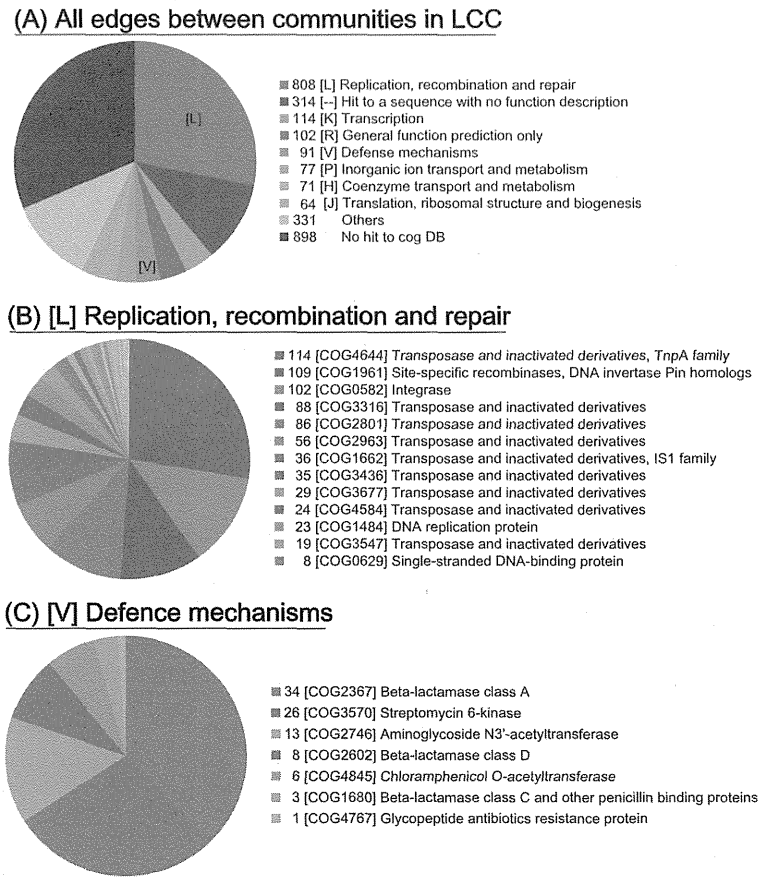
Clustering coefficient values in any communities in LCC was estimated as median 0.681 (SD: 0.125), indicating that no community consisted of homogenous plasmids. The community network analysis suggests that bacterial plasmids can be grouped into communities according to biologically relevant features.

2.4. Connections between Communities

2.4.1. Genes Involved in the Connections between Communities

The abovementioned multilevel community analysis suggests a crucial linkage among the 26 communities in LCC. Thus, we searched for genes involved in the unique connections between communities. Blast search against the COG database revealed that the "[L] Replication, recombination and repair" subgroup was the predominantly detected at 60.0% (2283 of 3806) as transposases on the edges (Figure 5), indicating that multiple IS-related transposases could be involved in HGT between communities. We found that most of the edges were related to antimicrobial resistance genes (see the red line edges between the communities in Figure 3), suggesting that the "[V] defence mechanism" category could play a crucial role in the connection for HGT due to antimicrobial selective pressure (Figure 5). This result suggests that genetic exchange events between communities could be driven by genes related to replication/recombination/repair functions (COG [L]), as well as genes related to AMR.

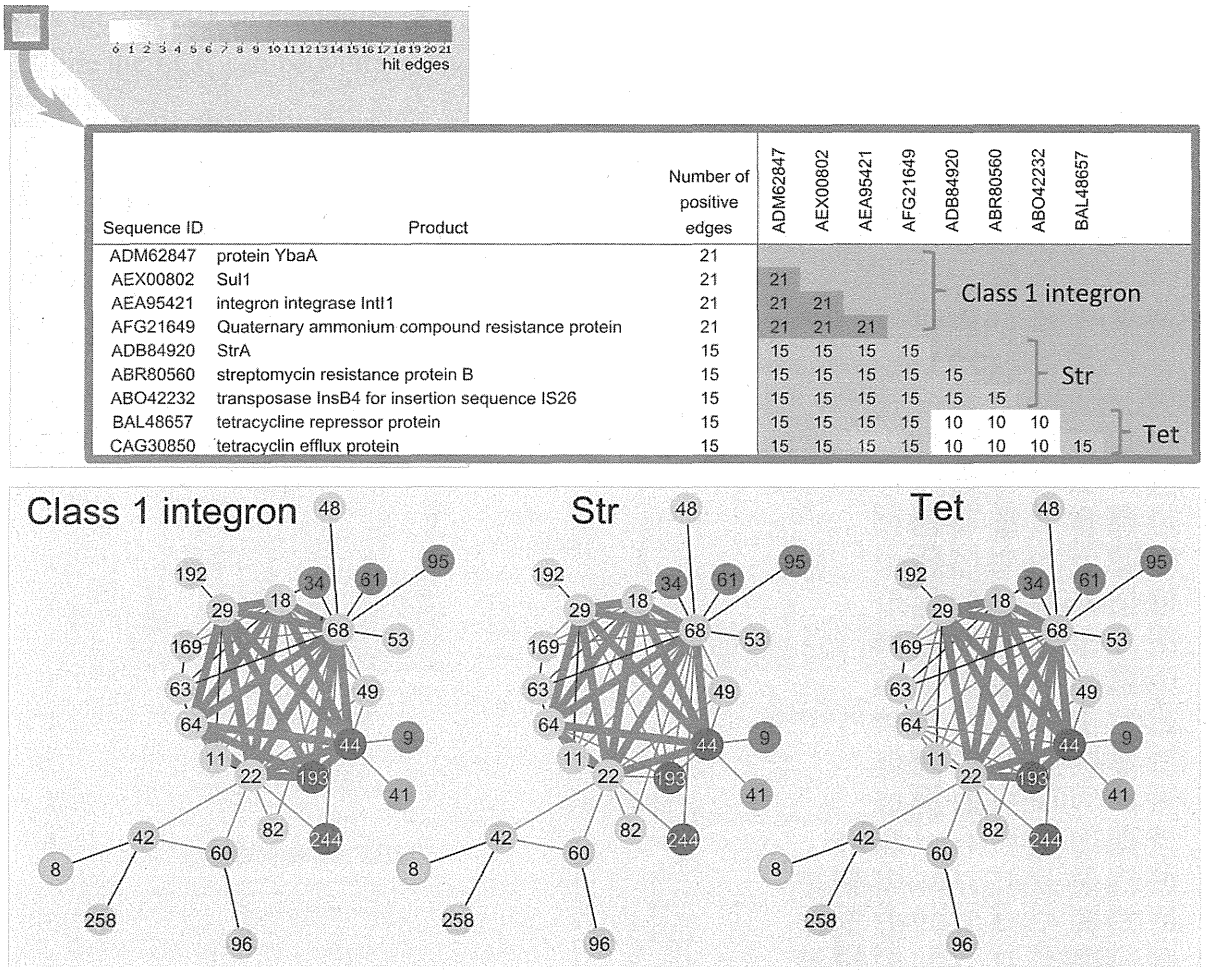
Figure 5. COG annotation for genes on the edges between communities. (**A**) COG categories on all of the edges in the LCC. (**B**) The COG ID for the category [L] of replication, recombination and repair. (**C**) The COG ID for the category [V] of defence mechanisms.



