Emergence and Transmission of Quinolone-Non-Susceptible *Haemophilus influenzae* in a Geriatric Hospital in Japan

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Background

- Quinolones generally exhibit potent antimicrobial activity against *Haemophilus influenzae* (*H.influenzae*).
- The nationwide surveillance studies of bacterial respiratory pathogens in Japan from 2019 to 2023 have consistently reported >99% susceptibility of *H.influenzae* to levofloxacin (LVFX)[1)2)].
- However, a persistently high prevalence of quinolone-non-susceptible *H.influenzae* was observed in a geriatric hospital, raising concerns about nosocomial transmission.
- We conducted an investigation to assess potential clonal spread.

Methods

- 52 *H.influenzae* isolates were collected (one per patient) at a geriatric hospital in Fukuoka Prefecture, Japan, between November 2018 and March 2020.
- 51 isolates were obtained from sputum and 1 from ocular discharge.
- Antimicrobial susceptibility testing was performed by broth microdilution method according to CLSI M100-ED34.
- Whole-genome sequencing was performed using the Miseq platform.
- Core-genome MLST (cgMLST) was performed using Ridom SeqSphere+, with *H.influenzae* 8P36H1 as the seed genome and 104 quiery genomes from NCBI GenBank, resulting in a scheme of 1,011 core loci.

Results

- All 52 isolates were non-typeable *H.influenzae* (NTHi).

