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Current Status and Spatiotemporal Evolution of Antibiotic Residues in Livestock and Poultry Manure in China

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Abstract: The use of antibiotics in the livestock and poultry industries has raised significant concern about environmental and health problems. In light of this, accurate knowledge of antibiotic residues in livestock and poultry manure is important for pollution management and strategic decision-making at the national level. This study aims to provide a comprehensive report on antibiotic residues in livestock and poultry manure in China using the published data of 3751 livestock and poultry feces in 29 provincial-level units over the past 20 years. In this study, the overall status of antibiotic residues in livestock and poultry feces was analyzed by mathematical statistics. Moreover, the spatio-temporal variation characteristics were analyzed by spatial statistics, and the differences among livestock and poultry species were evaluated by subgroup analysis. The finding indicated that tetracyclines (TCs), quinolones (QLs), sulfonamides (SAs), and macrolides (MLs) were the most abundant residues in livestock and poultry manure. The spatial and temporal variation revealed that the overall trend of antibiotic residues decreased gradually, and the spatial distribution was primarily concentrated in the southeast of Hu Line, exhibiting a "northeast-southwest" distribution. The distribution range also decreased slightly, with the residues of tetracyclines (TCs), quinolones (QLs), sulfonamides (SAs), and pleuromutilins (PMs) showing a significant spatial hot spot. The center of gravity of antibiotic residue shifted to the southwest between 2003 and 2021. In comparison to cow and sheep manure, the tetracyclines (TCs), sulfonamides (SAs), and macrolides (MLs) in pig and chicken manure were higher. The results can serve as a reference for the control and reduction of antibiotic pollution in livestock and poultry manure, as well as the wise utilization of those resources and achieving goals for clean agriculture.

Keywords: antibiotic; manure of livestock and poultry; spatial distribution; livestock and poultry species

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1. Introduction

The environmental and health problems caused by antibiotics have received widespread attention. The three main sources of antibiotics in the environment are livestock farms, wastewater treatment plants, and chemical manufacturing plants [1]. Antibiotics used in livestock and poultry are not fully absorbed by animals. Approximately 60–90% of the antibiotics remain in animal manure in their original form or as metabolites, and these antibiotics eventually make their way into agricultural soils as organic fertilizers [2]. The introduction of antibiotics into the environment may affect soil microorganisms, thereby affecting soil nutrient cycling, enriching and poisoning plant tissues, and leading to the development of drug-resistant bacteria and antibiotic resistance genes (ARGs) in the environment [3,4]. According to One Health's concept of human-animal-environmental integration, antibiotics left in animal feces could end up posing potential health risks to humans [5].

At present, there is no threshold limit for antibiotic residues applied in animal manure as organic fertilizer in China. In order to improve the measures of returning livestock and poultry manure to farmland and to prevent antibiotic pollution of the farming environment from the source, it is helpful to understand the antibiotic residues in livestock and poultry manure. However, large-scale investigations of antibiotic residues in livestock and poultry manure face many challenges. On the one hand, antibiotic detection requires high-performance analytical techniques (e.g., detection limit, limit of quantitation) [6]. On the other hand, it is currently difficult to advance a general method for veterinary antibiotic determination due to the abundance of species and complex residues [7]. Because of these challenges, large-scale antibiotic testing investigations are costly and difficult to achieve. Subject to the constraints of the aforementioned factors, the main problem to be addressed in this study is how to express the spatio-temporal characteristics of antibiotic residues in livestock and poultry manure in China.

Meta-analysis is an efficient method for extracting empirical data through statistical analysis using published literature in order to achieve a comprehensive study of the entire scale system [8]. Currently, the method has been extensively used in agriculture, ecology, and other fields. In recent years, meta-analysis has been used to characterize antibiotic residues and pollution in the environment [9,10], proving its feasibility in the study of antibiotic residues in livestock and poultry manure. However, the object of relevant research is mainly single livestock and poultry manure, and the residual environment is concentrated primarily in soil, surface waters, and vegetation. Overall, antibiotic residues in livestock and poultry manure in China are not well analyzed and researched.

Therefore, in this study, we focus on the spatio-temporal pattern and driving factors of antibiotic residues in livestock and poultry manure in China. A total of 151 articles published between 2003 and 2021 were retrieved from the study cases. In addition to characterizing the antibiotic residues in manure from different livestock and poultry species, spatial statistics were used to characterize the spatial distribution and migratory patterns of antibiotics. Moreover, subgroup analysis was conducted in addition to the analysis of key driving factors. The results of this study will contribute to the management of the resource use of livestock and poultry manure in China and the formulation of relevant policies.

2. Materials and Methods

2.1. Data Sources and Extraction

In this study, all case data were collected from major research articles on antibiotic residues in livestock and poultry manure in mainland China published between 1 January 2003 and 31 October 2022. Using "livestock and poultry" or "pigs, chickens, cattle, sheep", "antibiotics" or single antibiotics (tetracyclines, quinolones, sulfonamides, macrolides, pleuromutilins, β-lactam, aminoglycosides, lincosamides, chloramphenicol, cephalosporins, polypeptides, nitroimidazoles, nitrofurans) and "feces" or "manure" as the key words, the search was performed on the China National Knowledge Network (CNKI) database and Web of Science, using a search of literature.

Selection criteria for the study cases are: (1) the study site must be within mainland China; (2) it must be field measured data, excluding artificial summary data; (3) the data must be the study of antibiotic levels in livestock and poultry manure, excluding urine, sewage, etc.; (4) the source of antibiotics in fecal matter must be routine farmed excretion, excluding artificial addition and feeding control.

2.2. Data Extraction and Preprocessing

2.2.1. Data Extraction

The data extracted from each paper includes the following: (1) first author, title, and year of publication; (2) the sampling location, which should be subject to the provincial unit; (3) sampling time (year); (4) type of antibiotic/mean value/number of samples (with each farm as a sample); (5) species of livestock and poultry, including pigs, chickens, cattle, and sheep.

2.2.2. Tests and Sensitivity Analyses of the Data

Following data extraction, the database was separated into six files based on the types of antibiotics used and then classified into studies based on region and livestock species. Then, data extremes and publication bias were tested. According to distribution statistics, there are extreme values. However, since this study is observational, extreme values must be included in the analysis as objective conditions. This study suffers from a significant publication bias, as researchers and readers tend to pay more attention to livestock and poultry with a high level of antibiotic residues in their feces. On the other hand, it is preferable to publish papers in the area of specific livestock and poultry (livestock and poultry that account for a large proportion of the breeding industry). Thus, the subgroup analysis of cattle and poultry species in the present study may well compensate for publication bias.