2.4.2. Frequently Identified Gene Combination among the Edges between Communities

Since shared genes on the edge between communities could be a possible candidate for recent HGT genes, frequently shared gene was extracted from the total non-redundant 1506 genes on the 66 edges in LCC. The combination of ybaA, sul1, intI1 and qacE Δ 1 were most frequently identified on 21 edges (Figure 6). This combination has been well characterized as class 1 integron, which is known as a major player of indiscriminate dissemination of AMR [23]. In addition, the combinations of —insB, strA, and strB" (streptomycin resistance marker) and —tetR and tetA" (tetracycline resistance marker) were also frequently found on 15 edges, respectively. The str and tet combinations were not found on the co193 and co 64-related edges, respectively.

Figure 6. Frequently hit sequence on the 66 edges in LCC. Heatmap of sequence pairs of 1506 sequences on the 66 edges in LCC. Close-up of top 9 frequently hit sequences. Class 1 integron (21 edges), *str* (15 edges) and *tet* (15 edges) genes on the edges were shown in bold red line.



In addition, we confirmed whether class 1 integron could be transmitted *en bloc.* The basic components of class 1 integrons consist of IntI1, QacEdelta1, Sul1 and YbaA (Table 2: 01-02/03-04-05). Forty plasmids from the 3793 complete plasmid sequences in this study have been identified to carry the contiguous components of a class 1 integron. Further investigation suggested that additional AMR genes are integrated into the class 1 integron as cassette gene (Table 2). A class 1 integron group

including additional aminoglycoside resistance (01-12-02-04-05) was found in communities co18 (plasmid: DQ364638 and AP000342), co29 (plasmid: AB605179), and co68 (plasmid: HQ201416). Furthermore, class 1 integrons with integrated trimethoprim-resistant dihydrofolate reductase (01-36-12-02-04-05) was found in communities co29 (FN432031) and co64 (JX566770). These results strongly suggest that complete class 1 integrons together with additional integrated AMR genes could be transmitted among communities. Such AMR markers could play a crucial role for recent HGT, leading to contribute to the vast linkages among variable plasmid communities as the global dissemination of AMR.

Table 2. The class 1 integron mediated en bloc transmission of AMR genes among communities.

Order of gene groups	Community							Total
	co18	co22	co29	co44	co64	co68	co193	
01-02-04-05						1		1
01-09-02-04-05		1						1
01-11-02-04-05		1						1
01-12-02-04-05	2		1			1		4
01-36-02-04-05						1		1
01-07-08-02-04-05							1	1
01-15-20-02-04-05		1						1
01-34-59-02-04-05						2		2
01-36-12-02-04-05			1		1			2
01-36-18-02-04-05						1		1
01-49-08-02-04-05				2				2
01-08-27-19-02-04-05						1		1
01-26-17-09-02-04-05						1		1
01-35-58-09-02-04-05						1		1
01-54-28-12-02-04-05						1		1
01-57-32-56-02-04-05						1		1
01-08-16-53-12-02-04-05	1							1
01-08-22-29-52-02-04-05						1		1
01-08-24-09-38-02-04-05						1		1
01-09-02-04-40-30-04-05						1		1
01-13-50-31-09-02-04-05		1						1
01-23-08-12-21-02-04-05						1		1
01-25-08-12-31-02-04-05						1		1
01-60-19-60-34-02-04-05						1		1
01-08-02-04-40-44-45-04-05						1		1
01-11-06-42-41-37-39-02-04-05		1						1
01-12-06-42-41-37-39-02-04-05		3						3
01-14-06-42-41-37-39-02-04-05		1						1
01-33-09-02-04-40-44-45-04-05						1		1
01-10-09-02-04-40-48-46-02-04-05						1		1
01-07-47-02-04-40-51-55-43-03-04-05						1		1
01-08-22-29-52-02-04-40-44-45-04-05						1		1
Total	3	9	2	2	1	22	1	40

Table 2. *Cont.*

Gene group	Products	
01	integron integrase IntI1.	class 1 integron component
02, 03	quaternary ammonium compound-resistance protein QacEdelta1.	
04	sulphonamide resistant dihydropteroate synthase Sul1.	
05	protein YbaA.	
06	aminoglycoside 3'-*N*-acetyltransferase protein *aacC*.	aminoglycoside resistance
07	aminoglycoside 3'-*N*-acetyltransferase.	
08	aminoglycoside acetyltransferase.	
09	aminoglycoside adenylyltransferase.	
10	aminoglycoside *N*(6')-acetyltransferase.	
11–14	aminoglycoside resistance protein *aadA*.	
15	aminoglycoside-2'-adenylyltransferase.	
16	acetyltransferases *aac(3)-Ia*.	
17	putative aminoglycoside 6'-*N*-acetyltransferase.	
18	putative aminoglycoside adenyltransferase.	
19	class D β-lactamase OXA-10.	β -lactamase
20	class D β-lactamase OXA-21.	
21	class D β-lactamase OXA-2.	
22	class D β-lactamase OXA.	
23	metallo-β-lactamase GIM-1.	
24	metallo-β-lactamase IMP-6.	
25	metallo-β-lactamase VIM-1.	
26	chloramphenicol acetyltransferase catB2.	chloramphenicol resistance
27	chloramphenicol acetyltransferase catB8.	
28, 29	chloramphenicol acetyltransferase.	
30	chloramphenicol aminotransferase.	
31	chloramphenicol resistance protein CmlA1.	
32	dihydrofolate reductase DfrA5.	dihydrofolate reductase
33-35	dihydrofolate reductase.	
36	trimethoprim-resistant dihydrofolate reductase type I DhfrA1.	
37–40	transposase.	
41	molecular chaperone GroEL.	
42	molecular chaperone GroES.	
43	fluoroquinolone resistance protein QnrB2.	
44	quinolone-resistance determinant Qnr.	
45–52	Others	
53–60	hypothetical protein.	

