

Article

Global Spread and Molecular Characterization of CTX-M-Producing *Salmonella* Typhimurium Isolates

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Abstract: This study aimed to determine the global prevalence and molecular characterization of CTX-M-producing *Salmonella* Typhimurium isolates. A total of 330 (15.2%, 330/21779) *bla*_{CTX-M}-positive *S. Typhimurium* were obtained from the public databases in July 2021. Thirteen variants were found in the 330 members of the *bla*_{CTX-M} group, and *bla*_{CTX-M-9} (26.4%, 88/330) was the most prevalent. The majority of *bla*_{CTX-M}-positive *S. Typhimurium* were obtained from humans (59.7%, 197/330) and animals (31.5%, 104/330). The number of *bla*_{CTX-M}-positive *S. Typhimurium* increased annually ($p < 0.0001$). These isolates were primarily found from China, the United Kingdom, Australia, the USA, and Germany. In addition, these isolates possessed 14 distinct sequence types (ST), and three predominated: ST34 (42.7%, 141/330), ST19 (37.0%, 122/330), and ST313 (10.3%, 34/330). The majority of ST34 *S. Typhimurium* isolates were distributed in China and mainly from swine. However, the majority of ST19 were distributed in the United Kingdom and Australia. Analysis of contigs showed that the major type of *bla*_{CTX-M}-carrying plasmid was identified as IncI plasmid (52.9%, 27/51) and IncHI2 plasmid (17.6%, 9/51) in 51 *bla*_{CTX-M}-positive *S. Typhimurium* isolates. In addition, WGS analysis further revealed that *bla*_{CTX-M} co-existed with nine antibiotic-resistant genes with a detection rate over 50%, conferring resistance to five classes of antimicrobials. The 154 virulence genes were detected among these isolates, of which 107 virulence genes were highly common. This study revealed that China has been severely contaminated by *bla*_{CTX-M}-positive *S. Typhimurium* isolates, these isolates possessed numerous ARGs and virulence genes, and highlighted that continued vigilance for *bla*_{CTX-M}-positive *S. Typhimurium* in animals and humans is urgently needed.



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1. Introduction

Salmonella is an important foodborne pathogen that has a nearly ubiquitous distribution among humans, animals, and the open environment. According to the WHO, there over 90 million people are infected by *Salmonella* annually, and 150,000 people die from *Salmonella* infection [1]. Over 2600 *Salmonella* serotypes have been identified and can be referred to as typhoidal or non-typhoidal (NTS); the latter are present in different animal reservoirs and are responsible for self-limiting gastrointestinal syndromes [2]. *S. Typhimurium* can cause potential threat to human health through the consumption of contaminated food or water [3]. Through estimates of the global invasive non-typhoidal *Salmonella* disease, a study recently found that *S. Typhimurium* is emerging in several African countries [4]. After its oral acquisition, *S. Typhimurium* travels down the intestinal tract and reaches the large intestine, where most of its replication is thought to occur [5].

Treatment of invasive salmonellosis has been compromised due to the emergence of *Salmonella* isolates with single or multidrug resistance to a number of first-line agents. Consequently, the third generation cephalosporins, such as ceftriaxone, have become treatment modalities of choice for therapy against severe *Salmonella* infections [6]. However,

the increasing prevalence of cephalosporin-resistant *Salmonella* is also an emerging problem in recent years [7]. Resistance to cephalosporins is mainly due to the acquisition of extended-spectrum β -lactamase genes (ESBLs), among which CTX-M-type enzymes are currently most common—usually located on transmissible plasmids—and can disseminate among the Enterobacteriaceae family [8]. The number of reported cases in various ESBL-producing *Salmonella* serotypes has been increasing worldwide in recent years, with the predominant CTX-M group that was recently detected in poultry and poultry products in different countries [9,10].

In general, *Salmonella* virulence factors have a crucial role in systemic infections [11]. Virulence genes are located on various locations of the genome, including *Salmonella* pathogenicity islands (SPIs) and several mobile genetic elements such as prophages and plasmids [12]. SPI-1 and SPI-2 encode for Type III secretion system (TTSS) and play an important role in delivering different effector proteins into the host that mediates pathogenesis [13]. SPI-1 encodes for genes such as *invA*, *sipABD*, and *sopBD* involved in the invasion of epithelial cells, whereas SPI-2 encodes the genes *sifA* and *ssaR* related to the survival and replication of *Salmonella* within phagocytic cells [14]. In addition, the virulence plasmids carrying virulence genes, such as the *spv* genes, play a role in *Salmonella* multiplication within its host cell, increasing the severity of enteritis [15].