2.3. Geographic Centroid and Trajectory of Migration Calculations

2.3.1. Geographic Centroid Calculations

In this study, the centroid model was used to compute the geographical centroid of antibiotic residues. Using this method, the location (longitude and latitude) can be estimated from the centroid of antibiotic residues over the time period under study. The coordinates of the geographic centroid of antibiotic residues were calculated using the following equation:

$$X_t = \frac{\sum_{i=1}^{n} (A_{i,t} \times X_i)}{\sum_{i=1}^{n} A_{i,t}}$$

$$Y_t = \frac{\sum_{i=1}^{n} (A_{i,t} \times Y_i)}{\sum_{i=1}^{n} A_{i,t}}$$

where X_t and Y_t are the coordinates of the geographic centroid of antibiotic residues in the t year of province i, X_i and Y_i are the coordinates of targeted province i, n represents the number of provinces in which antibiotic residues were detected in livestock and poultry manure, and $A_{i,t}$ denotes mean value of antibiotic residues in the t year of province i (μg/kg). The values of t are four sections: 2003–2007, 2008–2012, 2013–2017, and 2018–2021.

2.3.2. Trajectory of Migration of the Geographic Centroid

The angle (θ) and distance (d) of the centroid moving were calculated using the following equations:

$$\theta = \arctan\left[\frac{Y_{k+m} - Y_k}{X_{k+m} - X_k}\right]$$

The distance of the centroid moving as follows:

$$d = \sqrt[2]{\left[(X_{k+m} - X_k)^2 + (Y_{k+m} - Y_k)^2\right]}$$

θ is the angle of centroid moving; d is the distance of centroid moving (km); G_k (X_k, Y_k) and G_{k+m} (X_{k+m}, Y_{k+m}) denote coordinates of the geographic centroid of antibiotic residues in the k year and $k + m$ year, respectively; m represents the interval between the k year and the $k + m$ year.

2.4. Standard Deviational Ellipse

The standard deviation ellipse (SDE) is a spatial statistical method that can accurately depict the spatial distribution characteristics of geographical elements [11]. The center of the SDE is the geographic centroid of the antibiotic in the manure. The direction of the major axis of the SDE (the angle between the major axis and true north and clockwise rotation) reflects the trend direction of antibiotic residue distribution in livestock and poultry manure, while eccentricity (the ratio of the major axis to the minor axis) reflects the spatial distribution of elements. The surface of the SDE reflects the dispersion of the elements. The direction of SDE is determined using the formula below:

$$\alpha = \frac{\left[\left(\sum_{i=1}^{n} \widetilde{x}_i^2 - \sum_{i=1}^{n} \widetilde{y}_i^2\right) + \sqrt{\left(\sum_{i=1}^{n} \widetilde{x}_i - \sum_{i=1}^{n} \widetilde{y}_i\right)^2 + 4\left(\sum_{i=1}^{n} \widetilde{x}_i\widetilde{y}_i\right)^2}\right]}{2\sum_{i=1}^{n} \widetilde{x}_i\widetilde{y}_i}$$

The standard deviation of the XY axis in SDE is expressed as follows:

$$d_x = \sqrt{2}\sqrt{\frac{\sum_{i=1}^{n}\left(\widetilde{x}_i\cos\alpha - \widetilde{y}_i\sin\alpha\right)^2}{n}}$$

$$d_y = \sqrt{2}\sqrt{\frac{\sum_{i=1}^{n}\left(\widetilde{x}_i\sin\alpha + \widetilde{y}_i\cos\alpha\right)^2}{n}}$$

where, $\widetilde{x}_i$ and $\widetilde{y}_i$ denote the coordinates of each study object to the SDE center; α is the angle of elliptic rotation (i.e., the angle between the major axis and true north and clockwise rotation); d_x and d_y represent the standard deviation along the X-axis and Y-axis, respectively.

2.5. Hotspot Analysis (Getis-Ord Gi*)

Hotspot analysis is a spatial statistical method to study spatial clustering. Using hotspot analysis, it is possible to obtain the location of clusterings of high- or low-value elements in space. Its principle is to look at each factor in the adjacent factor environment. The factor should have a high value and be surrounded by other factors with a high value; that is, the factor should become a hot spot with significant statistical needs.

2.6. Data Analysis

Excel 2021 was used for data preprocessing and statistical analysis. SPSS 26 was used for one-way analysis of variance. ArcMap 10.8 and Origin 2022 were used for spatial statistical analysis and mapping, respectively.

3. Results

3.1. Overall Status of Antibiotic Residues in Livestock and Poultry Manure

The overall status of antibiotic residues in livestock and poultry manure in China is presented in Table 1 below. Antibiotic residues were found in the feces of 3751 livestock and poultry farms in 29 provinces. As illustrated in Table 1, monitoring studies mainly focus on tetracyclines (TCs), quinolones (QLs), sulfonamides (SAs), macrolides (MLs). and pleuromutilins (PMs), indicating that they have higher attention and data quality.

Table 1. Statistics on antibiotic residues in livestock manure in China.

Element	Tetracyclines	Quinolones	Sulfonamides	Macrolides	Pleuromutilins	Others	Total
Provinces	29	26	24	19	16	19	29
Farms	3402	2456	2613	1701	583	1658	3751
Mean [a]	18,779.52	1689.09	1929.71	1414.92	336.45	1457	7845.99
Standard deviation	80,722.66	21,724.75	5551.21	8269.28	753.80	5278.50	50,370.85
Species	pig, chicken, cattle, sheep	pig, chicken, cattle, sheep	pig, chicken, cattle, sheep	pig, chicken, cattle, sheep	pig, cattle	pig, chicken, cattle	pig, chicken, cattle, sheep

[a] Unit: μg/kg.

The mean of antibiotic residues could reflect the overall situation of antibiotic residues in livestock and poultry manure, such that TCs > SAs > QLs > others > MLs > PMs. The degree of scatter in the data was reflected in the standard deviation. Results indicated that the contents of all kinds of antibiotics showed a high degree of dispersion, i.e., the residual amount of antibiotics in livestock and poultry manure was highly variable across the country. Therefore, it was crucial to analyze the space and time dimensions and subgroups.