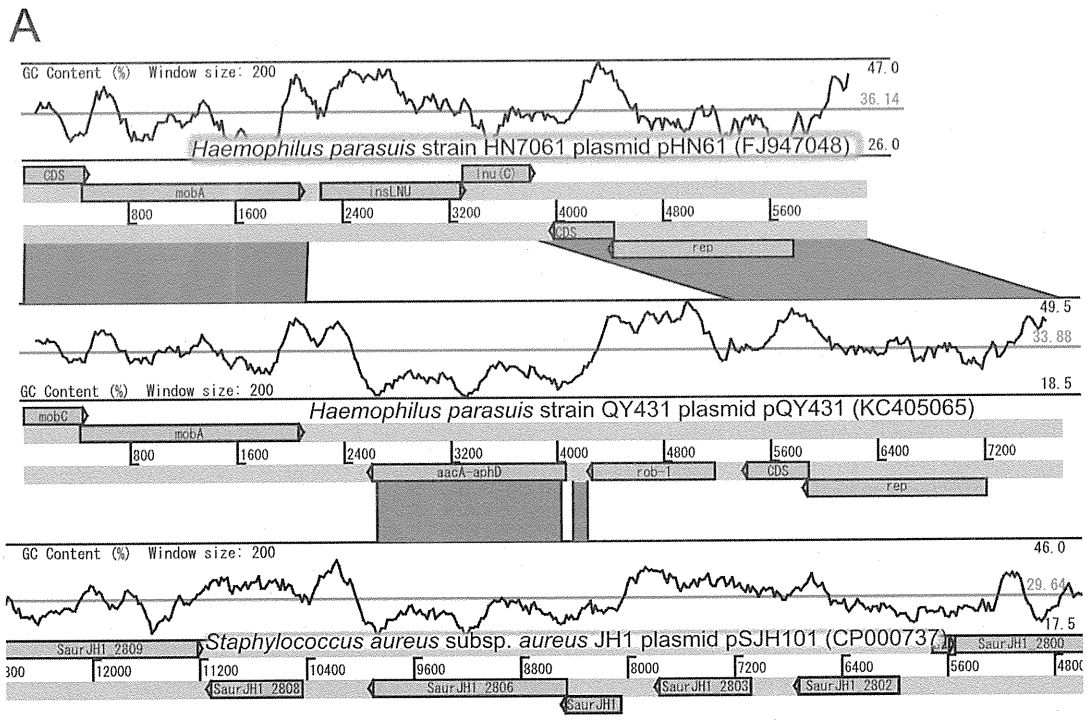
2.4.3. Connections between Plasmid Communities from Different Divisions

The community network analysis revealed unique linkages between *Bacilli* (co42 and co60) and *Gammaproteobacteria* (co22) (Figures 1B and 3). The plasmids from *Staphylococcus* and *Pasteurellaceae* were connected by two plasmids from *Pasteurella multocida* (pCCK411, GenBank_ID: FR798946) and *Haemophilus parasuis* (pQY431, GenBank_ID: KC405065) (Figure 1B).

The pQY431 in *H. parasuis* appeared to have acquired a bifunctional ACC/APH gene (*aacA-aphD*, AGK85216.1) from a plasmid in *Staphylococcus* spp., because GC-content of ACC/APH gene corresponds to the average of *S. aureus* plasmid, while it is lower than the average of *H. parasusis* plasmid. This plasmid also have a ß-lactamase (bla_{ROB-1}, AGK85217) from another plasmid in *Pasteurellaceae* species (Figure 7A).

In addition, the pCCK411 plasmid in *P. multocida* shares a kanamycin resistance gene (*aphA3*, CBZ06037) with *Staphylococcus* plasmids and the bla_{ROB-1} gene from another *Pasteurellaceae* plasmids. Interestingly, higher GC content in this region in *Staphylococcus* suggests that this gene might be acquired from other plasmids such as *Pasteurella multocida* (Figure 7B). An additional blastp search with the NCBI nt database indicated that the identical sequences of the *aacA-aphD* and *aphA3* genes were detected in plasmids from the bacteria from the *Bacilli* class, such as *Staphylococcus*, or *Enterococcus* plasmids.

Figure 7. Pairwise comparisons of the (**A**) *Haemophilus parasuis* and (**B**) *Pasteurella multocida* plasmids carrying the *aacA-aphD* and *aphA3* genes compared to *Staphylococcus aureus* plasmids. The light-blue boxes represent the genes on the plasmids. The red and blue bars represent the homologous regions in the forward and inverted directions, respectively. The plasmids carrying the homologous genes are shown below the pairwise comparison. (**C**) Average GC-content of the host chromosomes.



