Vancomycin-Resistant Enterococci (VRE) in Nigeria: The First Systematic Review and Meta-Analysis

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Abstract: Vancomycin-Resistant Enterococci (VRE) are on the rise worldwide. Here, we report the first prevalence of VRE in Nigeria using systematic review and meta-analysis. International databases MedLib, PubMed, International Scientific Indexing (ISI), Web of Science, Scopus, Google Scholar, and African journals online (AJOL) were searched. Information was extracted by two independent reviewers, and results were reviewed by the third. Two reviewers independently assessed the study quality using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. OpenMeta analyst was used. The random effect was used, and publication bias was assessed using a funnel plot. Between-study heterogeneity was assessed, and the sources were analysed using the leave-one-out meta-analysis, subgroup analysis, and meta-regression. Nineteen studies met the eligibility criteria and were added to the final meta-analysis, and the study period was from 2009–2018. Of the 2552 isolates tested, 349 were VRE, and E. faecalis was reported the most. The pooled prevalence of VRE in Nigeria was estimated at 25.3% (95% CI; 19.8–30.8%; I² = 96.26%; p < 0.001). Between-study variability was high (I² = 0.011; heterogeneity I² = 96.26% with heterogeneity chi-square (Q) = 480.667, degrees of freedom (df) = 18, and p = 0.001). The funnel plot showed no publication bias, and the leave-one-out forest plot did not affect the pooled prevalence. The South-East region had a moderate heterogeneity though not significant (I² = 51.15%, p = 0.129). Meta-regression showed that all the variables listed contributed to the heterogeneity except for the animal isolate source (p = 0.188) and studies that were done in 2013 (p = 0.219). Adherence to proper and accurate antimicrobial usage, comprehensive testing, and continuous surveillance of VRE are required.

Keywords: Enterococcus; vancomycin resistance; systematic review; meta-analysis; Nigeria

1. Introduction

Enterococcus is a Gram-positive and catalase-negative bacterium. It is an important gastrointestinal tract normal flora of most warm-blooded animals and humans [1,2]. However, different species of Gram-positive cocci could be an opportunistic pathogen causing various infectious diseases [3,4]. Enterococcus species especially Enterococcus faecium and Enterococcus faecalis are two common causes of urinary tract infection [5,6], inflammation of the lining of the heart and its valves, intra-abdominal abscesses, wound infections, bacteremia, and sepsis in human [7]. It has been proven that Enterococcus is the second leading cause of urinary tract and wound infections and the third leading cause of bacteremia in hospitals [8]. The inherent resistance to several antibiotics and their ability to cause infections has placed enterococci on the pedestal as an important hospital-acquired pathogen [9].
Hospital-acquired infection, especially that caused by Vancomycin-Resistant Enterococci (VRE), has been on the rise regardless of their low pathogenicity and virulence. VRE prevalence in the intensive care unit (ICU) of many hospitals worldwide is high and more so when patients have an underlying health condition such as diabetes mellitus, neutropenia, and impaired renal function [10]. In the treatment of infections caused by Enterococcus, vancomycin and sometimes with any other aminoglycoside, is used because of its bactericidal efficacy. These antibiotics are usually used to treat infections caused by methicillin-resistant Staphylococcus aureus and other Gram-positive bacteria [11,12]. Vancomycin is used as the last option in the treatment of Enterococcus [9] as its resistance to antibiotics is as a result of either an inherent or acquired machinery. Isolates of E. faecalis and E. faecium exhibit high resistance to vancomycin while the reverse is the case for E. gallinarum and E. flavescens as they exhibit low resistance [13]. Genetic elements known as van genes confer resistance to Enterococcus of which vanA and vanB present mostly in E. faecium occur the most and are well-distributed, especially among hospital isolates [13]. There is a disturbing trend following several reports on the resistance of enterococcus to linezolid and daptomycin, two potent antibiotics used against VRE infection [14,15] while Melese et al. [16] stated that the persistent increase in nosocomial infection caused by VRE is being reported by several studies.

One of the most important goals of meta-analyses is to provide an accurate and reliable result by increasing the sample size and reducing the width of the 95% CI from the range of the various applicable studies. Several studies are reporting VRE in Nigeria as a result of its role in the livestock industry and the health sector. Nigeria is beginning to generate a lot of revenue from the livestock industry recently as a result of the border closure. This simply means that a lot of farmers would want to sell their product in time and might result in the use of growth promoters such as avoparcin. It is therefore important that this sector is closely guarded given the risk of importation of an infected and tainted product. The knowledge of VRE distribution can be used to develop a policy to curtail the spread of resistant bacteria while addressing the prevention, control, and treatment as it is of public health significance. Such a policy would ensure that healthy livestock products are consumed, and resistant bacteria monitored. It is, however, necessary to obtain the pool prevalence of VRE in Nigeria from different sources using meta-analysis to enable the Nigeria Center for Disease Control (NCDC) to develop a policy and road map for its prevention and elimination. A meta-analysis would help us validate the results of various studies reporting VRE in Nigeria and put forward a measure that is accurate and reliable.

It is based on the above points that this paper was designed to determine the pooled prevalence of VRE using a systematic literature review and meta-analysis in Nigeria.