3.2. Spatial Distribution of Antibiotic Residues in Livestock and Poultry Manure

According to the natural break point (Jenks) classification method, the antibiotic residues in TCs, QLs, SAs, MLs, PMs, and others were categorized into six levels, representing the average antibiotic residues in livestock and poultry manure in each province (Figure 1). Dark-to-light colors represent antibiotic residues from high to low concentrations. Using the mean of each case as the weight, the SDE was calculated for each type of antibiotic residue. SDE covers 63% of the antibiotic residues in China, indicating the trend and rule of sample distribution with antibiotic residues as the weight.

Generally, the spatial distribution of the antibiotics showed that areas with high antibiotic residue were primarily concentrated in the southeastern part of the Hu Line (the eastern and southern provinces of China). Hu Line, which is a contrast line for dividing the population density in China, has also become the dividing line of urbanization level. The spatial distribution of antibiotic residues in China indicated significant variations, and the overall distribution of the residual antibiotic concentrations was in the "Northeast-Southwest" ward. The distribution of residual antibiotic concentrations in TCs and others was noticeably in the direction of "Northeast-Southwest", with the rotation angles of SDE 40.34° and 58.52°, respectively. The SDE rotation angle of antibiotic residue QLs, on the other hand, was 11.28°, and the direction of the distribution was closer to the "South-North" distribution. The SDE rotation angles of SAs, MLs, and PMs were 86.39°, 84.84°, and 77.51°, respectively, and the distribution direction was closer to the "East-West" distribution.

The area under the SDE curve reflected the spatial dispersion of antibiotic residues in livestock and poultry manure. According to the SDE area, QLs, PMs, and others showed a higher spatial aggregation effect than TCs, SAs, and MLs. The spatial accumulation of QLs was concentrated primarily in most of the regions of the provinces of Hebei, Shandong, Henan, Anhui, Jiangsu, Zhejiang, and Hubei. Spatially aggerated PMs are concentrated specifically in the provinces of Sichuan, Hunan, Jiangxi, Yunnan, and Guangdong. Others were mainly concentrated in Guangxi, Hunan, Hubei, Fujian, and Guangdong provinces.

Further revealing the spatial accumulation characteristics of antibiotic residues in cattle and poultry manure would aid in a more complete analysis of the spatial correlation of antibiotic residues. In this study, hot spot analysis (Getis-Ord Gi*) (95% confidence interval, CI) was performed for six classes of antibiotics to determine the local correlation types in each region from the perspective of statistics.

Results indicated that the six classes of antibiotics were statistically different in space, and there was a significant spatial correlation (95% confidence interval, CI) among the antibiotic residues of TCs, QLs, SAs, and PMs in livestock and poultry, and all of them were hot spots (Figure 2). The hotspot regions and their neighboring provinces had significant levels of antibiotic residues in the feces of livestock and poultry. Thus, the high-residue area of TCs could be judged to be Guangdong and its neighboring provinces. On the other hand, Shandong Province, Jiangsu Province, and neighboring provinces were regions with high residual QLs. Yunnan Province, Guangdong Province, and neighboring provinces were regions with high residual SAs. High residual PM was observed in Guizhou Province and its neighboring provinces.

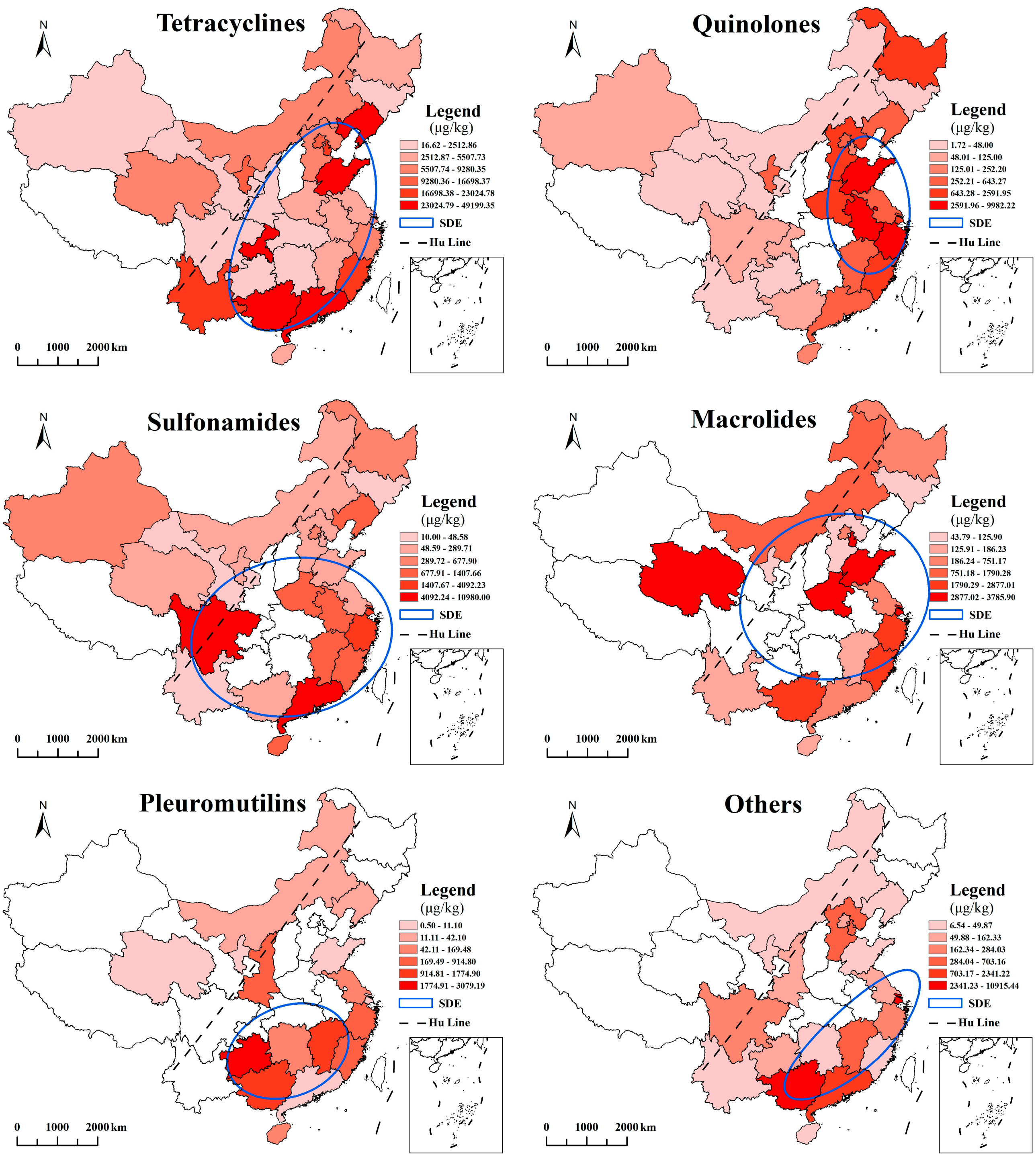

Figure 1. Classification maps of antibiotic residues in livestock and poultry manure (the standard map with the approval number GS (2022) 1873 downloaded from the Standard Map Service Network of the Ministry of Natural Resources, People's Republic of China, is made without modification of the base map).

