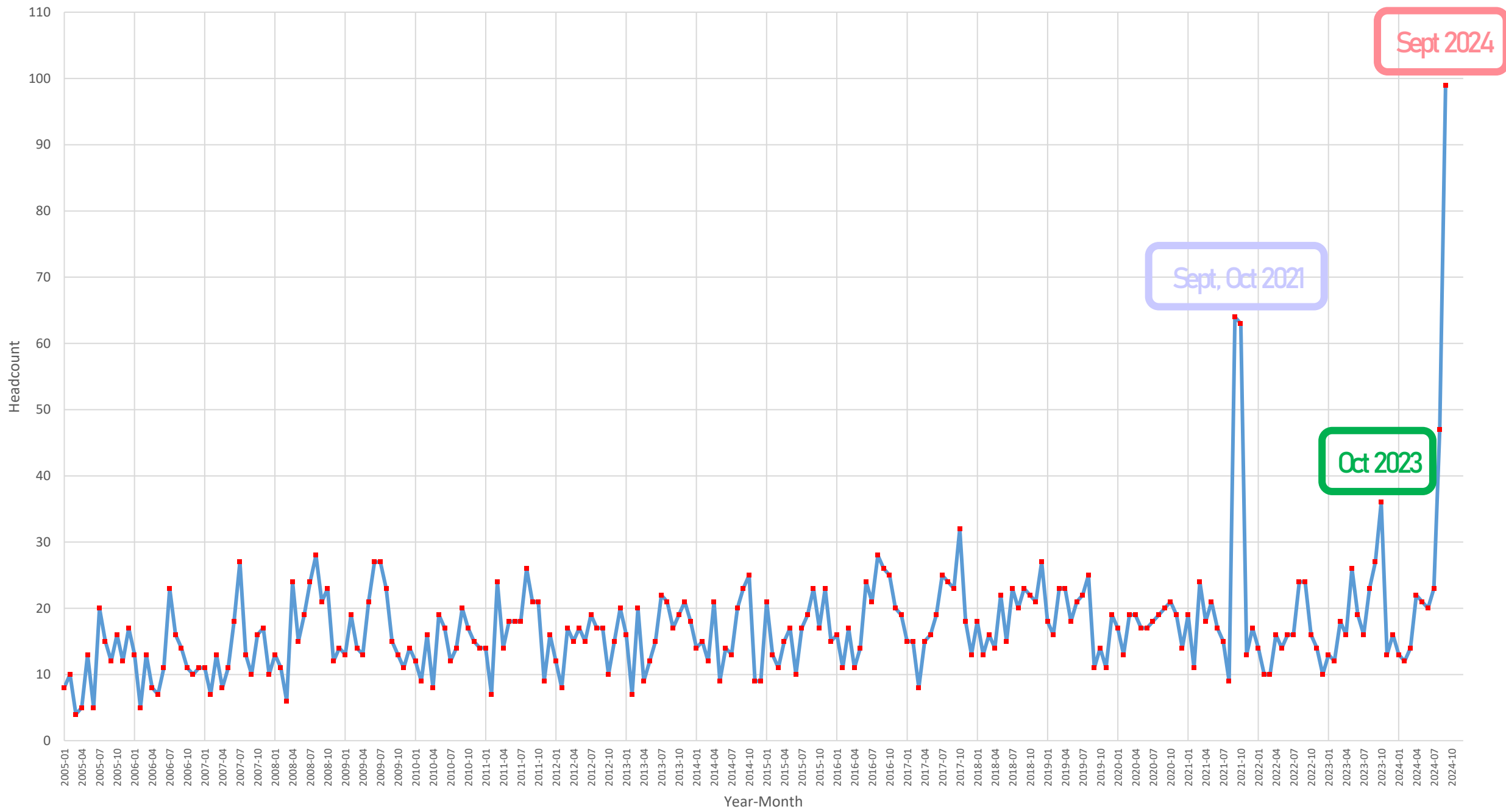
Identification no.	Yr	Serotype III subtype	Protein gene and IS profile	ST	Allele no.						
					AdhP	PheS	Atr	GlnA	SdhA	GlcK	Tkt
2	1993	1	R, IS861, IS1548, IS1381, ISSag1, ISSag2	19	1	1	3	2	2	2	2
142	1996	1	R, IS861, IS1548, IS1381, ISSag1, ISSag2	19	1	1	3	2	2	2	2
148	1996	1	R, IS861, IS1548, IS1381, ISSag1, ISSag2	19	1	1	3	2	2	2	2
284	2002	1	R, IS861, IS1548, IS1381, ISSag1, ISSag2	19	1	1	3	2	2	2	2
359	2002	1	R, IS861, IS1548, IS1381, ISSag1, ISSag2	19	1	1	3	2	2	2	2
19	1997	2	R, GBSil, IS861, ISSag1, ISSag2	17	2	1	1	2	1	1	1
172	1999	2	R, GBSil, IS861, ISSag1, ISSag2	17	2	1	1	2	1	1	1
175	1999	2	R, GBSil, IS861, ISSag1, ISSag2	17	2	1	1	2	1	1	1
187	2000	2	R, GBSil, IS861, ISSag1, ISSag2	17	2	1	1	2	1	1	1
155	1997	3	as, Alp2, ISSag1, ISSag2	23	5	4	6	3	2	1	3
93	2002	3	as, Alp2, ISSag1, ISSag2	23	5	4	6	3	2	1	3
28	1998	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2
146	1996	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2
132	2003	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2
135	1995	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2
162	1998	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2
163	1998	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2
165	1998	4	A, a, IS1381, ISSag1, ISSag2	283	9	5	7	1	3	3	2

^a Protein genes listed in the profiles include those for the C-α protein (A), the Rib protein (R), the C-α repeating unit (a), the C-α repeating-unit-like unit (as), C-α-like protein 2 (Alp2), C-α-like protein 3 (Alp3), and the C-β protein (B). Mobile genetic elements include GBSil, IS861, IS1548, IS1381, ISSa4, ISSag1, and ISSag2.