In this study, we first employed genomic analysis from a public database to conduct a global survey of epidemic characterization of CTX-M-producing *S. Typhimurium*. We then characterized the molecular characteristics, diversity, antibiotic-resistant genes, and virulence genotypes of these pathogens.

2. Results

2.1. Prevalence of *Bla_{ctx-M}*-Producing *S. Typhimurium* Identified from the Genome Database

In this study, we identified 330 *bla_{CTX-M}*-positive *S. Typhimurium* from 21,779 assembled genomes of *S. Typhimurium* from the NCBI database. Thirteen variants were found in the 330 members of the *bla_{CTX-M}* group, of which, the most predominant variants of *bla_{CTX-M}* were *bla_{CTX-M-9}* (26.4%, 88/330), followed by *bla_{CTX-M-55}* (68%, 204/330), *bla_{CTX-M-14}* (19.8%, 66/330), *bla_{CTX-M-15}* (16.5%, 55/330), *bla_{CTX-M-65}* (6.9%, 23/330), and *bla_{CTX-M-1}* (5.7%, 19/330) (Figure 1A). The majority of *bla_{CTX-M}*-positive *S. Typhimurium* were obtained from humans (59.7%, 197/330) and animals (31.5%, 104/330). A noteworthy observation was that swine (18.5%, 61/330) were the primary animal host in (Figure 1B). In addition, the *bla_{CTX-M-9}*, *bla_{CTX-M-55}*, and *bla_{CTX-M-14}* positive *Salmonella* isolates were obtained from animals and humans, and the latter was more dominant (Figure S1). During this period, we noticed a shift in the quantity of *bla_{CTX-M}*-positive *S. Typhimurium*. The percentage of *bla_{CTX-M}*-positive *S. Typhimurium* isolates increased from 2.1% (7/330) in 2014 and 10.3% (34/330) in 2015 to 14.2% (47/330) in 2019 and 37.0% (122/330) in 2020 (Figure 1C). The χ^2 test revealed a significant linear trend among the ordered years from 2014 to 2020 ($p < 0.0001$). These *bla_{CTX-M}*-positive *S. Typhimurium* isolates were distributed across 15 countries. China (34.5%, 114/330) has been severely contaminated by *bla_{CTX-M}*-positive *S. Typhimurium* isolates, followed by the United Kingdom (28.2%, 93/330), Australia (13.0%, 43/330), USA (5.5%, 18/330), Germany (4.5%, 15/330), and other countries (7.6%, 25/330) (Figure 1D).

2.2. Molecular Characterization of *Bla_{ctx-M}*-Producing *S. Typhimurium*

This group of 330 *bla_{CTX-M}*-positive *S. Typhimurium* isolates possessed 14 distinct ST. Three were predominant: ST34 (42.7%, 141/330), ST19 (37.0%, 122/330), and ST313 (10.3%, 34/330), but we could not find a matching ST for 13 of the database isolates (Table S1). It is worth mentioning that the majority of *bla_{CTX-M}*-positive ST34 *S. Typhimurium* isolates were distributed in China ($n = 94$). However, the majority of ST19 were distributed in the United Kingdom ($n = 63$) and Australia ($n = 34$) (Figure 2A). In addition, swine were one of the most dominant hosts in the *bla_{CTX-M}*-positive ST34 *S. Typhimurium* isolates (Figure 2B).