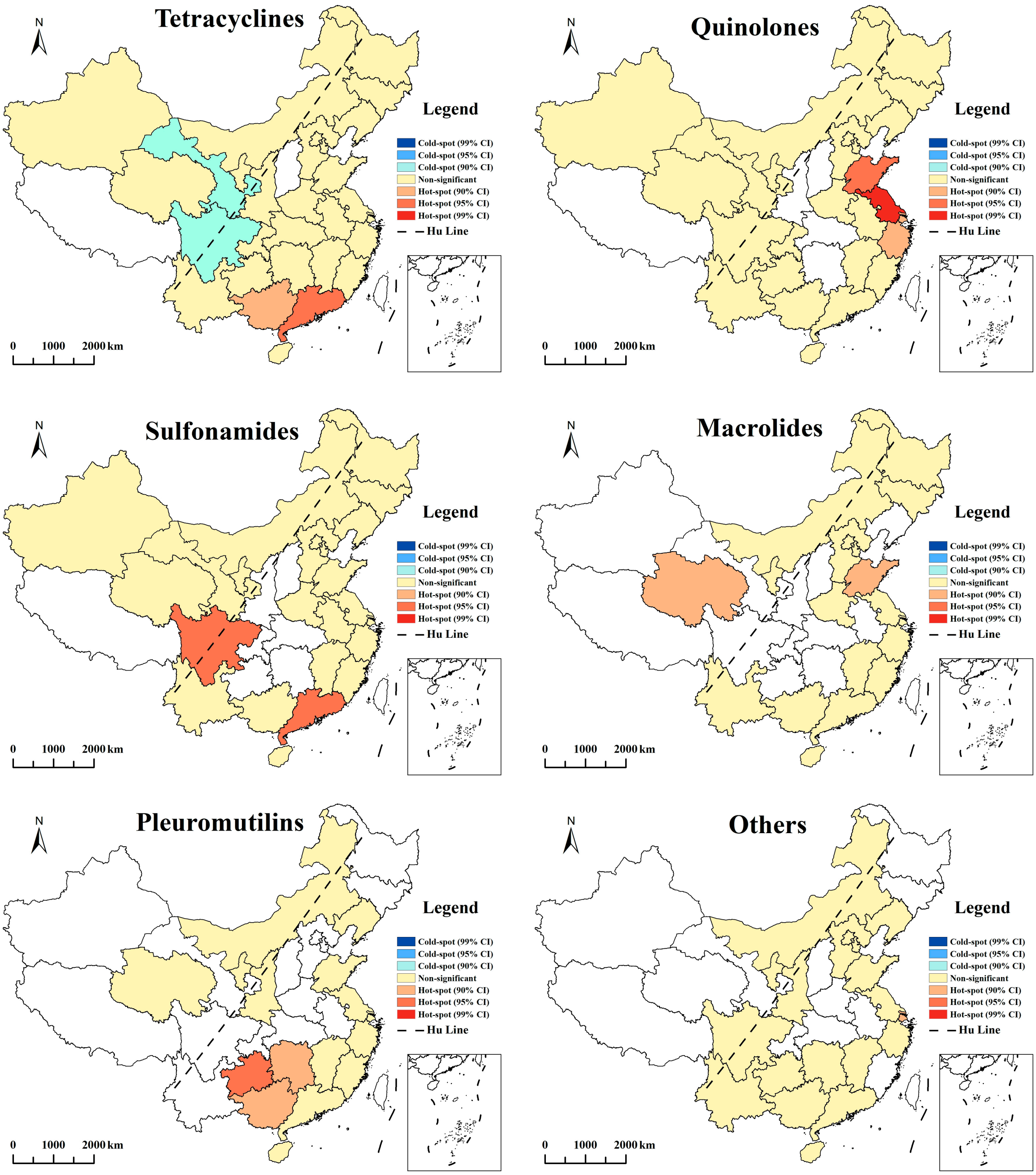

Figure 2. Cold and hot spot distribution maps of antibiotic residues in livestock and poultry manure (the standard map with the approval number GS (2022) 1873 downloaded from the Standard Map Service Network of the Ministry of Natural Resources, People's Republic of China, is made without modification of the base map).

3.3. Temporal Variation of Antibiotic Residues in Livestock and Poultry Manure

In this study, the residual amount of antibiotics in livestock and poultry manure in China was linearly fitted, and the overall trend showed a slow decline from 2003 to 2021, R^2 = 0.58 (Figure 3A). The results indicated that the antibiotic residues during this period decreased from 7457.56 μg/kg to 5342.86 μg/kg and fell by 28.36% with a mean annual rate of decline of 111.30 μg/kg.