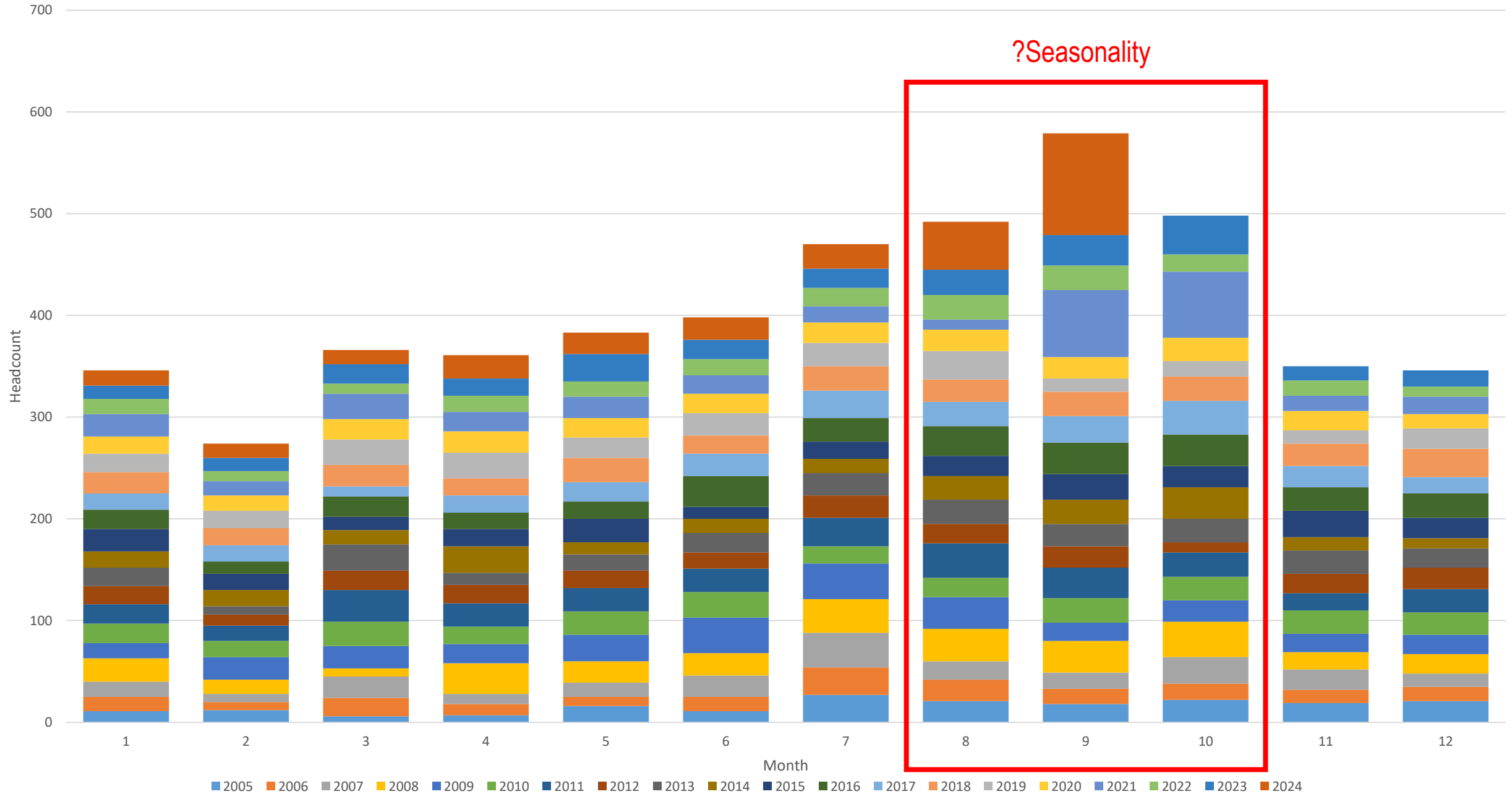
First documented ST283 in Hong Kong in 1995