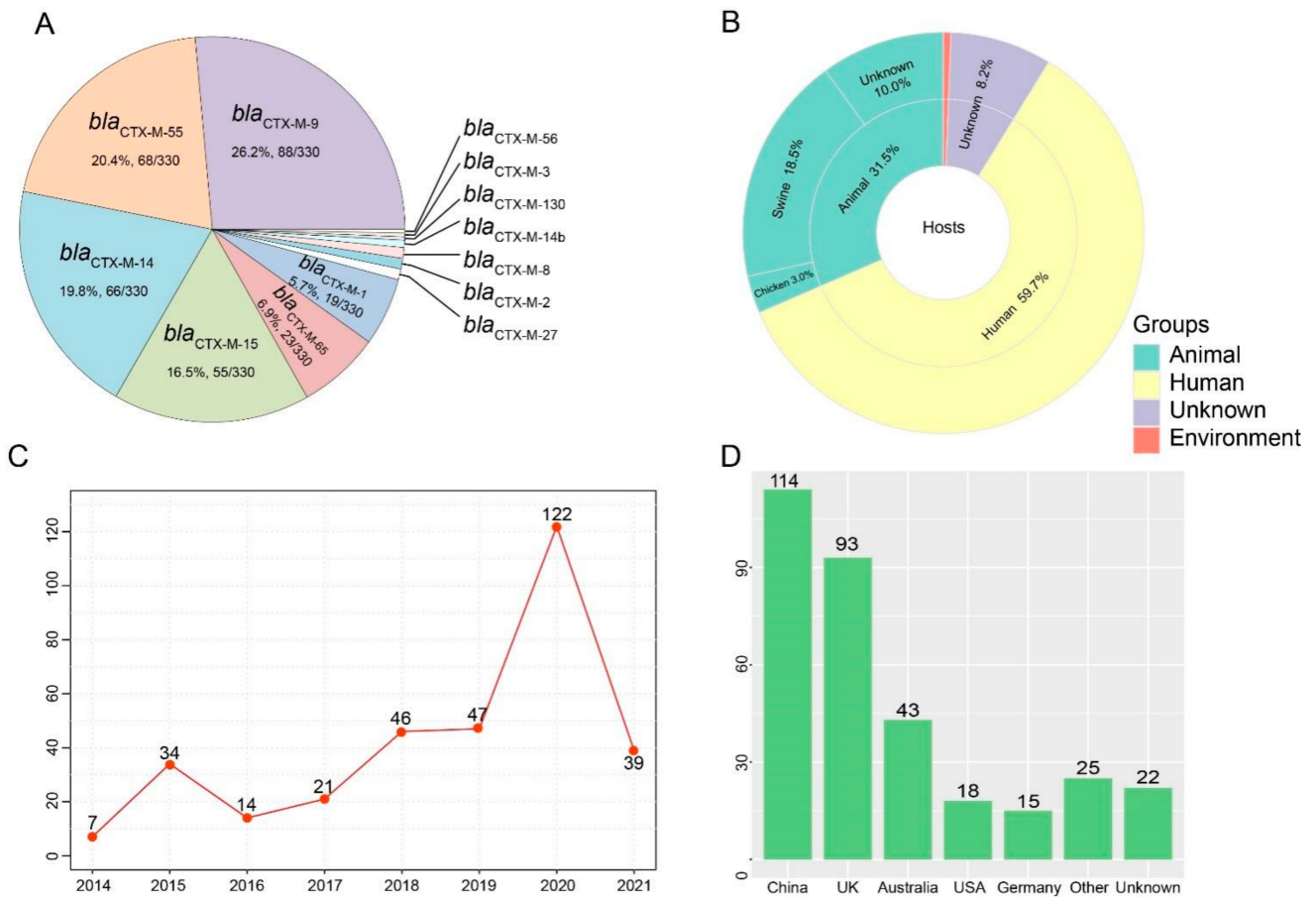


Figure 1. Prevalence of *bla*_{CTX-M}-positive *Salmonella* Typhimurium isolates. (A) The rate and number of variants in *bla*_{CTX-M} genes. (B) The hosts of *bla*_{CTX-M}-positive *S.* Typhimurium isolates. (C) The number of *bla*_{CTX-M}-positive *S.* Typhimurium isolates from 2014 to 2021. (D) The number of *bla*_{CTX-M}-positive *S.* Typhimurium isolates in different countries.