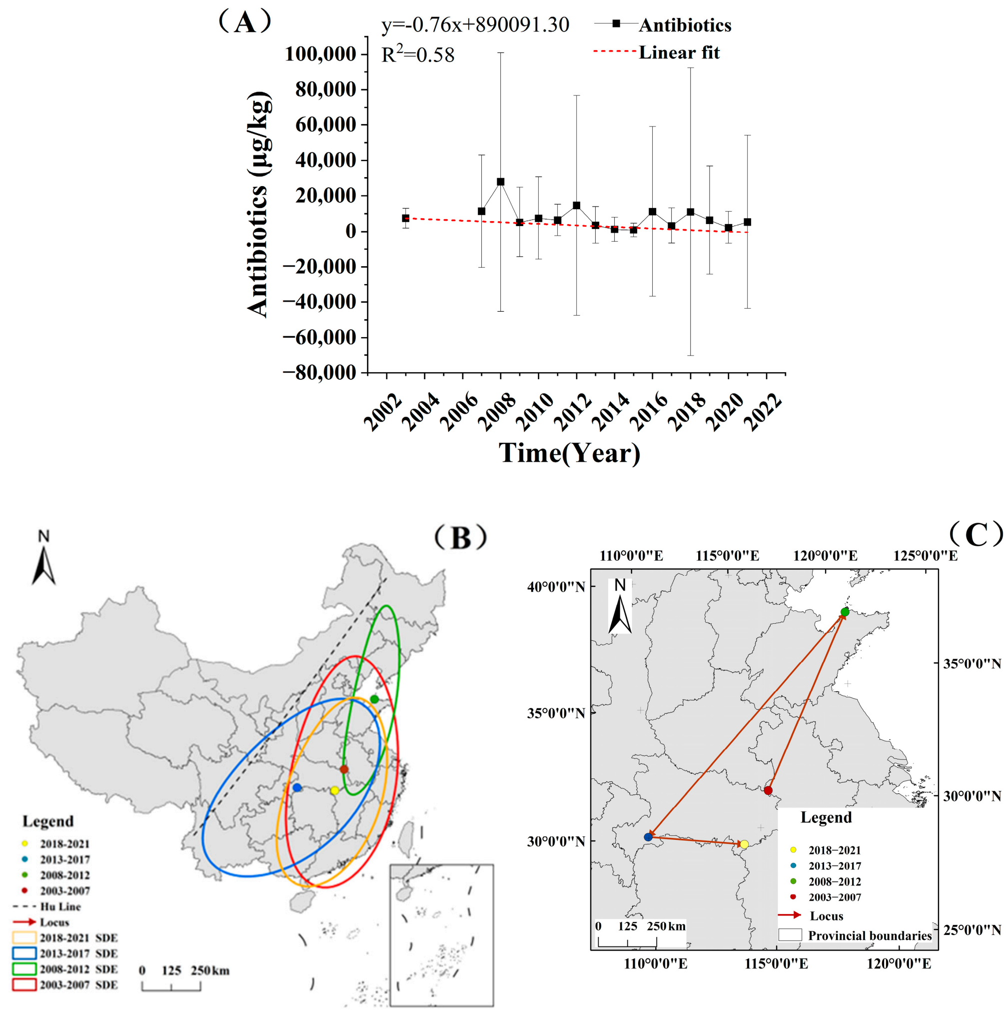

Figure 3. The spatial and temporal patterns of antibiotic residues in livestock and poultry manure in China. (**A**) Interannual trends in antibiotics. (**B**) Distribution of antibiotics in different periods (**C**) Migration trajectory of the antibiotic center of gravity. (The standard map with the approval number GS (2022) 1873 downloaded from the Standard Map Service Network of the Ministry of Natural Resources, People's Republic of China, is made without modification of the base map).

Due to the small number of sampling points in some years from 2003 to 2021, it was impossible to represent the whole year. Therefore, this study considered only five years as a stage and divided it into four periods for analysis. As it was clearly indicated, the X standard distance of the SDE exhibits a "northeast-southwest" trend throughout the entire time period (Figure 3C, Table 2). The X standard distance of remnant antibiotics over the 19 years was 9.08 km. The Y standard distance and the area of the ellipse were decreased by 228.71 km and 41.25 $\times$ 10^4 km^2, respectively. This study showed that the accumulation effect of antibiotic residues in cattle and poultry manure was slightly serious in the "northeast-southwest" direction, and the overall range of distribution was reduced. The clustering effect increased substantially between 2008 and 2012. At 120.54° E and 38.06° N, the ellipse with 258.65 km and 1096.30 km as the X and Y standard distances, respectively, might contain 63% of the antibiotic residues in the manure of livestock and poultry in China, with the district covering most of the provinces of Jilin, Liaoning, Hebei, Shandong, Jiangsu, and Anhui. This result may be related to the changes in the main livestock species and common livestock diseases in different regions.

Table 2. Migration and change of geographical center of gravity of antibiotic residues in livestock and poultry manure in China from 2003 to 2021.

Time	Center X (°)	Center Y (°)	X Stddist (km)	Y Stddist (km)	Area (10^4 km^2)	Direction (°)
2003–2007	115.45	31.77	531.87	1299.48	217.10	9.78
2008–2012	120.54	38.06	258.65	1096.30	89.05	15.28
2013–2017	109.87	30.34	675.38	1178.73	250.08	42.22
2018–2021	114.11	29.66	522.79	1070.77	175.85	19.50

The geographic centroid of antibiotic residues in livestock and poultry manure showed noticeable spatial migration between 2003 and 2021. It migrated 252.66 km to the southwest by 9.03°, and the geographic centroid of antibiotic residues migrated from the west of Anhui to the southeast of Hubei. During each time period, the mean migration rate was 853.82 km/5a. The geographic centroid rate of antibiotic residue during 2008–2012 and 2013–2017 was the highest, and it migrated 1310.69 km in the southwest direction at 28.4°.

3.4. The Variation of Antibiotic Residue Contents among Different Livestock and Poultry Species

Since livestock and poultry species could also affect antibiotic residues in manure, the variation of antibiotic residues among different livestock and poultry species was presented in this study. A subgroup analysis of antibiotic residues in the manure of different livestock and poultry species was conducted (Figure 4). According to the weighted mean values, there were three distinct groupings of variation. TCs, SAs, and PMs, which have larger residues in pig manure, were part of the first group. In contrast, the second group (MLs) had the highest content of chicken manure. The third group (QLs, Others) had higher residues in cow manure.

TCs, SAs, and MLs residues showed significant differences in all kinds of livestock and poultry manure ($p < 0.05$). TCs in pig and chicken manure were significantly higher than those in cattle and sheep manure. On the other hand, the residues in cattle manure were significantly higher than those in sheep. The residual amount of SAs in pig manure was significantly higher than that of other animals' manure understudy. Moreover, the residual amount of SAs in chicken and cattle manure was significantly higher than that of sheep. Moreover, the residue of MLs in pig and chicken manure was significantly higher than that of sheep. Based on the forementioned expression, considering all animal manure understudy, it can be summarized that the highest and lowest antibiotic residues were investigated in pig and sheep manure, respectively, in this study. The differences between the residues of feces of QLs, PMs, and others in various types of livestock and poultry were not significant; thus, we shall refrain from delving into specifics at this point.