Local data on invasive GBS and ST283

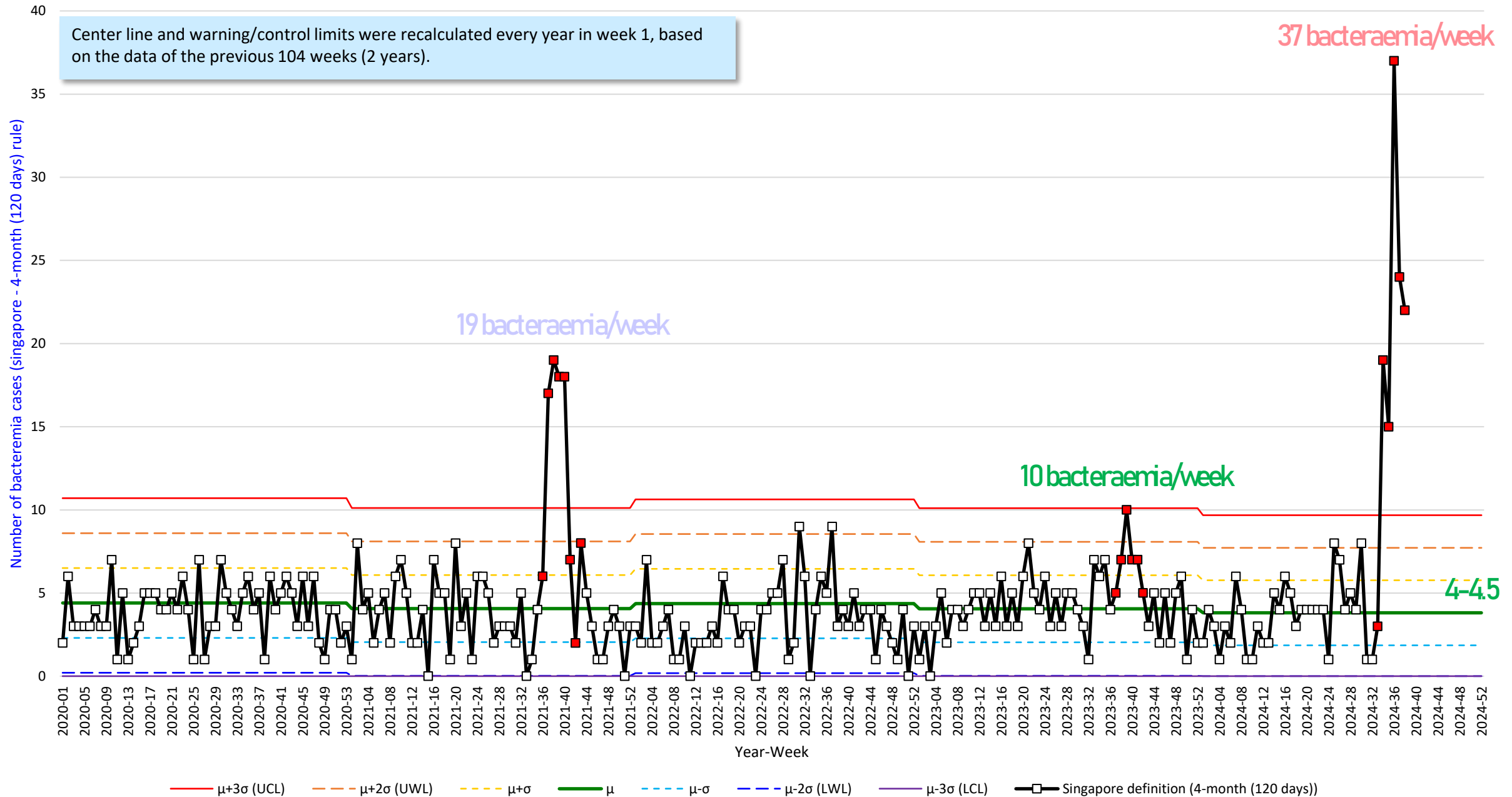
Monthly number of HA patients aged ≥ 5 with GBS isolated in selected specimen types related to invasive infection



Monthly number of HA patients with GBS isolated in selected specimen types related to invasive infection






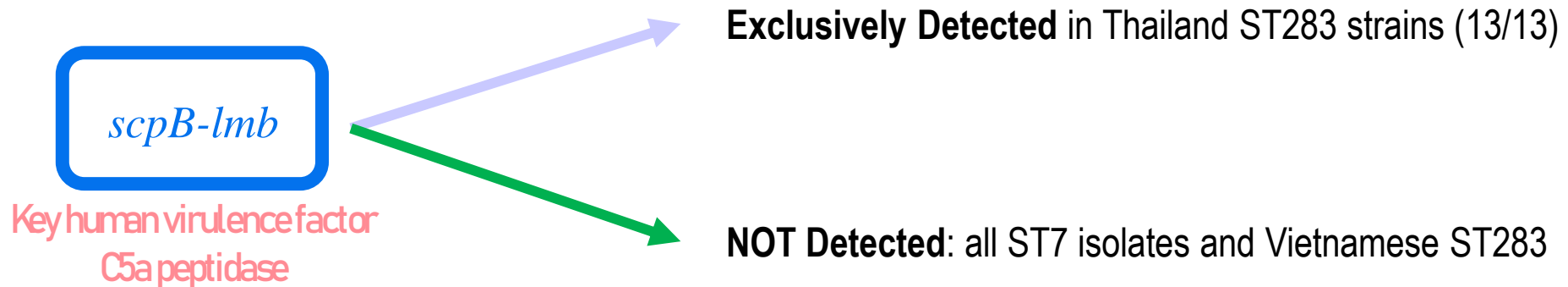
C chart: Weekly number of GBS bacteremia cases in HA (Singapore paper definition)



Article

Geographical, Temporal and Host-Species Distribution of Potentially Human-Pathogenic Group B *Streptococcus* in Aquaculture Species in Southeast Asia

Wanna Sirimanapong ^{1,†}, Nguyễn Ngọc Phước ^{2,†} , Chiara Crestani ³ , Swaine Chen ⁴ and Ruth N. Zadoks ^{5,*} 



What we already know:

1. **Lack** of fish-borne cases of human ST7 reported
2. ST283 is the main cause of iGBS in **Thailand**
3. **Lack of report** of fish-borne ST283 iGBS in **Vietnam**