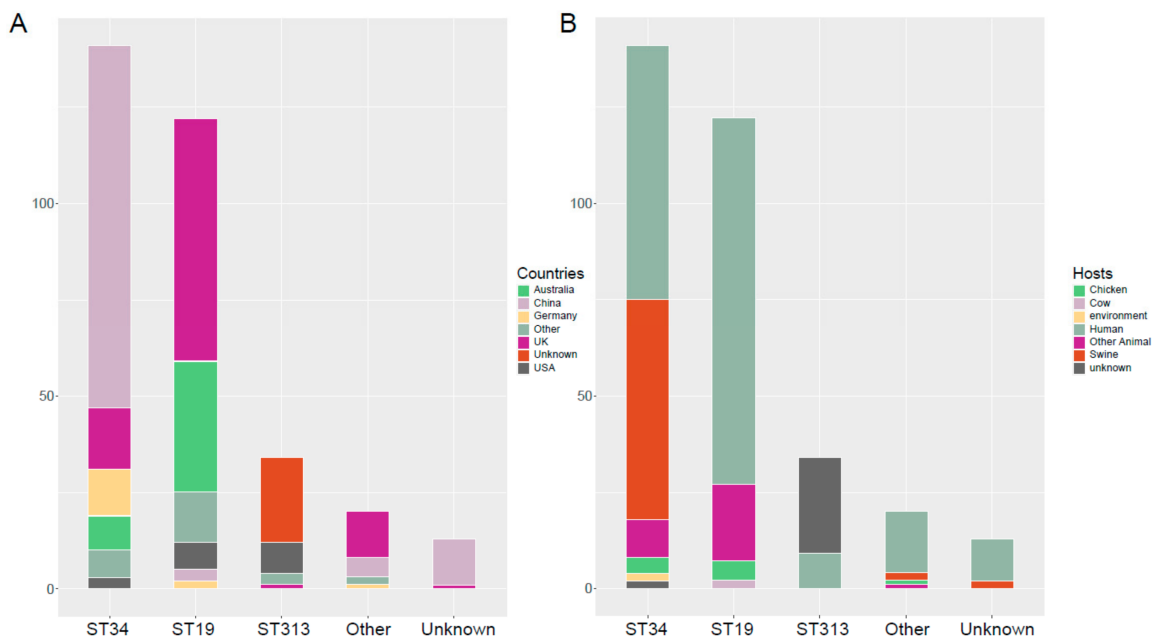


Figure 2. Geographic distribution and host diversity of the dominant ST *bla*_{CTX-M}-positive *S.* Typhimurium isolates. (A) Geographic distribution the dominant ST *bla*_{CTX-M}-positive *S.* Typhimurium isolates. (B) Host diversity of the dominant ST *bla*_{CTX-M}-positive *S.* Typhimurium isolates.

2.3. Plasmid Analysis

The contigs carrying *bla*_{CTX-M} were confirmed as numerous types of plasmids in 51 *bla*_{CTX-M}-positive *S. Typhimurium* isolates. As shown in Figure 3, the major type of *bla*_{CTX-M}-carrying plasmid was identified as IncI plasmid (52.9%, 27/51), followed by IncHI2 plasmid (17.6%, 9/51), IncA/C plasmid (7.8%, 4/51), and IncB//O/K/Z plasmid (7.8%, 4/51). Additionally, an analysis of WGS indicated that *bla*_{CTX-M}-positive *S. Typhimurium* isolates in this study were carrying 17 types of Inc plasmids (Figure 4). IncHI2 (69.1%, 228/330) and IncHI2A (68.8%, 227/330) were the most prevalent type of plasmid, followed by IncFIB plasmid (33.9%, 112/330) and IncFII plasmid (30.9%, 102/330).

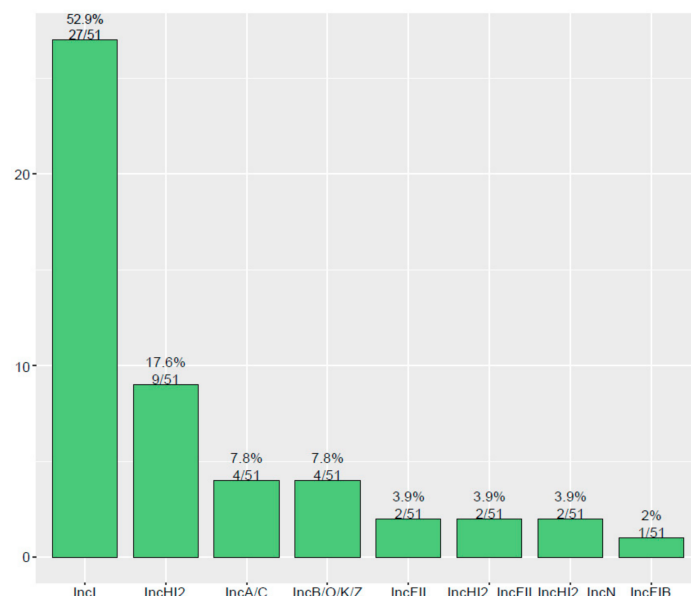


Figure 3. The diversity of plasmid types carrying *bla*_{CTX-M} among 51 *bla*_{CTX-M}-positive *S. Typhimurium* isolates.