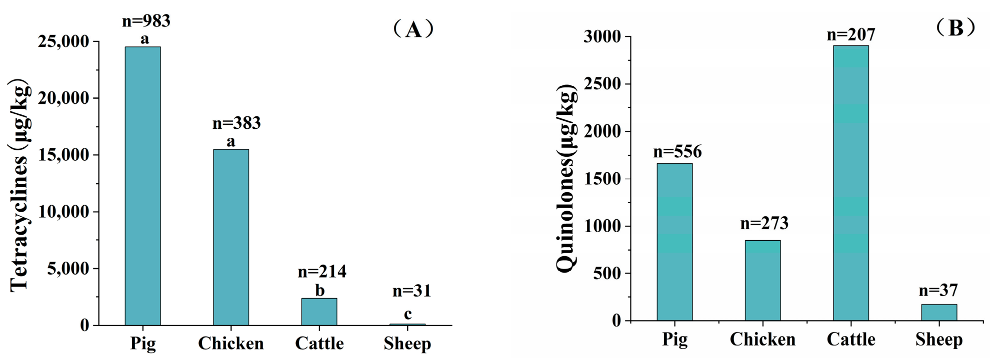

Figure 4. *Cont.*

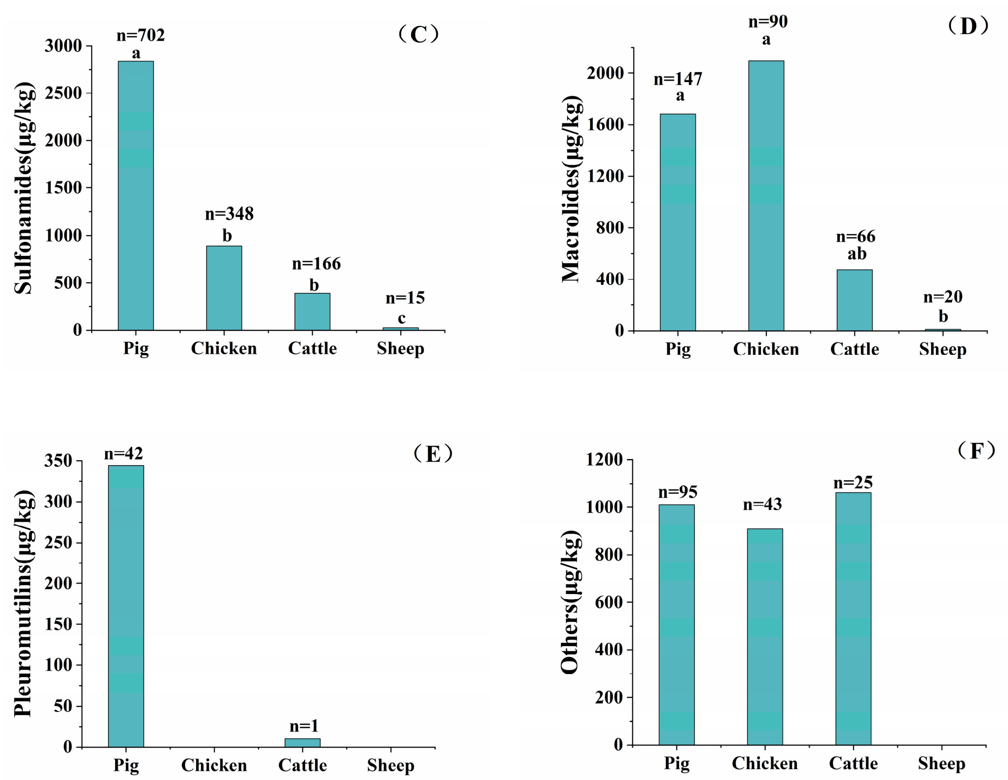

Figure 4. Antibiotic residues in the feces of different livestock and poultry species ("*n*" represents the number of samples in each group. The letter "abc" indicates the significance of the difference between the treatments, and two treatments with the same letter are not significant).

4. Discussion

4.1. Analysis of the Causes of Antibiotic Residues in Livestock and Poultry Manure in China

Antibiotics used in animal farms in China can be divided into feed medication, drug administration by drinking water, parenteral administration, and other routes of administration. According to the Official Veterinary bulletin (Table 3), 24,391.82 tons of antibiotics were injected into the bodies of livestock and poultry through feed medication and drinking water administration during 2018–2020, accounting for 78.42% of the total amount of antibiotics administered throughout the year, among which 60–90% of antibiotics would be eliminated from the body with urine and manure [12–14]. Therefore, antibiotics excreted directly with drug prototypes were the main source of antibiotic residues in manure, which were absorbed into the bodies of livestock and poultry through feed medication and drug administration by drinking water.

Table 3. Ways of antibiotic administration for livestock and poultry in China.

Time	Feed Medication (%)		Drug Administration by Drinking Water (%)		Parenteral Administration (%)		Other Routes of Administration (%)	
	Dosage (t)	Ratio (%)	Dosage (t)	Ratio (%)	Dosage (t)	Ratio (%)	Dosage (t)	Ratio (%)
2018	18,525.66	62.22	5702.44	19.15	3566.02	11.98	1979.98	6.65
2019	19,102.79	61.81	5451.56	17.64	3492.65	11.30	2856.66	9.24
2020	13,184.73	40.23	11,208.27	34.20	3572.53	10.90	4810.76	14.68
Mean	16,937.73	54.75	7454.09	23.66	3543.73	11.39	3215.80	10.19

Based on the purpose of use, antibiotics for animals in China could be divided into two categories: growth promotion and therapeutic (before the Announcements 194 and 246 issued by the Ministry of Agriculture and Rural Affairs of the People's Republic of China). Growth-promoting antibiotics were mainly used to prevent disease and promote the growth of livestock and poultry. Research has shown that such antibiotics could promote the weight increase of livestock and poultry by 5–6% and increase the feed conversion rate by 3–4% [15,16]. There were several hypotheses about its growth-promoting mechanism, which mainly focused on intestinal microbial regulation and immune system regulation [17,18]. Therapeutic antibiotics were used to treat diseases in livestock and poultry. In China, from 2018 to 2020, antibiotics that have been used for growth promotion accounted for 53.2%, 48.12%, and 28.69% of total dosing, respectively. Despite the proportion gradually decreasing, dosing was still high at 15,412.68 t, 14,871.05 t, and 9403.21 t, respectively. In addition, most growth-promoting antibiotics were feed medication and drinking water administration by means of feed addition, and the main types were TCs (chlorotetracycline and oxytetracycline), accounting for about 22% of the total dosage, which was consistent with the highest antibiotic residues of TCs in livestock and poultry manure. Therefore, antibiotics used for growth promotion are one of the main causes of antibiotic residues in livestock and poultry manure.