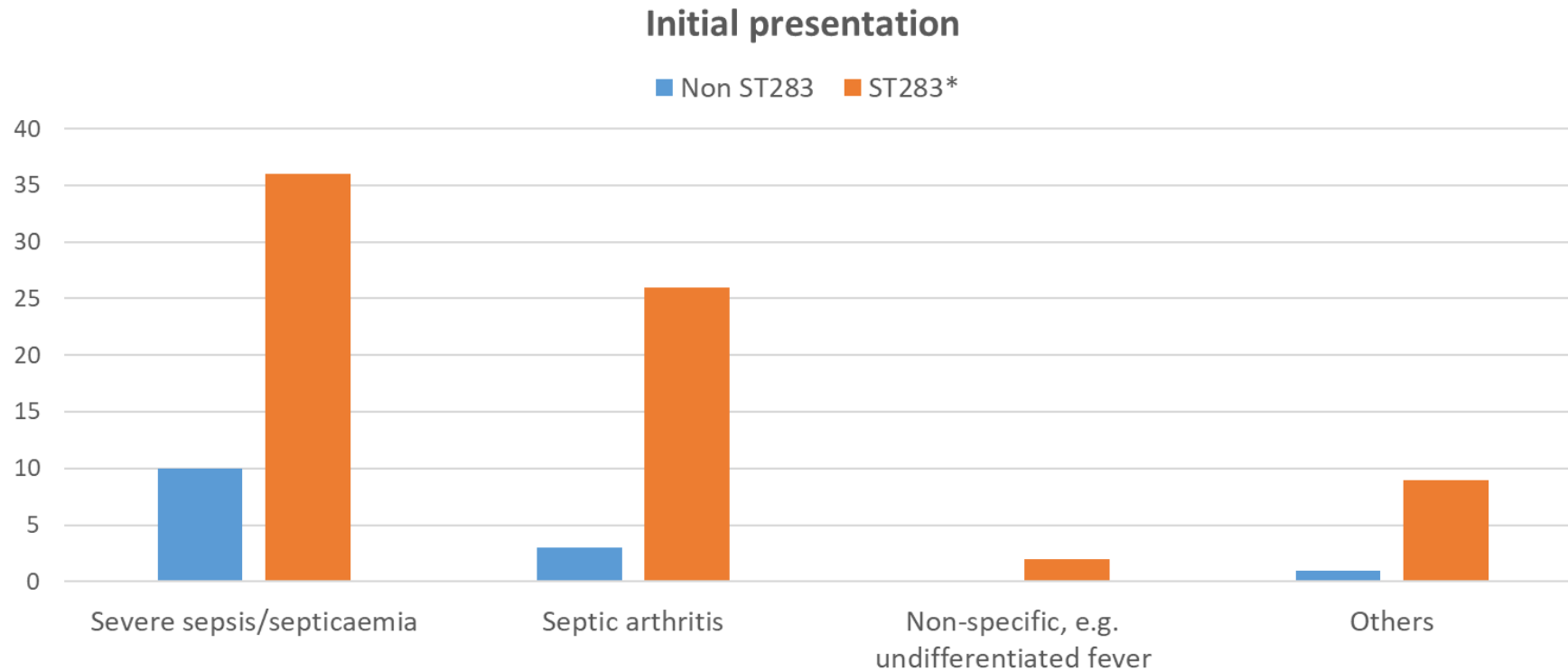
Invasive GBS with typing results (preliminary data, n = 87, 1 Aug–16 Sep 2024)

	Non ST283	ST283*
Number of patients	14 (16%)	73 (84%)
Median age (range)	69.5 (0–95)	69 (35–95)
Sex	Female 8 (57%)	Female 38 (52%)
Cluster (top three)	KWC 4 (29%) NTEC 3 (21%) HKWC 2 (12%); KCC 2 (12%)	KWC 23 (32%) KCC 15 (21%) HKEC 10 (14%); NTEC 10* (14%)
Specialty (top three)	Medicine 6 (43%) Orthopaedics 3 (21%) O&G 2 (14%)	Medicine 42 (58%) Orthopaedics 26 (36%) AED 3 (4%)
First positive specimen	Blood 12 (86%) Joint fluid 2 (14%)	Blood 57 (78%) Joint fluid 14 (19%)
Penicillin sensitivity of isolated GBS	100% (14/14)	100% (73/73)
Median time from admission to the first positive specimen collection	3.9 hours (0.4 hours – 58.6 days)	4.1 hours (0.45 hours – 6.6 days)
Ever to ICU/HDU	0	9 (12%)
Number of deaths	1 (7.1%)	3 (4.1%)
Median time from admission to death	33 days	3 days

* including 3 cases of Serotype III-4 (indicative of ST283) conducted by multiplex PCR

Invasive GBS with typing results (preliminary data, n = 87, 1 Aug–16 Sep 2024)

Initial presentation	Non ST283	ST283*
Severe sepsis/septicaemia	10 (71%)	36 (49%)
Septic arthritis	3 (21%)	26 (36%)
Non-specific, e.g. undifferentiated fever	0 (0%)	2 (3%)
Others	1 (7%)	9 (12%)



* including 3 cases of Serotype III-4 (indicative of ST283) conducted by multiplex PCR

Invasive GBS with typing results (preliminary data, n = 87, 1 Aug–16 Sep 2024)

	Non ST283 (n = 14)	ST283* (n = 73)
With chronic medical illness	12 (86%)	45 (62%)
Diabetes mellitus	7 (50%)	25 (34%)
Immunocompromised	4 (29%)	4 (5%)

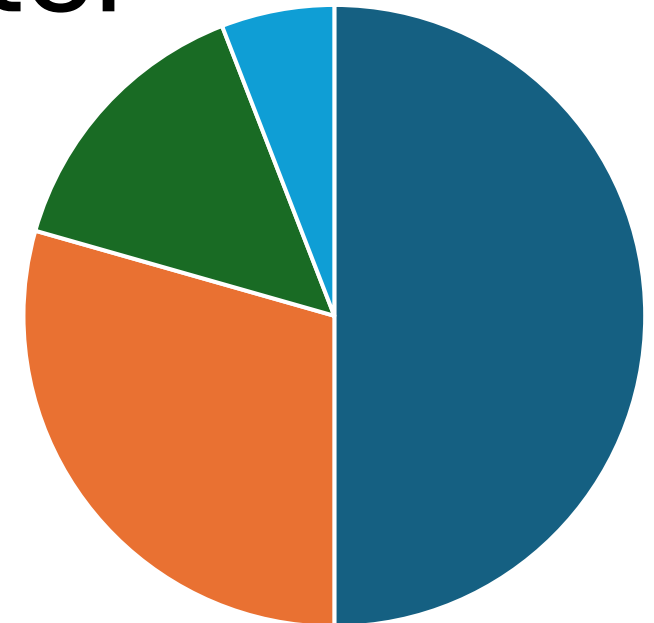
* including 3 cases of Serotype III-4 (indicative of ST283) conducted by multiplex PCR