2.4. Other ARGs

In addition to *bla*_{CTX-M}, a total of 26 ARGs were identified among these *S. Typhimurium* isolates and conferred resistance to ten classes of antibiotics (Figure 4). Of these, nine ARGs were common with a detection rate of over 50%, including aminoglycoside-resistant genes *acc* (100%, 330/330), *aadA* (51.8%, 171/330), *ant* (63.3%, 209/330), *aph* (68.8%, 227/330); β -lactam-resistant genes *bla*_{CMY} (100%, 330/330) and *bla*_{TEM} (57.9%, 191/330); trimethoprim-resistant gene *drfA* (60.0%, 198/330); sulphonamide-resistant gene *sul* (89.7%, 296/330); and tetracycline-resistant gene *tet* (87.6%, 289/330). Notably, colistin-resistant genes *mcr-1*, *mcr-3*, and *mcr-9* were detected in 62, 7, and 86 *bla*_{CTX-M}-positive *S. Typhimurium* isolates, respectively. Carbapenem-resistant gene *bla*_{NDM-5} was detected in two *bla*_{CTX-M}-positive *S. Typhimurium* isolates.

2.5. Virulence Factor

Among the 330 *bla*_{CTX-M}-positive *S. Typhimurium* isolates, we detected 154 virulence genes (Table S1). Of these, 107 virulence genes were highly common, with a detection rate over 79%. In contrast, the detection rate of 38 virulence genes were low (<10%). Of note was the detection rate of some virulence genes that ranged from 26.4% to 31.8%, including *grvA*, *spvB*, *spvC*, *spvR*, *pefA*, *pefB*, *pefC*, *pefD*, and *rck* (Figure 5A). The majority of *bla*_{CTX-M}-positive *S. Typhimurium* isolates carried 107 virulence genes (34.8%, 115/330), followed by 106 (18.5%, 61/330), 114 (8.8%, 29/330), 115 (8.5%, 28/330), 108 (7.6%, 25/330), and 116 (7.3%, 24/330) (Figure 5B).