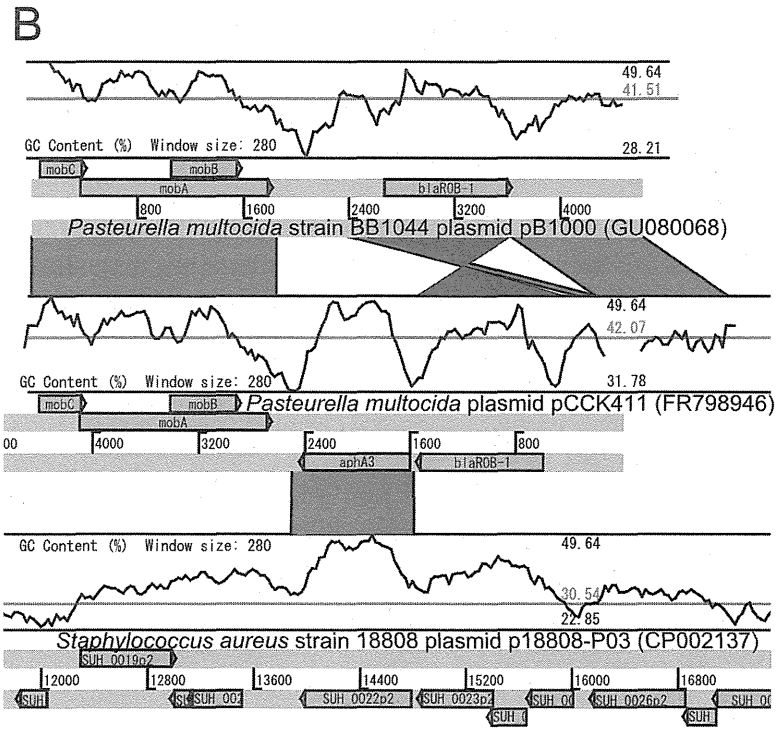
Plasmids carrying *aacA-aphD* protein identical to KC405065

co22 → *Haemophilus parasuis* strain QY431 plasmid pQY431 (KC405065)

co42
- *Staphylococcus aureus* plasmid pLW043 (AE017171); pSK1 (GU565967); pSK41 (AF051917); pTZ2162 (AB304512); SAP014A (GQ900379); SAP017A (GQ900382); SAP068A (GQ900421); SAP069A (GQ900422); SAP079A (GQ900432); SAP080A (GQ900433); SAP082A (GQ900434); pSJH101 (CP000737); pSJH901 (CP000704); VRSAp (AP003367)
- *Staphylococcus cohnii* strain 2-8 plasmid pSS-01 (JF834909)
- *Staphylococcus epidermidis* plasmid pSK105 (GQ900462); SAP016A (GQ900381)
- *Staphylococcus* sp. CDC25 plasmid SAP018A (GQ900383)
- *Enterococcus faecium* plasmid pMG1 DNA (AB206333)

co60 → *Enterococcus faecalis* V583 plasmid pTEF1 (AE016833)

Figure 7. *Cont.*



Plasmids carrying the *aphA3* gene identical to FR798946

co22 → *Pasteurella multocida* plasmid pCCK411 (FR798946)

co42
- *Staphylococcus aureus* USA300_TCH1516 (CP000731)
  pLAC-P03 (CP002149), p18811-P03 (CP002143),
  p18810-P03 (CP002141), p18809-P03 (CP002139),
  p18808-P03 (CP002137), p18807-P03 (CP002135),
  p18806-P03 (CP002134), p18805-P03 (CP002132),
  SAP052A (GQ900412), SAP051A (GQ900410), SAP050A (GQ900409),
  SAP049A (GQ900407), SAP046A (GQ900403), SAP027A (GQ900388),
  SAP015A (GQ900380)
- *Staphylococcus epidermidis* RP62A plasmid pSERP (CP000028)

co60
- *Enterococcus faecium* plasmid pS177 (HQ115078)
  pF856 (JQ663598), DO plasmid 2 (CP003585),
  DO plasmid 2 (CP003585)

C

Pasteurellaceae	*Haemophilus parasuis*	39.7-40.1%	(avg. 39.8%)	13 strains
	Pasteurella multocida	40.2-41.0%	(avg. 40.4%)	22 strains
Firmicutes	*Staphylococcus aureus*	32.2-33.0%	(avg. 32.8%)	463 strains
	Enterococcus faecalis	37.0-38.4%	(avg. 37.3%)	329 strains
	Enterococcus faecium	37.6-38.2%	(avg. 37.9%)	201 strains

Of particular note, *Haemophilus/Pasteurella* spp. required an external supplement of V-factor (NAD) from staphylococci for growth support [24]. In addition, the *Pasteurellaceae Hin* subclade (*H. influenzae, P. multocida*) possessed the natural competence and transformation ability [25]. These observations support the hypothesis that the *aacA-aphD* gene in *H. parasuis* (pQY431) was introduced through close contact with *Firmicutes* such as staphylococci. Contrary, there has been no evidence how *Staphylococcus* could acquire the *aphA3* gene, but the close relationship may have promoted gene exchange between plasmids originating from different phyla.

This study revealed high relationship between *Pasteurellales* and *Staphylococcus* (Figure 7), although previous report characterized the gene transfer between *Actinobacteridae* and *Gammaproteobacteria* [13]. Such difference generated from the difference of parameter threshold, *i.e.*, Tamminen *et al.* (2012) required at least five shared homologous sequencess and 95% aa identity to connect plasmids, while this study picked up plasmid connections from at least one shared homologous sequences at 100% aa identity, indicating more stringent threshold could display a potential recent HGT in this study.