4 Death cases with typing result available

	Non ST283 (cc19)	ST283		
Age (years)	65	63	74	75
Sex	M	M	M	F
Past medical history	ESRF, Ca rectum, Cryptogenic liver cirrhosis	Ankylosing spondylitis, hyperlipidemia	Hypertension	OA knee, hyperlipidemia
First positive specimen	Blood	Blood	Blood	Blood
Days from admission to the first positive specimen collection	0 day	0 day	1 day	0 day
Days from admission to death	26 days	0 day	3 days	3 days
Had contact with aquatic products	No	Unknown	Yes (Visited wet market and had fish contact)	Yes (Visited wet market and had fish contact)
Initial presentation upon admission	Hypotension, turbid urine	Right knee pain with stiffness	Decrease GC	Vomiting, fatigue, myalgia

Invasive Group B Streptococcus in Kowloon West Cluster

Invasive GBS



■ PMH ■ CMC ■ YCH ■ NLTH

Invasive GBS with typing results (preliminary data, n = 34, 1 Aug–16 Sep 2024)

	Non ST283	ST283
Number of patients	5 (15%)	29 (85%)
Median age (range)	78 (31-95)	70 (49-95)
Sex	Female 5 (100%)	Female 18 (62%)
Specialty (top three)	Medicine 3 (60%) O&G 1 (20%) EMW (20%)	Medicine 15 (52%) Orthopaedics 7 (24%) Surgery 4 (14%)
First positive specimen	Blood 5 (100%)	Blood 27 (93%) Joint fluid 2 (7%)
Penicillin sensitivity of isolated GBS	100% (14/14)	100% (73/73)
Ever to ICU/HDU	0	7 (24%)
Number of deaths	0	1 (3.4%; died 3 days after admission)
Septic arthritis	0	10 (34%; 6 culture positive)
Non-specific, e.g. undifferentiated fever	4 (80%)	13 (45%)
With septic shock on presentation	0	4 (14%)
Meningitis	0	2 (7%)
Good past health	0	8 (28%)
Diabetes mellitus	1 (20%)	5 (17%)
Immunocompromised	1 (20%)	2 (5%)

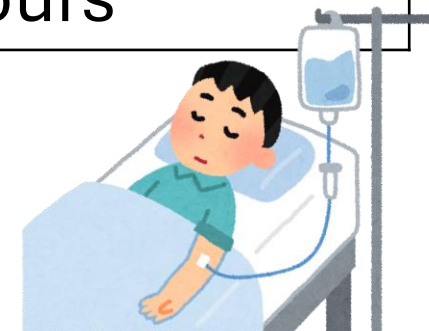
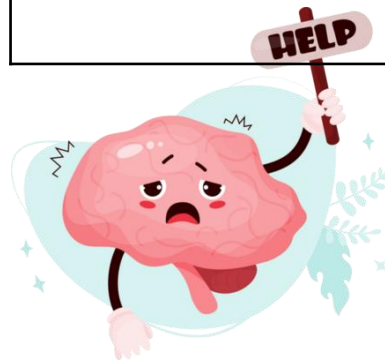


Learning points

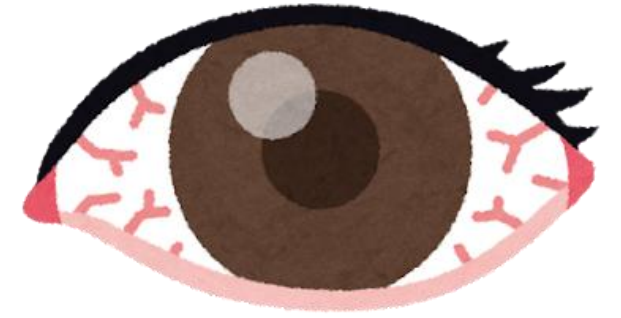


- Need to think of **infection** despite there is absence of fever (sinus tachycardia)
- Do not easily attribute decreased sensorium to sepsis alone
- **Low threshold for lumbar puncture** to rule out CNS infection if suspicious (decreased sensorium, confusion)
- Chose antibiotics that **cross blood brain barrier** with CNS dose promptly as patients can deteriorate rapidly
- Coadjunctive **dexamethasone** as part of an empiric therapy regimen at the same time of antibiotics administration (up to 12 hours)

Antibiotics (IV)	Dosage (Adults with normal renal function)
Ampicillin	2 g every 4 hours
Penicillin G	4 million units every 4 hours
Ceftriaxone	2 g every 12 hours
Cefotaxime	2 g every 4-6 hours
Vancomycin	15 – 20 mg/kg/dose every 8-12 hours



Learning points



- Patients with **good past health** are also affected
- Wounds may have healed upon presentation ☐ important to **elicit contact history**
- **Rapid downhill course** requiring ICU care
- Elicit **eye symptoms** (redness, pain, conjunctival injection, blurring of vision) and consult eye early

Learning points



- Patients may have **multiple joint involvements**
- Beware of acute worsening of chronic joint pain/ back pain despite absence of fever
- In patients with persistent symptoms, consider early **imaging** and **joint aspiration**
- Early **source control** is advised



Hypervirulent Clone of Group B *Streptococcus* Serotype III Sequence Type 283, Hong Kong, 1993–2012