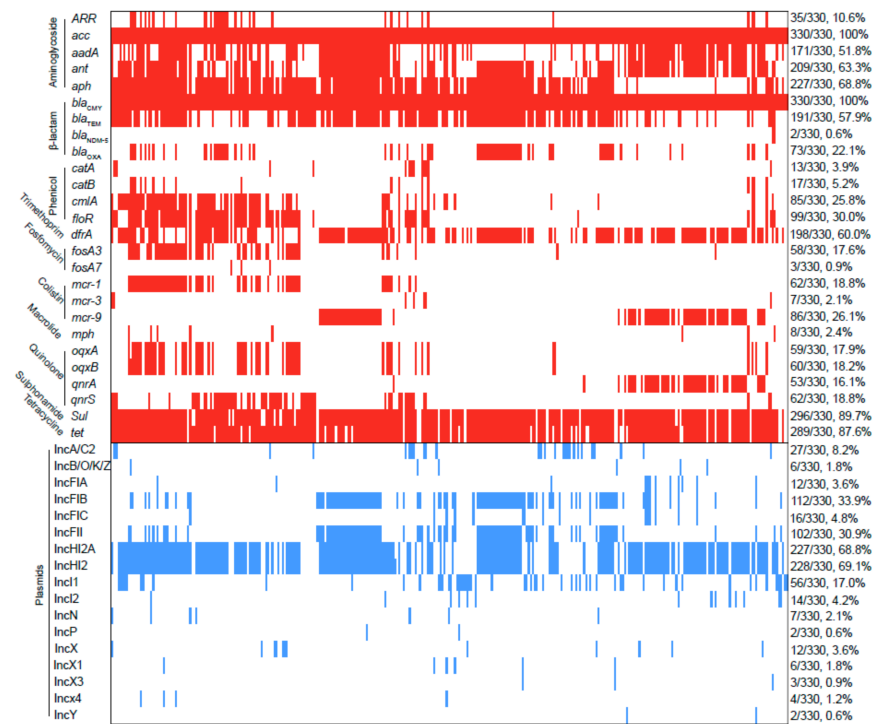


Figure 4. Analysis of ARGs and plasmids among 330 *bla*_{CTX-M}-positive *S. Typhimurium* isolates. The red and blue squares represent positivity for ARGs and plasmid Inc types, respectively.

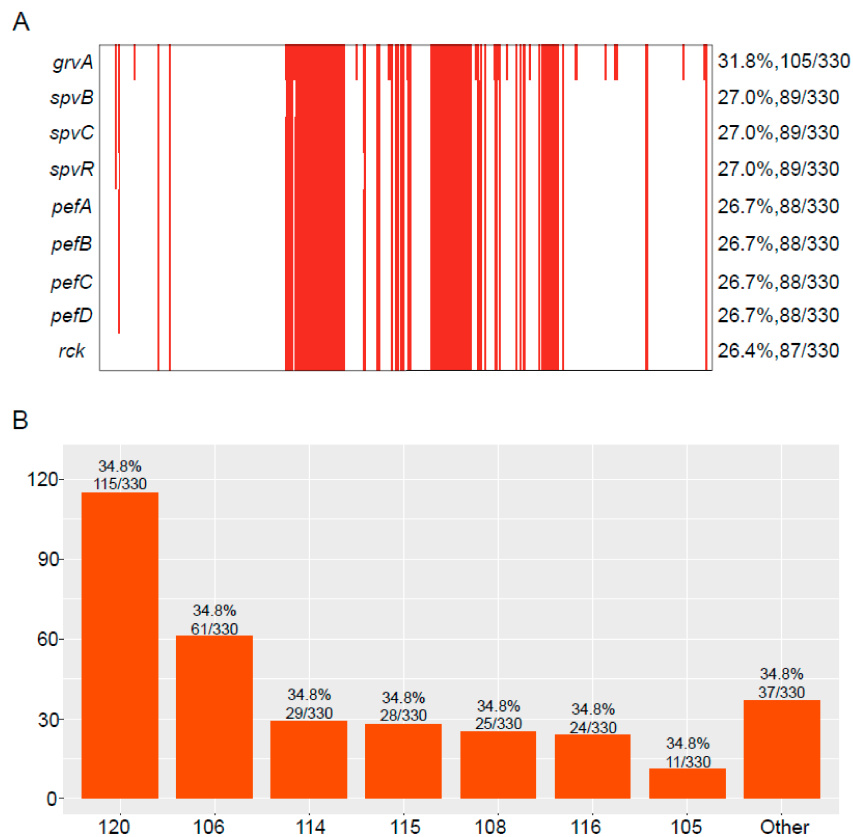


Figure 5. Virulence genes were identified in *bla*_{CTX-M}-positive *S. Typhimurium* isolates. (A) The detection rate of virulence genes in *bla*_{CTX-M}-positive *S. Typhimurium* isolates; the red represents positive for virulence genes. (B) The number of isolates carrying different numbers of virulence genes.

3. Discussion

At present, it is concerning that the increasing incidence of infections is caused by ESBL-producing organisms, especially *Salmonella* spp., because they are resistant to most of the β -lactam antimicrobials and other antimicrobial classes [16,17]. During the last decade, the most encountered ESBL genes were the CTX-M enzyme family, primarily carried by transferable plasmids and transposons [18]. In this study, all 330 *bla*_{CTX-M}-positive *S. Typhimurium* were collected from humans and animals, especially swine. These isolates were distributed across 15 countries. The countries possessing the greatest amount of *bla*_{CTX-M}-positive *S. Typhimurium* isolates were China, UK, Australia, USA, and Germany [19–23]. In addition, we noticed an increase in quantity of *bla*_{CTX-M}-positive *S. Typhimurium* isolates from 2014 to 2020. This may be related to the increased rate of *Salmonella* after 2009 in food animals [24].