In addition, the mean of antibiotic residues was that TCs > SAs > QLs > others > MLs > PMs in China. The most major reason maybe growth-promoting antibiotics were feed medication and drinking water administration by means of feed addition, and the main types were TCs (aureomycin, oxytetracycline), accounting for about 22% of the total dosage, which was consistent with the highest antibiotic residues of TCs in livestock and poultry manure. The residual amount of SAs ranked second, mainly because there are many varieties of SAs, which are mainly used to prevent and treat bacterial infections such as diarrhea. At present, it is also one of the most used veterinary antibiotics; the adsorbability and degradability of SAs in animal intestines are poor, and a large proportion of drug prototypes will be excluded in vitro. In addition, veterinary antibiotic half-lives in animal manure are also important factors affecting residual quantity. TCs, QLs, and SAs have a long half-life of approximately 100 days, whereas MLs and β-Lactam have a very short half-life.

One of the major reasons for antibiotic residues in the manure of different livestock and poultry species was the imbalanced development of the livestock and poultry industries. According to the China Animal Husbandry and Veterinary Yearbook, the number of pigs and poultry raised in China in 2020 will account for 35.27% and 41.68%, respectively, while the total number of cattle and sheep raised will account for 12.9%. Rapid farming development was the main reason for antibiotic residues in pig and poultry manure. Moreover, the physiological structure of livestock and poultry may also cause the difference in antibiotic residues in manure. For example, the intestine of poultry was shorter than that of vertebrates, which may result in shorter gut residence times, less absorption, and greater excretion of antibiotics administered in mixed diets [19].

4.2. The Cause of Spatial and Temporal Variation in Antibiotic Residues

4.2.1. The Cause of Spatial Variation

The spatial distribution of antibiotic residue content in China showed significant variations. One of the reasons was that the distribution characteristics of antibiotic residues in livestock and poultry manure were directly affected by the development of the industry. An important index for the development of the breeding industry is the number of livestock and poultry raised. According to the China Animal Husbandry and Veterinary Yearbook (Figure 5A,B), the quantity of livestock and poultry breeding in China showed an overall increase of 9.38% from 2008 to 2021. Based on the spatial distribution, the breeding quantity in southeast and south-central regions, which were the centers of domestic industry, maintained rapid growth, and the distribution characteristics of antibiotic residues in livestock and poultry manure were largely consistent.

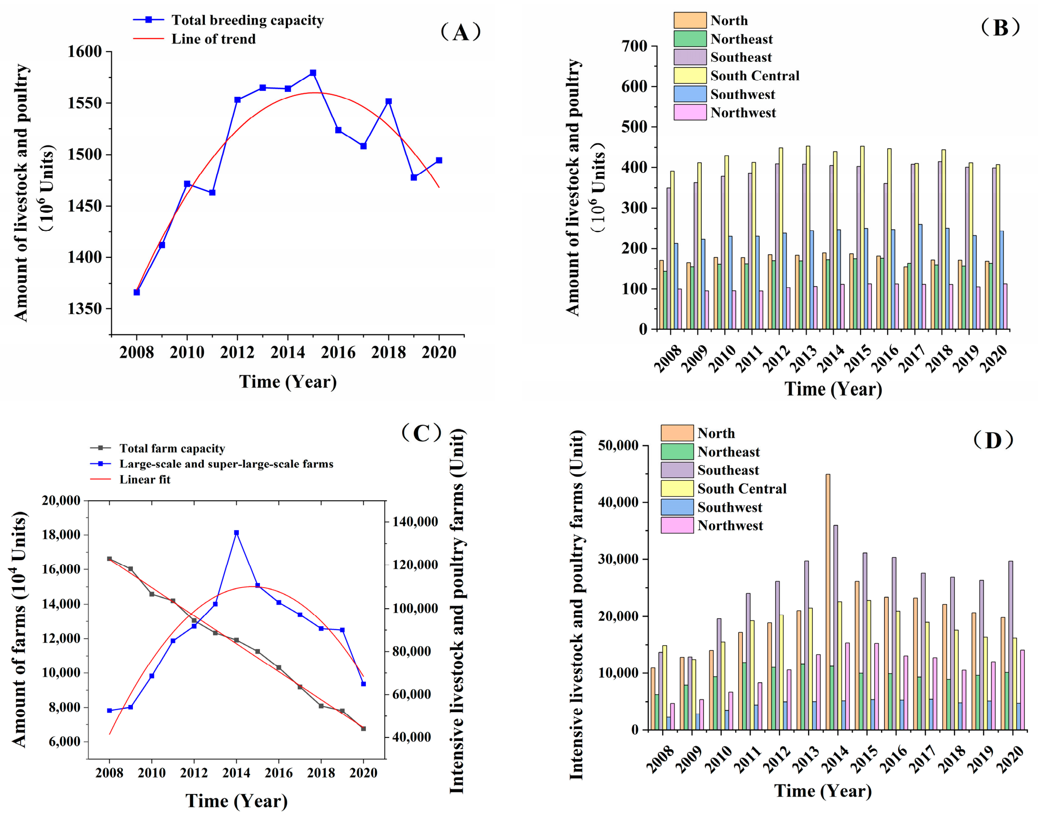

Figure 5. Development of the industry of livestock and poultry in China. (**A**). Amount of livestock and poultry which is converted to pig equivalent; (**B**) Amount of Livestock and poultry in six region of China; (**C**) Total number of farms and Intensive livestock and poultry farms; (**D**) Amount of intensive livestock and poultry farms in six region of China.

4.2.2. The Cause of Temporal Variation

Overall antibiotic residues in livestock and poultry manure decreased from 2003 to 2020 as a result of productivity, methods of breeding, policies, and regulations.