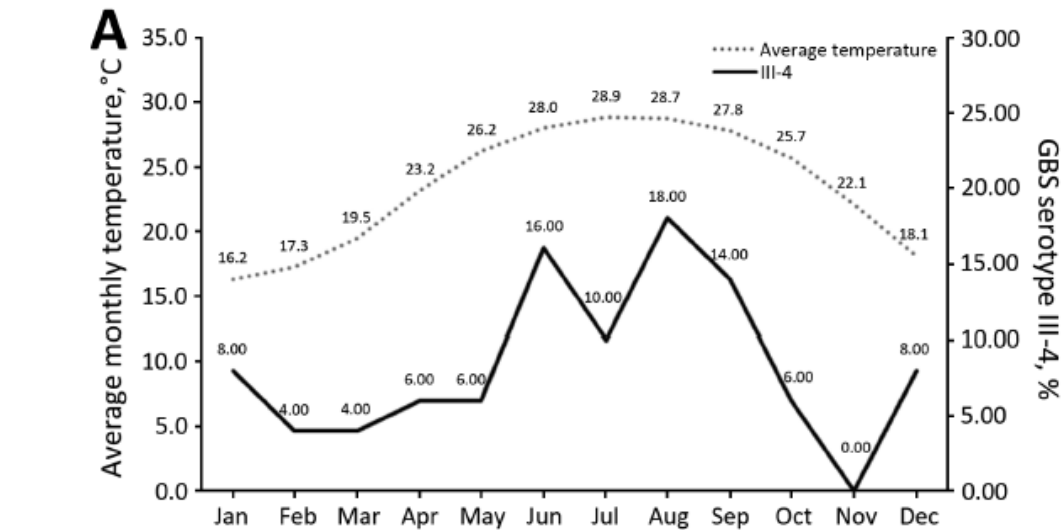


Table 2. Distribution of GBS serotypes in patients with group B *Streptococcus* invasive disease, |

Serotype	Nonpregnant adults, n = 267			Nec
	Meningitis†	Nonmeningitis‡	p value	
Ia	1 (3.0)	32 (97.0)	0.53	4 (21.1)
Ib	1 (2.1)	46 (97.9)	0.28	2 (14.3)
II	0	17 (100.0)	0.31	0
III-1	1 (3.6)	27 (96.4)	0.66	5 (26.3)
III-2	0	13 (100.0)	0.38	16 (35.6)
III-3	0	3 (100.0)	0.68	2 (66.7)
III-4	7 (15.9)	37 (84.1)	<0.001	1 (20.0)
V	2 (7.1)	26 (92.9)	0.64	0
VI	0	10 (100.0)	0.44	0
VII	0	3 (100.0)	0.68	0
VIII	0	0	NA	0
IX	0	0	NA	0
NT	0	1 (100.0)	0.81	0
Total	12 (5.3)	215 (94.7)	NA	30 (26.5)

*GBS, group B *Streptococcus*; NA, nonapplicable; NT, nontypeable. Bold indicates statistical significance; p values determined by Fisher exact or χ^2 test.
†Meningitis was confirmed by cerebrospinal fluid culture of GBS.
‡Nonmeningitis was confirmed by GBS culture from sterile body site or from cerebrospinal fluid.

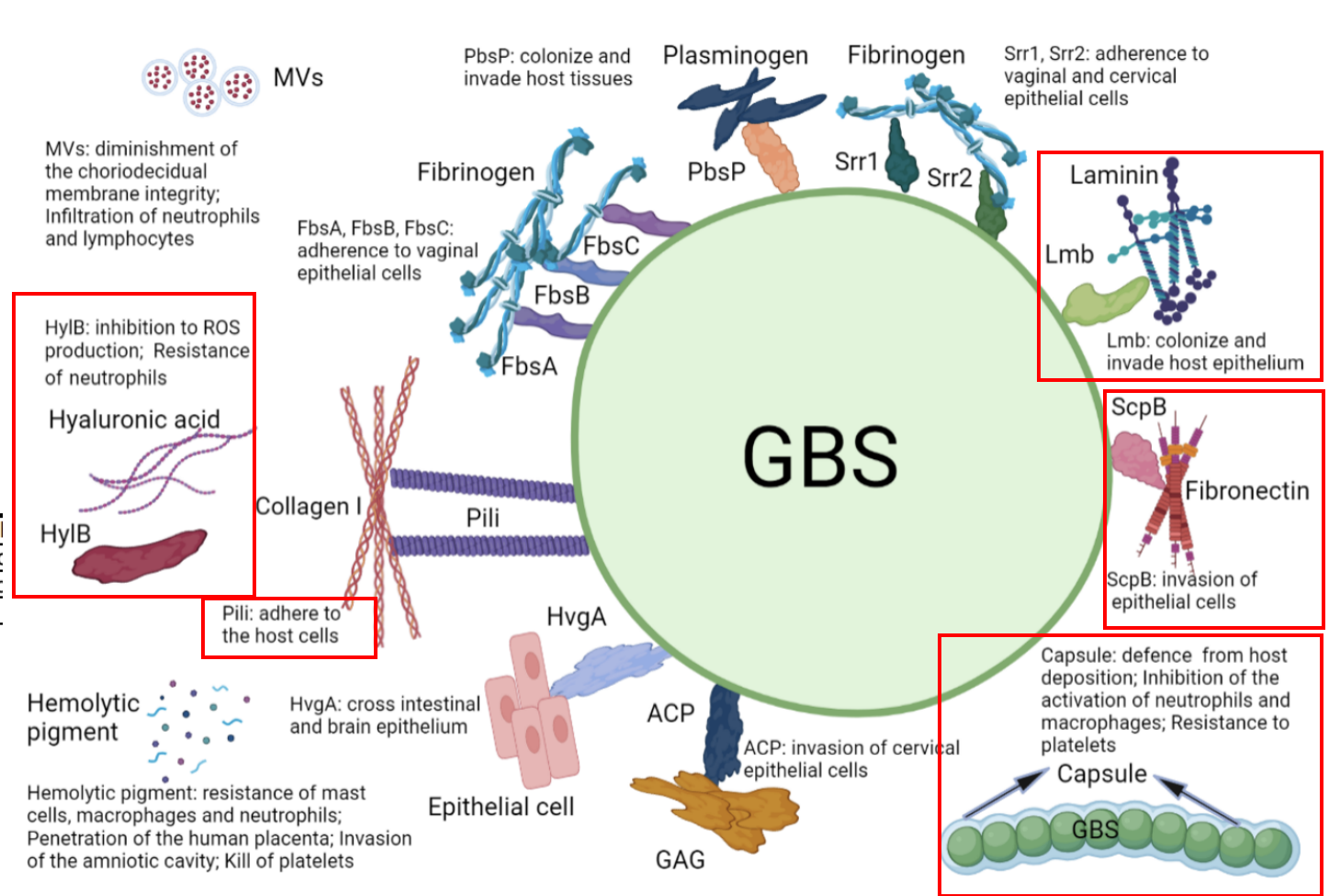
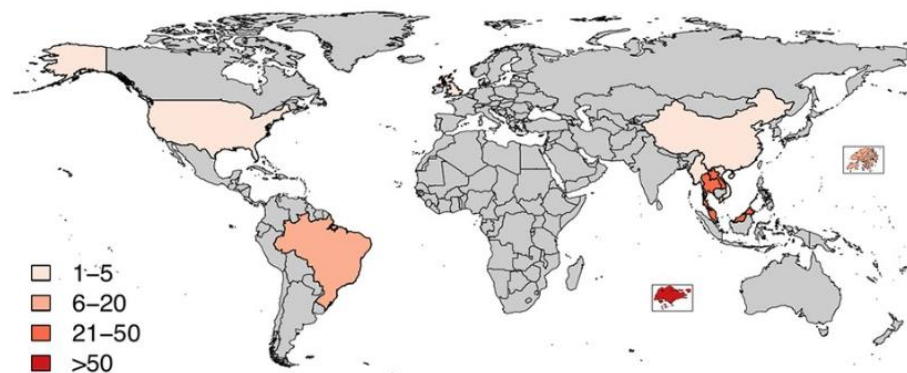