This group of 330 *bla*_{CTX-M}-positive *S. Typhimurium* isolates possessed 14 distinct ST, with three predominant: ST34, ST19, and ST313. Previous studies have shown that ST19, ST34, and ST313 are commonly found STs of *S. Typhimurium*. Recently, one of the most prevalent *S. Typhimurium*, ST34, was widely reported in Europe, North America, Asia, and Australia [25]. In addition, ST34 *S. Typhimurium* isolates have acquired strong biofilm-forming ability and were often reportedly carrying the colistin-resistant genes (*mcr-1*, *mcr-3*, *mcr-5*, and *mcr-9*) and even the *bla*_{NDM} gene [25–27]. ST19 and ST34 were the most common STs in Asia. However, ST19 isolates were resistant to fewer antibiotic classes than ST34 isolates [27]. Thus far, ST19 has been reported from humans, reptiles, ovine, swine, poultry, food, and bovine from France, Mexico, China, Germany, Scotland, Portugal, Qatar, Korea, Ireland, the United States, the United Kingdom, and Denmark, according to Enterobase [28]. ST313 is a relatively newly emerged sequence type and closely related to the ST19 group of *S. Typhimurium*, which has caused a devastating epidemic of bloodstream infections across sub-Saharan Africa [29].

The *bla*_{CTX-M} genes were mainly located on IncI plasmid in the *S. Typhimurium* isolates, followed by IncHI2 and IncA/C plasmids. Additionally, 17 types of Inc plasmids were identified among the *bla*_{CTX-M}-positive *S. Typhimurium* isolates. IncHI2 and IncHI2A were the most prevalent type of plasmid, followed by IncFIB and IncFII plasmids. IncI plasmids were closely associated with the spread of several ESBL genes. The *bla*_{CTX-M} gene was located on IncI1 plasmids in all of the isolates, which were obtained from slaughterhouses located in seven districts in France [30]. A previous study has shown that IncA/C and IncHI2 were the most common types of plasmids among ESBL-producing *Salmonella*, and they often carried multiple antibiotic-resistant genes, including *strB*, *qnrS*, *tet(A)*, *sul*, and *dfrA14* [31]. Additionally, the numerous types of plasmids may serve as important vehicles for the spread of ARGs [32].

In addition to *bla*_{CTX-M}, a total of 26 ARGs were identified among the *S. Typhimurium* isolates and conferred resistance to ten classes of antibiotics, including quinolone, aminoglycoside, β -lactam, sulphonamide, trimethoprim, tetracycline, phenicol, macrolide, fosfomicin, and colistin. Consistent with a previous study, most of the *bla*_{CTX-M}-positive isolates carried acquired-resistance determinants associated with three or more drug classes [33]. Notably, a few *bla*_{CTX-M} genes co-existed with *mcr-1*, *mcr-3*, *mcr-9*, and *bla*_{NDM-5}, conferring resistance to colistin and carbapenem, which were considered as the last-resort antibiotics used for the treatment of infections caused by multidrug-resistant Gram-negative bacteria [34].

An important trait of *Salmonella* is that they can invade, survive, and multiply in a host cell in the presence of genetic determinants for virulence. Virulence genes have been extensively studied in *Salmonella* [35]. In this study, a total of 154 virulence genes were identified in the 330 *bla*_{CTX-M}-positive *S. Typhimurium* isolates, and most of the isolates carried 107 virulence genes. Of these, the detection rate of some virulence genes ranged from 26.4% to 31.8%, including *grvA*, *spvB*, *spvC*, *spvR*, *pefA*, *pefB*, *pefC*, *pefD*, and *rck*. The gene *grvA* (for Gifsy-2-related virulence) is located on the prophage Gifsy-2; *grvA* null mutant showed an increase in the virulence of serovar *Typhimurium* in mice [36]. *SpvB*

facilitated *Salmonella* survive and replicate within macrophages via perturbing cellular iron metabolism [37]. The protein encoded by the *spvC* gene has a phosphorylated threonine lyase activity that inhibits MAP phosphokinase. The pathogenicity of *Salmonella* strains greatly increases when both *spvB* and *spvC* genes co-exist in the bacteria [38]. The *spvR* encodes a positive activator for the following four genes, *spvABCD* [39]. Plasmid-encoded fimbriae (Pef) of *Salmonella* are among the fimbriae whose expression have been observed in animals. Pef fimbriae biogenesis depends on the *pef* operon, located on the virulence plasmid of *S. Typhimurium*. This operon encodes the major Pef fimbriae subunit *pefA*, the usher protein *pefC*, required for the assembly of the fimbriae, and the *pefD* periplasmic chaperone for *pefA* [40]. Recent research has shown that *rck* protein is able to induce the *Salmonella* entry mechanism. *rck* mimics natural host cell ligands and triggers engulfment of the bacterium by interacting with the epidermal growth factor receptor [41].