Intensive and large-scale farming could reduce antibiotic overuse in terms of environmental control and management, resulting in reduced antibiotic residues in livestock and poultry manure. According to the China Animal Husbandry and Veterinary Yearbook (Figure 5C,D), the total number of livestock and poultry farms decreased by 63.70% from 2008 to 2020. On the other hand, the number of large-scale and super large-scale livestock operations increased from 46,891 to 94,558 in 2008, with an overall increase of 101.65%. This clearly indicates that China's livestock and poultry breeding trends were shifting toward intensive large-scale breeding, while the number of small and medium aquaculture farms was gradually declining. Intensive and large-scale breeding can improve the efficiency of biosecurity prevention and control, help in the prevention and control of animal diseases, standardize production management, and effectively reduce antibiotic overuse, which is also one of the key factors for the decreasing trend of antibiotic residues in livestock and poultry manure in China. As the abuse of antibiotics in livestock and poultry farming has received increasing attention, the National Action Plan for Reducing the Use of Veterinary Antimicrobial Drugs (2021–2025) and the Veterinary Medicine Production Quality Management Practice (2020 revision) have been issued, which prohibit the production and sale of antibacterial feed additives for growth promotion by producers and sellers of veterinary drugs. Antibiotic abuse was fundamentally prohibited by policy and regulation. At the same time, antibiotic substitutes such as enzyme preparations, microbial preparations, traditional Chinese medicine preparations, and antimicrobial peptides have been developed and produced successively, realizing the reduction of antibiotics in a more environmentally friendly and sustainable way [20–22].

4.2.3. The Cause of Temporal Variation

The geographic centroid of antibiotic residues in livestock and poultry manure migrated visibly between 2003 and 2021, which was related to multiple factors such as industrial development, policy, and blight.

Since the 1990s, it can be broken down into two stages, with 2014 serving as the dividing point. The first stage was the development stage of improving quality and efficiency (1997–2014), and the second stage was the comprehensive transformation and upgrading stage focusing on environmental protection (2015–present) [23]. In the first stage, China promulgated a series of policies and measures to promote the development of animal husbandry, such as the Opinions of The State Council on Promoting the Sustainable and Healthy Development of Animal Husbandry, the Opinions of The State Council on Promoting the Sustainable and Healthy Development of the Dairy Industry and the National Development Plan for Beef and Mutton Production (2013–2020), and so on [24]. In this stage, China's animal husbandry was developing rapidly, and the breeding quantity in northeast China increased by 19.5%, higher than that in other parts of the country (Figure 5B). Its rapid growth may be accompanied by the abuse of antibiotics, which may be one of the important reasons for the migration of the geographic centroid of antibiotic residues to the northeast of China. In the second phase, in the context of vigorously promoting green agricultural development in China, livestock and poultry farming is an important part of Chinese agriculture, and the livestock and poultry pollution control problem has become a political issue. The Regulation on Pollution Prevention and Control of Large-scale Livestock and Poultry Farming is China's first administrative regulation on pollution prevention and control of agriculture and rural areas at the national perspective. Since then, pollution prevention and control in livestock and poultry farming have reached a turning point, and the policy of no-breeding areas has been implemented nationwide. The Action Plan for Soil Pollution Prevention, Control and the Action Plan for Water Pollution Prevention and Control and other environmental protection policies have been promulgated successively, resulting in "production restraint benefits" for livestock and poultry breeding. Moreover, the implementation of the above policies in the eastern region was better than that in the central and western regions, which directly led to the migration of livestock and poultry breeding areas to the west [25].

From 2003 to 2021, a number of large-scale livestock and poultry outbreaks occurred in China, including H7N9 bird flu in 2012 and 2014, Peste des Petits Ruminants (PPR) in 2014, and African swine fever in 2018. On one hand, the epidemic affected the quantity of livestock and poultry produced, and on the other hand, the densely populated eastern region and developed logistics increased the risk of epidemic inflow. These factors may also have contributed to the westward migration of the breeding industry and the relocation of the geographic centroid of antibiotic residues in the region [26,27].

4.3. Influence on Environmental Safety and Human Health

Farmland is the primary source of livestock and poultry manure. On agricultural land, manure (containing residual antibiotics) is often used as organic fertilizer. The introduction of antibiotics into the environment, such as farmland fertilization, will lead to environmental pollution [28]. Currently, there has been a great deal of research into the environmental pollution of antibiotics, which manifests itself primarily in three aspects: impact on soil micro-organisms, toxicity to plants and induction of resistance genes.

Antibiotics are not easy to degrade once applied to soil with manure [29], as they can be built up in the soil over a long time after biotransformation, leaching, adsorption/resolution, and other processes [30]. It is also possible that the mixed accumulation of multiple antibiotics may produce combined toxicity, which may affect the microbial species and community structure in the soil [31]. It has been reported that antibiotics can interfere with the community structure by changing the relative abundance of some microorganisms through selective action (inhibiting protein/cell wall/DNA synthesis), thus affecting the conversion of substances and nutrients in the soil. Moreover, the effects of antibiotics on the composition of the microbial flora can cause changes in the soil microbial population and genetic diversity [32].

Similar to the above-stated side effects, the toxic effects of antibiotics on plants are manifested in their effects on the rate of germination, root system, hypocotyl, and leaf growth, which can directly affect the yield of the crop [33–35]. Plant uptake of antibiotics is primarily active and complemented by passive uptake. Moreover, antibiotics present in soil are bioconcentrated (especially in vegetables) and can accumulate in plant tissues [36], posing a threat to the health of humans.

Residues of antibiotics in livestock and poultry manure directly lead to a pool of ARGs, which can cause pollution of ARGs in the environment [37–39]. ARGs have become a global public health problem [40]. The antibiotic screening pressure results in the production of antibiotic-resistant bacteria and ARGs. ARGs can be transferred between generations and between different bacteria, which may cause non-pathogenic bacteria to pass ARGs on to pathogenic bacteria, and the spread of ARGs will cause potential threats to the environment and human health [7,41]. It has been estimated that ARGs cause 25,000 deaths per year in the European Union alone and 700,000 deaths globally [42].

5. Conclusions

This paper reviewed monitoring-related studies about residues of antibiotics (i.e., TCs, QLs, SAs, MLs, PMs, etc.) in livestock and poultry manure from 2003 to 2021 in China. The average residues of TCs, QLs, SAs, and MLs in livestock and poultry waste in China are higher than others. The spatial and temporal changes showed that the overall residue showed a slow decline trend, and the spatial distribution was mainly concentrated in the southeast of the Hu Huanyong line, and the overall distribution was "northeastern-southwest", in which the residues of TCs, QLs, SAs, and truncated PMs showed significant spatial hot spots. From 2003 to 2021, the center of gravity of antibiotic residues shifted to the southwest. The TCs, SAs, and MLs in pig manure and chicken manure were higher than those in cow manure and sheep manure. Finally, we believe that the results of this study provide data support for understanding the status of antibiotic pollution in livestock and poultry manure in China and serve as a reference for the control and reduction of antibiotic pollution in livestock and poultry manure, which ultimately contributes to the implementation of wise utilization of those resources and achieving goals for clean agriculture in China.

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