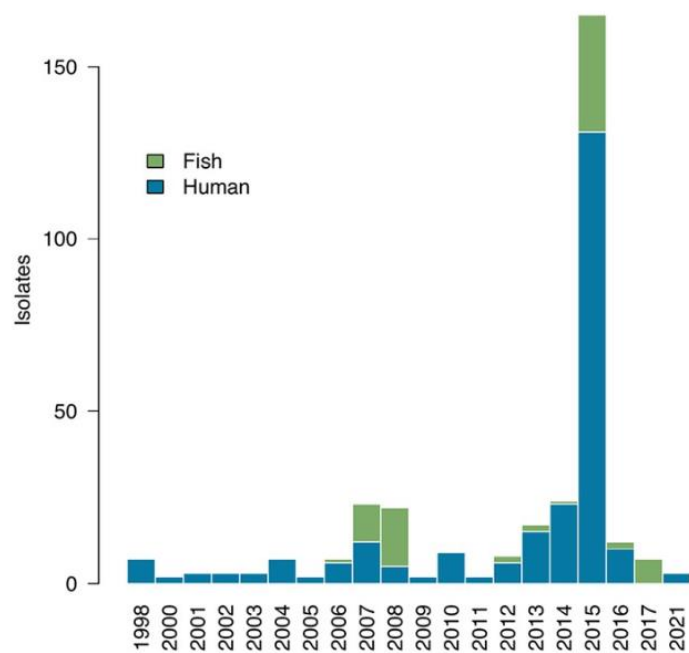
Figure 1. Summary of GBS virulence factors elucidated in this review, with their specific targets and mechanisms.

Microorganisms **2022**, *10*, 2483. <https://doi.org/10.3390/microorganisms10122483>