2.5. Distribution of Inc Types among Plasmid Communities

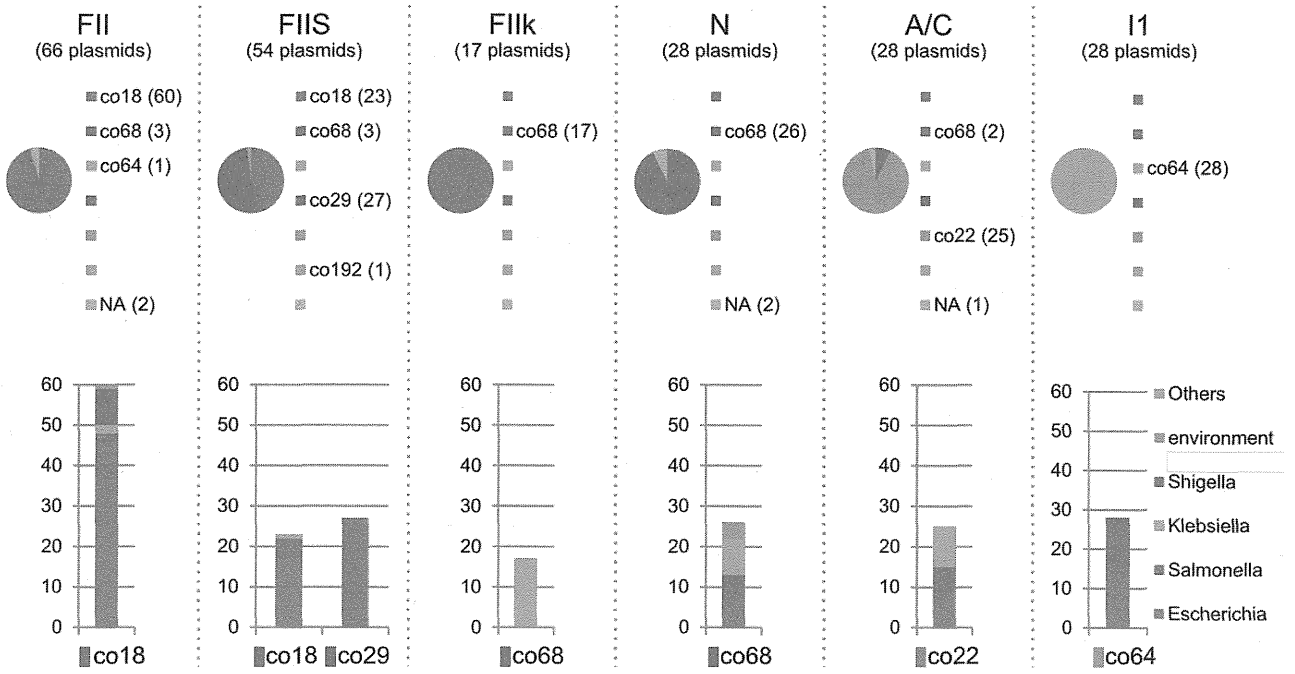
Plasmids can be categorised by the plasmid replicon incompatibility group (Inc-group), using PCR-based methods to identify the replicons of the major plasmid families found in *Enterobacteriaceae* [26]. We performed *in silico* replicon typing for all of the plasmids against 22 known Inc groups (Table 3). The Inc types could be assigned to some plasmids in the LCC, and showed strong correlations between the community and the Inc type (e.g., IncFII: co18, FIIS: co18 and co29, FIIk: co68, N: co68, A/C: co22, I1: co64, and P: co193, in Table 3). IncFII-co18 and IncFIIS-co18 were found predominantly in *Escherichia*, while IncFIIk-co68 was found predominantly in *Klebsiella* and IncFIIS-co29 was found predominantly in *Salmonella* (Figure 8). In contrast, IncA/C-co22 was composed of plasmids from various bacterial genera (Figure 8), suggesting that IncA/C has greater dissemination potential among *Enterobacteriacea*. IncN-co68 was closely related between *Escherichia* and *Klebsiella*. In addition, IncI1-co64 was closely related between *Escherichia* and *Salmonella*, suggesting that frequent potential transmissions can occur between these two bacterial genera. Interestingly, significantly larger amount of plasmids in both co22 and co68 could not be assigned for Inc type, implying the variety of Inc types remain to be elucidated.

Table 3. Distribution of Inc types and communities.

Inc type	Community							
	co11	**co18**	**co22**	**co29**	**co64**	**co68**	**co192**	**co193**
A/C	-	-	25	-	-	2	-	-
B/O	-	3	-	-	1	1	-	-
FIA	-	5	-	-	-	3	-	-
FIB	-	5	-	-	-	-	-	-
FIB-M	-	-	-	-	-	1	-	-
FII	-	60	-	-	1	3	-	-
FIIk	-	-	-	-	-	17	-	-
FIIS	-	23	-	27	-	3	1	-
HI1	-	1	-	-	-	1	-	-
HI2	-	-	-	-	-	5	-	-
HIB-M	3	-	-	-	-	-	-	-
I1	-	-	-	-	28	-	-	-
K	-	1	-	-	3	-	-	-
L/M	-	-	-	-	-	7	-	-
N	-	-	-	-	-	26	-	-
P	-	-	-	-	-	-	-	7
R	-	-	2	-	-	3	-	-
T	-	1	-	-	-	1	-	-
U	-	-	-	-	-	3	-	-
W	-	-	2	-	-	3	-	-
X1	-	1	-	7	-	-	-	-
X2	-	-	-	-	-	1	-	-
Not Assigned	1	13	83	37	3	144	2	10
Total	4	113	112	71	36	224	3	17

Shaded communities showed significant over-representation with p-value < 0.001 by chi-square test.

Figure 8. Components of the major Inc-type plasmids. The components of the communities of the major Inc-type plasmids and the bacterial components for each community are shown (Table 3).



2.6. Distribution of AMR among Plasmid Communities

Apart from the Inc-type related communities, the associations of AMR genes within communities were also investigated. CTX-M ß-lactamase is a broadly disseminated ESBL in *Enterobacteriacea* [27]. The CTX-M-1 and CTX-M-9 subgroups were broadly classified into multiple communities (co18, co22, co29, co64, and co68) (Figure 9A), while the CTX-M-2 subgroup was classified only as co68. More than 80% (40/49) of plasmids carrying the CTX-M ß-lactamase were found in co18 or co68. In addition, CTX-M-1 and CTX-M-9 were the most frequently found in the IncFII replicon plasmid (Table 4), suggesting that the dissemination of the CTX-M genes is linked to Inc replicon-dependent plasmid communities between co18 and co68 (Figure 3). Intriguingly, the abovementioned communities (co18, co22, co29, co64, and co68) were tightly connected to each other according to the community network analysis (Figure 3). Most of the plasmids carrying CTX-M-1 and CTX-M-9 were derived from *Escherichia* or *Klebsiella*, while most of the plasmids carrying CTX-M-2 were from *Salmonella* and *Klebsiella*.

As well as the class 1 integron, CTX-M ß-lactamases have been acquired through insertion sequence mediated transposition into a certain Enterobacterial plasmid with a possible natural competence from *Kluyvera* species [23,27]. The CTX-M-1 and -9 can be identified in multiple communities in this study (Figure 9A). Therefore, further dissemination of CTX-M-1 and -9 could be generated by plasmid transfer itself. In addition, the CTX-M-1 and -9 positive mobile element could transpose into other broad-host range plasmids, leading to wide dissemination of ESBL in Enterobacteriacea. On the other hand, CTX-M-2 subgroup is identified in only co68, suggesting that CTX-M-2 positive plasmid disseminates between *Salmonella* and *Klebsiella* species (Figure 9A).