Figure 1. Quinolone susceptibility

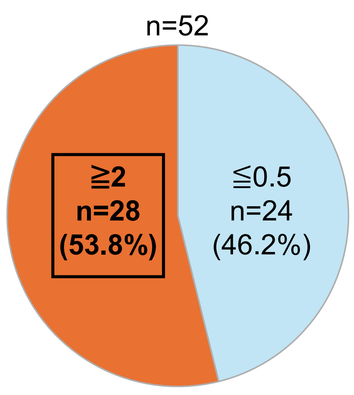
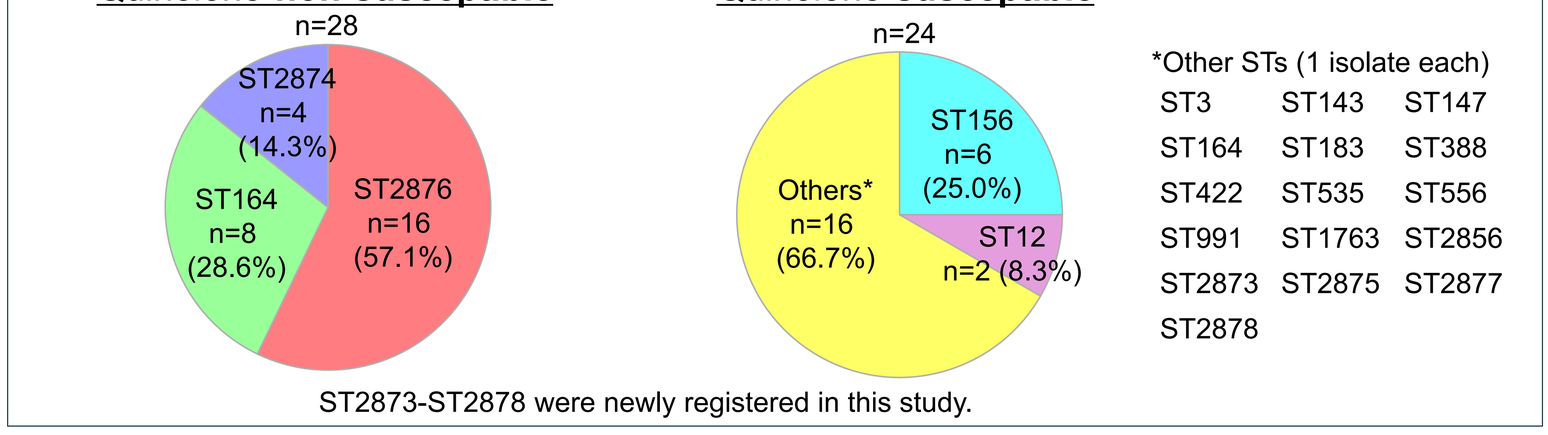
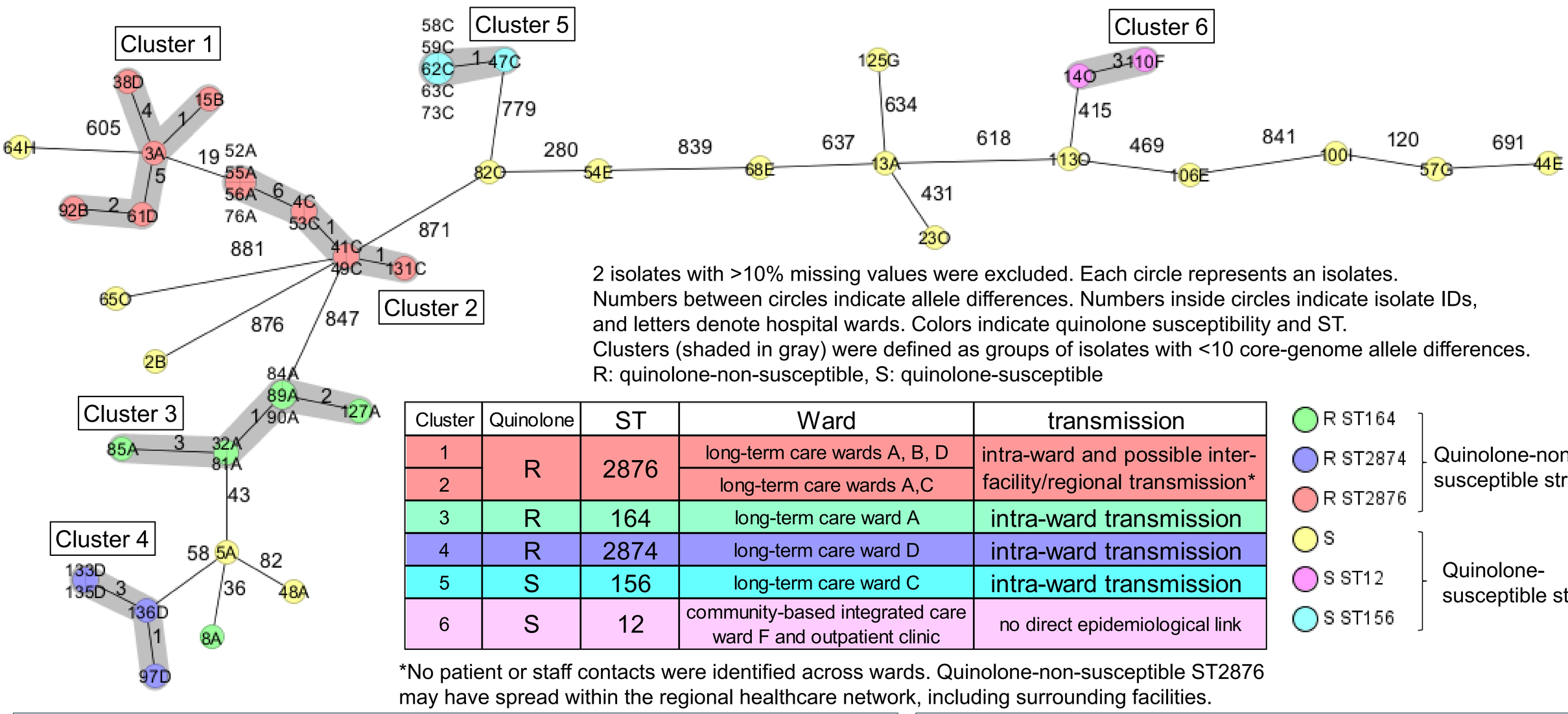


Figure 2. MLST distribution by quinolone susceptibility



ST2873-ST2878 were newly registered in this study.