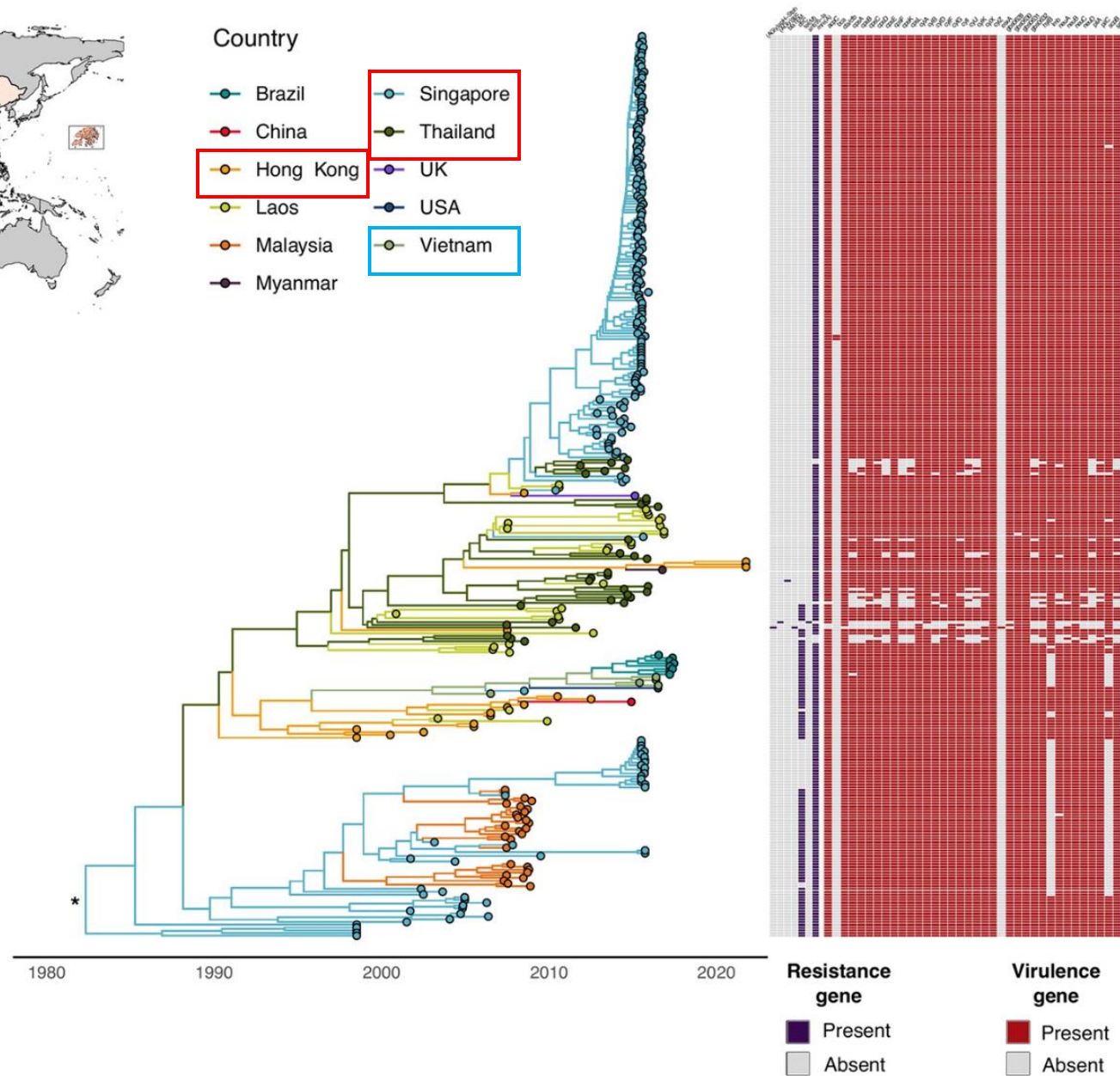
a



b



c



Health and Food Safety Advice

✓ DO'S

- Maintain personal, food and environmental hygiene;
- Keep **hands clean** and cover **wound with waterproof adhesive dressings** at all times;
- **Wear gloves when handling aquatic products;**
- **Wash hands** with liquid soap and water if having contact with aquatic products which are not fully cooked;
- Ensure food is **thoroughly cooked** when consuming **hot pot food** or **congee** items which **consist of aquatic products**



✗ DON'TS

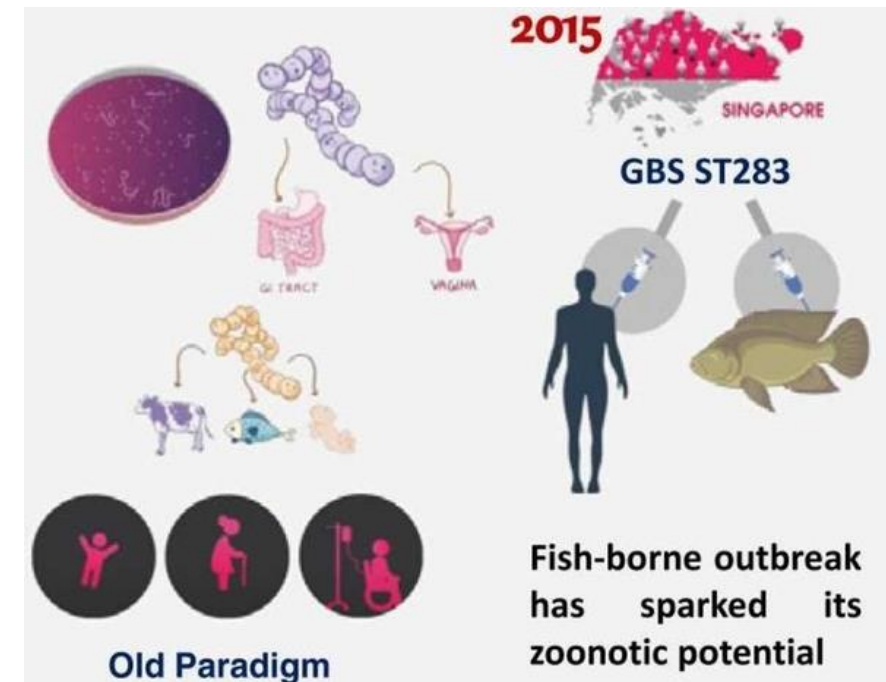
- Do not touch aquatic products directly with bare hands; and
- Do not eat any freshwater fish sashimi, raw or undercooked freshwater aquatic products.



New paradigm for invasive GBS

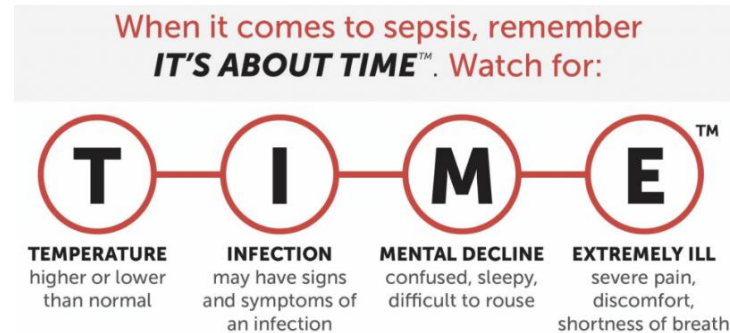
History to elicit:

- Occupation (chef, wet market vendor)
- Visited wet market within past 1 week?
- Handled fish within past 1 week? What type of fish?
- Ate undercooked fish (hotpot)/ seafood within past 1 week? (freshwater fish related; cross contamination -> saltwater fish possible)



Take home messages

- Precautions when handling/consuming aquatic products
- Patients may present with severe sepsis without fever and specific symptoms
- Important to elicit history of fish contact (also ask the family members)
- Obtain blood culture before starting antibiotics
- Watch out for deep seated infections such as CNS infection, septic arthritis, endophthalmitis, and endocarditis
- Source control



Initial resuscitation for sepsis and septic shock (begin immediately)

- 1 Measure lactate level*
- 2 Obtain blood cultures before administering antibiotics
- 3 Administer broad-spectrum antibiotics
- 4 Begin to rapidly administer 30mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