The carbapenemases *K. pneumoniae* carbapenemase (KPC) and New Delhi metallo-ß-lactamase (NDM-1) were unique to the co22 and co68 communities (Figure 9B). KPC was only found in co68, mainly in IncFIIk and IncN plasmids. NDM-1 was found in co22 and co68. Moreover, the NDM-1 in co22 was related only to the IncA/C plasmids. Meanwhile, the NDM-1 in co68 was not related to any Inc plasmids (Table 4 and Figure 9C). NDM-1 was closely related to co18/co22/co68 communities including plasmids carrying CTX-M and KPC. Thus, co22/co68 have the most potential for the dissemination of AMR genes in *Enterobacteriacea*.

Figure 9. Components of the communities with AMR genes. (**A**) The CTX-M-1, -2 and -9 subgroups and the community and bacterial components. (**B**) KPC carbapenemase and the bacterial components. The plasmids carrying KPC are only found in co68. (**C**) The communities and bacterial components of the plasmids carrying the NDM-1 gene (Table 4).

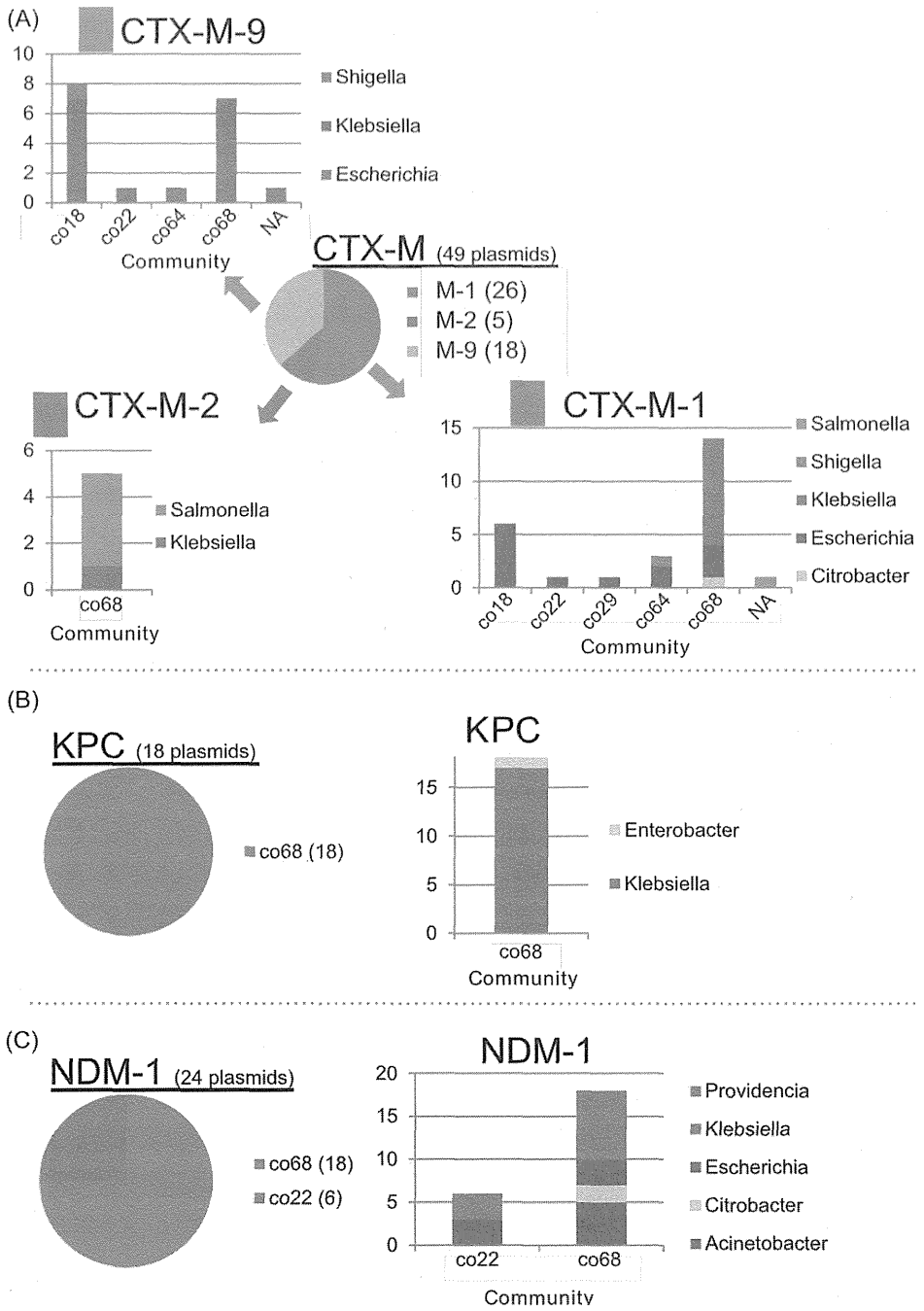


Table 4. Distribution of Inc types, antimicrobial resistance genes, and communities.

Inc type	CTX-M			KPC				NDM-1	
	M-1	M-2	M-9	2	3	4	10	co22	co68
FII	7		8						1
FIIk	4			5	2				1
N	2	1	3	1	1	1			
A/C			1					6	
L/M	2					1			2
I1	3								
FIB-M	1								1
FIA	1								
FIIS			1						
HI1									1
HI2	1								
K			1						
R				1					
Not Assigned	5	4	4	4	1		1		12
Total	26	5	18	11	4	2	1	6	18

3. Experimental Section

3.1. Download and Selection of Complete Plasmids Sequences

Complete plasmid candidates were downloaded in GenBank format from NCBI using the following key words: ((bacteria[Organism]) AND complete[Title]) AND plasmid[Title].

Among the downloaded sequences, complete, non-provisional sequences with more than 2000 bp sequences were used for the following analysis. For the remaining sequences, the protein sequences were extracted according to the "FEATURES" information.