Figure 3. cgMLST based minimum spanning tree and cluster characteristics



2 isolates with >10% missing values were excluded. Each circle represents an isolates.
Numbers between circles indicate allele differences. Numbers inside circles indicate isolate IDs, and letters denote hospital wards. Colors indicate quinolone susceptibility and ST.
Clusters (shaded in gray) were defined as groups of isolates with <10 core-genome allele differences.
R: quinolone-non-susceptible, S: quinolone-susceptible

Cluster	Quinolone	ST	Ward	transmission
1	R	2876	long-term care wards A, B, D	intra-ward and possible inter-facility/regional transmission*
2			long-term care wards A,C	
3	R	164	long-term care ward A	intra-ward transmission
4	R	2874	long-term care ward D	intra-ward transmission
5	S	156	long-term care ward C	intra-ward transmission
6	S	12	community-based integrated care ward F and outpatient clinic	no direct epidemiological link

R ST164, R ST2874, R ST2876: Quinolone-non-susceptible strains
S, S ST12, S ST156: Quinolone-susceptible strains

*No patient or staff contacts were identified across wards. Quinolone-non-susceptible ST2876 may have spread within the regional healthcare network, including surrounding facilities.

Table 1. Quinolone resistance-determining regions (QRDRs) and penicillin-binding protein 3 (PBP3) amino acid substitutions

			Quinolone resistance				β-lactam resistance						
			GyrA		ParC		PBP3						
CPFX MIC	ST	n	Ser84	Asp88	Gly82	Ser84	Ser357	Met377	Ser385	Leu389	Arg517	Asn526	*bla* TEM
≧2	2876	16	Leu	Asn	Asp	Arg	Asn	Ile	Thr	Phe		Lys	—
	164	8	Leu	Asn	Asp	Arg	Asn	Ile	Thr	Phe		Lys	—
	2874	4	Leu	Asn	Asp	Arg	Asn	Ile	Thr	Phe		Lys	—
≦0.5	156	6					Asn	Ile	Thr	Phe		Lys	—
	12	2										Lys	—
	3	1					Asn	Ile	Thr	Phe		Lys	—
	143	1	Leu				Asn	Ile	Thr	Phe		Lys	—
	147	1						Ile				Lys	—
	164	1	Leu	Asn			Asn	Ile	Thr	Phe		Lys	—
	183	1					Asn	Ile	Thr	Phe	His		—
	388	1											+
	422	1					Asn	Ile	Thr	Phe		Lys	—
	535	1					Asn	Ile	Thr	Phe		Lys	—
	556	1						Ile				Lys	—
	991	1		Asn			Asn	Ile	Thr	Phe		Lys	—
	1763	1					Asn	Ile	Thr	Phe		Lys	—
	2856	1					Asn	Ile	Thr	Phe		Lys	—
	2873	1					Asn	Ile	Thr	Phe		Lys	—
	2875	1					Asn	Ile	Thr	Phe		Lys	—
	2877	1											—
	2878	1	Leu			Arg	Asn	Ile	Thr	Phe		Lys	—

All quinolone-non-susceptible isolates were high-BLNAR[3)].
QRDR substitutions were found in 4 (16.7%) quinolone-susceptible isolates, suggesting elevated CPFX MICs.

Table 2. Patient characteristics by quinolone susceptibility

	Quinolone-susceptible (n=24)	Quinolone-non-susceptible (n=28)	*P* value
Age, years	75.3 ± 11.8	82.6 ± 13.7	0.023
Male	15 (62.5%)	11 (39.3%)	0.164
Long-term care ward	10 (41.7%)	27 (96.4%)	<0.001
Quinolone use within 90 days	2 (8.3%)	1 (3.6%)	0.590
β-lactam use within 90 days	11 (45.8%)	16 (57.1%)	0.578
Oral intake	12 (50.0%)	3 (10.7%)	0.002
BMI	19.4 ± 4.7	16.2 ± 3.7	0.009
Daily sputum suction*	10 (41.7%)	24 (85.7%)	0.001
Treated for pneumonia	20 (83.3%)	14 (50.0%)	0.019
30-day mortality	0	6 (21.4%)	0.025

*Defined as requiring sputum suction ≧2 times per day for ≧3 consecutive days.
Data are presented as mean ± SD or number of patients (%).

Discussion & Conclusion

- The high prevalence of quinolone-non-susceptible *H.influenzae* was mainly due to intra-ward transmission in long-term care wards.
- These isolates were more common in patients unable to take orally and requiring daily sputum suction, highlighting the need to review suction procedures and reinforce standard precautions.

References
1) J Infect Chemother 29:731-743, 2023
2) J Infect Chemother 31:102781, 2025
3) Antimicrob Agents Chemother 45:1693-1699, 2001