There are several limitations of this study. First, the increase in genomes in the public repository may be related to the development of sequencing technology rather than an actual increase. Second, not all genomes of isolates will upload to the database. Finally, the phenotypes of antibiotic resistance and virulence genes and the transfer of resistance genes were not evaluated in this study.

4. Materials and Methods

4.1. Materials

A total of 21,779 assembled genomes of *Salmonella Typhimurium* were downloaded from the NCBI database in 8 July 2021 <https://www.ncbi.nlm.nih.gov/assembly>. The detailed information (collected year, hosts, and location) was obtained from the pathogens database (<https://www.ncbi.nlm.nih.gov/pathogens>, accessed on 8 July 2021).

4.2. Methods

All the genomes of *S. Typhimurium* were applied to a filter for the presence of *bla*_{CTX-M} and other antibiotic-resistant genes using ResFinder (<https://cge.cbs.dtu.dk/services/ResFinder/> accessed on 29 July 2021). The contigs carrying *bla*_{CTX-M} genes were extracted for the identification of plasmid types by PlasmidFinder software. Multilocus sequence types (MLST) and replicating type of plasmid were identified using MLST and PlasmidFinder (<https://cge.cbs.dtu.dk/services> accessed on 29 July 2021). Virulence factors were identified using the Virulence Factor Database (<http://www.mgc.ac.cn/VFs/main.htm> accessed on 13 September 2021). The heatmaps were visualized with the “pheatmap” package. The histogram, stack bar diagram, pie diagram, and line chart were plotted with “ggplot2” and colour was used with the “RColourBrewer” package. The χ^2 test and Fisher’s exact test were used to perform the statistical analysis. For all models, we considered $p < 0.01$ statistically significant and then performed 2-sided probability on those results by using SPSS version 23.0.

5. Conclusions

In conclusion, we identified 330 *bla*_{CTX-M}-positive *S. Typhimurium* isolates from the public database. Thirteen variants were found in the 330 members of the *bla*_{CTX-M} group, and *bla*_{CTX-M-9} was the most prevalent. The majority of *bla*_{CTX-M}-positive *S. Typhimurium* were obtained from humans and animals. The number of *bla*_{CTX-M}-positive *S. Typhimurium* increased annually. These isolates were primarily detected in China, the United Kingdom, Australia, the USA and Germany. In addition, these isolates possessed 14 distinct ST, and three were predominant: ST34, ST19, and ST313. The majority of ST34 *S. Typhimurium* isolates were distributed in China and were mainly from swine. However, the majority of ST19 were distributed in the United Kingdom and Australia. The major types of *bla*_{CTX-M}-carrying plasmid were identified as IncI plasmid and IncHI2 plasmid. In addition, *bla*_{CTX-M} co-existed with nine antibiotic-resistant genes with a detection rate of over 50%, conferring resistance to five classes of antimicrobials. The 154 virulence genes were detected among these isolates, of which 107 virulence genes were highly common. This study provides new

insights into clinical antibiotic therapy for *Salmonella* infection and provides a foundation for further scientific research.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/antibiotics10111417/s1>, Figure S1: The analysis of hosts carrying the most common CTX-M allelic variants; Table S1: The detection rate of 154 virulence genes in 330 *bla*_{CTX-M}-positive *S. Typhimurium* isolates.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in supplementary material.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviation

The lists of abbreviation used in this study.

MLST	Multilocus sequence types
WGS	Whole genome sequencing
Inc	Incompatible
ARGs	Antibiotic resistance genes
WHO	World Health Organization
ESBL	Extended-spectrum β -lactamase
SPI	<i>Salmonella</i> pathogenicity island
TTSS	Type III secretion system
NCBI	National Center for Biotechnology Information

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