3.2. Network Analysis

We performed the blastp searches [28] to identify orthologous genes between plasmids with parameter the -F F, -g T. The hits with e-values less than 1E-10, cover ratios more than 90% and length difference of 0.9 < query/subject < 1.1 with several identity cut-off values (100, 99, 90, 80, 70, 60, and 50%) were regarded as shared genes. We also searched for shared proteins using the uclust program v6.0.307 [29] with the following parameters after sorting by sequence length: -cluster_smallmem -minsl 0.9 -minqt 0.9 -maxqt 1.1 -query_cov 0.9 -target_cov 0.9. Subsequently, network analyses were performed using the R igraph library [21]. The plasmid communities were detected using the edge.betweenness.community, multilevel.community, label.propagation.community, infomap.community, walktrap.community, and fastgreedy.community methods in the igraph library by default parameter settings. For instance, if two plasmids share n genes, the edge weight parameter will be defined as n. Based on the intensity of the detected weight parameter on each edge, CCs were summarized into each community by the above method.

3.3. Inc Typing and Searching for Mobile Elements

Inc types were inferred from blastn searching with e-values less than 1E-10, cover ratios more than 90% against the PCR amplicons based on primer sequences for PBRT replicon typing [26].

3.4. Detection of CTX-M Genes

The CTX-M genes were prepared as follows. Candidate sequences for the CTX-M genes were retrieved from fasta formatted NCBI data using the key word "CTX-M". The sequences with lengths of at least 291 aa that did not belong to synthetic constructs (*i.e.*, lacking the "[synthetic construct]" search term) were extracted from the candidate sequences and were entered into the CTX-M database. We then performed a blastp search of the plasmid genes against the CTX-M database. The genes with greater than 90% identity for more than 280 aa in length were considered plasmid CTX-M genes. Finally, the plasmid CTX-M genes and CTX-M database sequences were aligned using the mafft program [30]. A phylogenetic tree was then constructed using the MEGA 5 program [31]. The groupings of the plasmid CTX-M genes were inferred according to the phylogenetic tree and the review from Bonet *et al.* [27].

3.5. Detection of Other Antibiotic Resistance Genes

We performed blastp searches for all of the plasmid genes against the ARDB + CARD database [32,33]. The plasmid proteins having the top hit to one of the following accessions with e-values less than 1E-10 were regarded as KPC genes: AAG13410, AAS01762, AAU06362, ABX11263, AF297554, AF395881, AY034847, EU555534, EU729727, FJ234412, GQ140348, HM066995, HQ641421, YP_002286834, YP_002286834, YP_002286834, YP_002286834, YP_002286834, YP_002286834, YP_002286834, YP_002286834, YP_002286834, YP_002286981, and YP_002286981. Accordingly, those plasmid proteins with a top hit being the following accessions with e-values less than 1E-10 were considered NDM-1 genes: HQ328085 and HQ451074. Plasmids with no significant hits within this database were regarded as having no AMR genes.

4. Conclusions

We conducted a plasmidome network analysis for all of the available complete bacterial plasmids. Most of the plasmids were connected to a single LCC, which mainly consisted of plasmids from *Bacilli* and *Gammaproteobacteria*. The LCC was subdivided into dozens of communities, which consisted of plasmids from a mostly single class of bacteria. Such community network analysis facilitate displaying possible recent HGTs like a class 1 integron, *str* and *tet* resistance markers between communities. As well as the class 1 integron, the CTX-M ß-lactamase can be identified in multiple communities. Therefore further dissemination could be generated either by plasmid transfer itself or transposition of the CTX-M ß-lactamase into other broad-host range plasmids "enbloc", suggesting that this community network analysis could propose crucial information for the manner of dissemination in AMR. Intriguingly, HGT was noted between different phyla (*i.e.*, *Staphylococcus* and *Pasteurellaceae* (*P. multocida* and *H. parasuis*)), suggesting that both organisms can acquire AMR genes from closely contacting each other. The distributions of the Inc-type and AMR genes implied

that such genes generally circulate within communities composed of typical bacterial taxa. This plasmidome network analysis under very strict parameter settings provides remarkable discrimination power for plasmid-related recent HGT. It also provides a large-scale analysis of plasmid associations, improving our understanding of current plasmid dissemination and evolution among bacterial communities.

Acknowledgments

This work was supported by a Grant-in-Aid from the Ministry of Health, Labor, and Welfare, Japan (H24 Shokuhin-Ippan-008).

Author Contributions

Conceived and designed the analysis: Akifumi Yamashita, Makoto Kuroda. Performed the analysis: Akifumi Yamashita. Contributed reagents/materials/analysis tools: Akifumi Yamashita, Tsuyoshi Sekizuka. Wrote the paper: Akifumi Yamashita, Makoto Kuroda.

Conflicts of Interest

The authors declare no conflict of interest.

References and Notes

1. Johnson, T.J.; Nolan, L.K. Pathogenomics of the virulence plasmids of *Escherichia coli*. *Microbiol. Mol. Biol. Rev.* **2009**, *73*, 750–774.
2. Norman, A.; Hansen, L.H.; Sorensen, S.J. Conjugative plasmids: Vessels of the communal gene pool. *Philos. Trans. R Soc. Lond. B Biol. Sci.* **2009**, *364*, 2275–2289.
3. Andam, C.P.; Fournier, G.P.; Gogarten, J.P. Multilevel populations and the evolution of antibiotic resistance through horizontal gene transfer. *FEMS Microbiol. Rev.* **2011**, *35*, 756–767.
4. Wiedenbeck, J.; Cohan, F.M. Origins of bacterial diversity through horizontal genetic transfer and adaptation to new ecological niches. *FEMS Microbiol. Rev.* **2011**, *35*, 957–976.
5. Skippington, E.; Ragan, M.A. Lateral genetic transfer and the construction of genetic exchange communities. *FEMS Microbiol. Rev.* **2011**, *35*, 707–735.
6. Harris, S.R.; Cartwright, E.J.; Torok, M.E.; Holden, M.T.; Brown, N.M.; Ogilvy-Stuart, A.L.; Ellington, M.J.; Quail, M.A.; Bentley, S.D.; Parkhill, J.; *et al.* Whole-genome sequencing for analysis of an outbreak of meticillin-resistant staphylococcus aureus: A descriptive study. *Lancet Infect. Dis.* **2013**, *13*, 130–136.
7. He, M.; Miyajima, F.; Roberts, P.; Ellison, L.; Pickard, D.J.; Martin, M.J.; Connor, T.R.; Harris, S.R.; Fairley, D.; Bamford, K.B.; *et al.* Emergence and global spread of epidemic healthcare-associated clostridium difficile. *Nat. Genet.* **2013**, *45*, 109–113.
8. Imperi, F.; Antunes, L.C.; Blom, J.; Villa, L.; Iacono, M.; Visca, P.; Carattoli, A. The genomics of acinetobacter baumannii: Insights into genome plasticity, antimicrobial resistance and pathogenicity. *IUBMB Life* **2011**, *63*, 1068–1074.

9. Walker, T.M.; Ip, C.L.; Harrell, R.H.; Evans, J.T.; Kapatai, G.; Dedicoat, M.J.; Eyre, D.W.; Wilson, D.J.; Hawkey, P.M.; Crook, D.W.; *et al.* Whole-genome sequencing to delineate mycobacterium tuberculosis outbreaks: A retrospective observational study. *Lancet Infect. Dis.* **2013**, *13*, 137–146.
10. Davies, J.; Davies, D. Origins and evolution of antibiotic resistance. *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 417–433.
11. Canton, R.; Akova, M.; Carmeli, Y.; Giske, C.G.; Glupczynski, Y.; Gniadkowski, M.; Livermore, D.M.; Miriagou, V.; Naas, T.; Rossolini, G.M.; *et al.* Rapid evolution and spread of carbapenemases among enterobacteriaceae in europe. *Clin. Microbiol. Infect.* **2012**, *18*, 413–431.
12. Halary, S.; Leigh, J.W.; Cheaib, B.; Lopez, P.; Bapteste, E. Network analyses structure genetic diversity in independent genetic worlds. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 127–132.
13. Tamminen, M.; Virta, M.; Fani, R.; Fondi, M. Large-scale analysis of plasmid relationships through gene-sharing networks. *Mol. Biol. Evol.* **2012**, *29*, 1225–1240.
14. Fondi, M.; Bacci, G.; Brilli, M.; Papaleo, M.C.; Mengoni, A.; Vaneechoutte, M.; Dijkshoorn, L.; Fani, R. Exploring the evolutionary dynamics of plasmids: The acinetobacter pan-plasmidome. *BMC Evol. Biol.* **2010**, *10*, 59.
15. Brown Kav, A.; Sasson, G.; Jami, E.; Doron-Faigenboim, A.; Benhar, I.; Mizrahi, I. Insights into the bovine rumen plasmidome. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 5452–5457.
16. Brolund, A.; Franzen, O.; Melefors, O.; Tegmark-Wisell, K.; Sandegren, L. Plasmidome-analysis of esbl-producing escherichia coli using conventional typing and high-throughput sequencing. *PLoS One* **2013**, *8*, e65793.
17. Song, X.; Sun, J.; Mikalsen, T.; Roberts, A.P.; Sundsfjord, A. Characterisation of the plasmidome within enterococcus faecalis isolated from marginal periodontitis patients in norway. *PLoS One* **2013**, *8*, e62248.
18. Lima-Mendez, G.; van Helden, J.; Toussaint, A.; Leplae, R. Reticulate representation of evolutionary and functional relationships between phage genomes. *Mol. Biol. Evol.* **2008**, *25*, 762–777.
19. Dwight Kuo, P.; Banzhaf, W.; Leier, A. Network topology and the evolution of dynamics in an artificial genetic regulatory network model created by whole genome duplication and divergence. *Biosystems*. **2006**, *85*, 177–200.
20. Fondi, M.; Fani, R. The horizontal flow of the plasmid resistome: Clues from inter-generic similarity networks. *Environ. Microbiol.* **2010**, *12*, 3228–3242.
21. The Igraph Library. Available online: http://igraph.sourceforge.net (accessed on 20 June 2013).
22. Shannon, C.E. A mathematical theory of communication. *Bell Syst. Tech. J.* **1948**, *27*, 379–423, 623–656.
23. Gillings, M.; Boucher, Y.; Labbate, M.; Holmes, A.; Krishnan, S.; Holley, M.; Stokes, H.W. The evolution of class 1 integrons and the rise of antibiotic resistance. *J. Bacteriol.* **2008**, *190*, 5095–5100.
24. Niven, D.F.; O'Reilly, T. Significance of v-factor dependency in the taxonomy of haemophilus species and related organisms. *Int. J. Syst. Bacteriol.* **1990**, *40*, 1–4.
25. Redfield, R.J.; Findlay, W.A.; Bosse, J.; Kroll, J.S.; Cameron, A.D.; Nash, J.H. Evolution of competence and DNA uptake specificity in the pasteurellaceae. *BMC Evol. Biol.* **2006**, *6*, 82.

26. Carattoli, A.; Miriagou, V.; Bertini, A.; Loli, A.; Colinon, C.; Villa, L.; Whichard, J.M.; Rossolini, G.M. Replicon typing of plasmids encoding resistance to newer beta-lactams. *Emerg. Infect. Dis.* **2006**, *12*, 1145–1148.
27. Bonnet, R. Growing group of extended-spectrum beta-lactamases: The ctx-m enzymes. *Antimicrob. Agents Chemother.* **2004**, *48*, 1–14.
28. Altschul, S.F.; Gish, W.; Miller, W.; Myers, E.W.; Lipman, D.J. Basic local alignment search tool. *J. Mol. Biol.* **1990**, *215*, 403–410.
29. Edgar, R.C. Search and clustering orders of magnitude faster than blast. *Bioinformatics* **2010**, *26*, 2460–2461.
30. Katoh, K.; Standley, D.M. Mafft multiple sequence alignment software version 7: Improvements in performance and usability. *Mol. Biol. Evol.* **2013**, *30*, 772–780.
31. Tamura, K.; Peterson, D.; Peterson, N.; Stecher, G.; Nei, M.; Kumar, S. Mega5: Molecular evolutionary genetics analysis using maximum likelihood, evolutionary distance, and maximum parsimony methods. *Mol. Biol. Evol.* **2011**, *28*, 2731–2739.
32. Liu, B.; Pop, M. Ardb—antibiotic resistance genes database. *Nucleic Acids Res.* **2009**, *37*, D443–D447.
33. McArthur, A.G.; Waglechner, N.; Nizam, F.; Yan, A.; Azad, M.A.; Baylay, A.J.; Bhullar, K.; Canova, M.J.; de Pascale, G.; Ejim, L.; *et al.* The comprehensive antibiotic resistance database. *Antimicrob. Agents Chemother.* **2013**, *57*, 3348–3357.