2. Results

2.1. Search Results and Eligible Studies

Figure 1 shows the search results. A total of 500 studies were found, of which 120 were left after duplicates were removed. Of the 120 studies screened for eligibility, 97 were excluded as they did not meet any of the inclusion criteria. Twenty-three full-text articles were assessed for eligibility with four excluded since vancomycin was not used in their antimicrobial susceptibility test and had insufficient information. A total of 19 full-text studies were used for quantitative analyses.
Figure 1. PRISMA flow diagram for the selection of eligible articles included in the study.

2.2. Characteristics of the Eligible Studies

All the 19 studies included in this review were cross sectional by design. Most of the studies were reported from the South-West region \( n = 8 \) [17–24]. Other studies include the North-Central region \( n = 3 \) [25–27], South-East region \( n = 3 \) [28–30], South-South \( n = 4 \) [31–34], and North-West region \( n = 1 \) [35]. No study was reported in the North-East region of the country. Of the 2552 isolates tested, 349 were VRE. The sample size ranges from as low as 7 [17] to as high as 658 [20] and prevalence as high as 88.9% in the South-South region [31] to as low as 1.1% in the North-Central region [27] (Table 1). The highest number of VRE \( n = 77 \) was isolated from environmental sources in the study conducted in the South-West region of Nigeria. The study analysed the highest number of specimens compared to others [20]. Most of the studies utilised the disk diffusion method in their antimicrobial susceptibility testing except for [18] and [27], who utilised agar dilution and VRE chromogenic agar, respectively (Table 1). The majority of the data included in analyses were from clinical studies \( n = 8 \) which involved clinical specimens, and environmental studies \( n = 7 \) with others from animal studies \( n = 4 \) (Table 1). Details of the characteristics of the included studies are summarized in (Table 1) below and a map showing the spatial distribution and number of studies of VRE in Nigeria is shown in Figure 2.

Only 12 studies reported the reported the prevalence of VRE according to species (Table 2). \textit{E. faecalis} was the most reported with a prevalence of 62.98% (148/235) followed by \textit{E. faecium} with a prevalence of 21.70% (51/235).
Table 1. Characteristics of the selected studies reporting prevalence of Vancomycin-Resistant Enterococci (VRE) in Nigeria.

| Author, Publication Year | Study Year | Study Area | Isolate Sources | Sample Size | Number Positive | Prevalence (%) | Detection Method |
|--------------------------|------------|------------|-----------------|-------------|----------------|----------------|-----------------|
| Olawale et al., 2011 [17]| 2009       | South-West | Clinical specimens | 7           | 3              | 42.9           | Disc diffusion  |
| Ayodeji et al., 2011 [18]| 2010       | South-West | Environmental    | 78          | 14             | 18             | Agar dilution   |
| Ogundeyinbo & Okusoo, 2013 [25]| 2012 | North-Central | Environmental | 95          | 32             | 33.7           | Disc diffusion  |
| Olawale et al., 2014 [19]| 2012       | South-West | Environmental    | 246         | 10             | 4.1            | Disc diffusion  |
| Anyanwu & Obetta, 2015 [28]| 2015       | South-East | Animal           | 75          | 5              | 6.7            | Disc diffusion  |
| Olawale et al., 2015 [20]| 2013       | South-West | Environmental    | 658         | 77             | 11.7           | Disc diffusion  |
| Ayeni et al., 2016 [21]| 2015       | South-West | Animal           | 60          | 39             | 65             | Disc diffusion  |
| Nsofor et al., 2016 [29]| 2016       | South-East | Clinical         | 34          | 7              | 20.59          | Disc diffusion  |
| Ekuma et al., 2016 [22]| 2013       | South-West | Clinical         | 319         | 13             | 4.07           | E test          |
| Adesida et al., 2017 [23]| 2017       | South-West | Clinical         | 65          | 9              | 13.85          | Disc diffusion  |
| David et al., 2017 [24]| 2017       | South-West | Clinical         | 69          | 27             | 39.13          | Disc diffusion  |
| Enenya et al., 2017 [35]| 2014       | North-West | Environmental    | 16          | 4              | 25             | Disc diffusion  |
| Ndubuisi et al., 2017 [26]| 2017       | North-Central | Clinical        | 102         | 34             | 33.3           | Disc diffusion  |
| Foka et al., 2018 [31]| 2018       | South-South | Environmental    | 9           | 8              | 88.9           | Disc diffusion  |
| Abasiubong et al., 2019 [32]| 2018 | South-South | Clinical         | 19          | 13             | 68.4           | Disc diffusion  |
| Anyanwu et al., 2019 [30]| 2018       | South-East | Animal           | 30          | 7              | 23.3           | Disc diffusion  |
| Igbinosa & Beshiru., 2019 [33]| 2018       | South-South | Animal           | 59          | 22             | 37.3           | Disc diffusion  |
| Igbinosa & Raje, 2019 [34]| 2017      | South-South | Environmental    | 64          | 23             | 35.9           | Disc diffusion  |
| Shettima & Iregbu, 2019 [27]| 2015      | North-Central | Clinical        | 545         | 6              | 1.1            | VRE Chromogenic agar |

Table 2. Species distribution of VRE across studies.

| Author, Publication Year | E. faecium | E. faecalis | E. gallinarum | E. casseliflavus | E. mundtii | E. hirae | E. dispar | Total |
|--------------------------|------------|-------------|---------------|------------------|------------|----------|-----------|-------|
| Olawale et al., 2011 [17]| 1          | 2           | -             | -                | -          | -        | -         | 3     |
| Olawale et al., 2014 [19]| -          | 10          | -             | -                | -          | -        | -         | 10    |
| Olawale et al., 2015 [20]| -          | 77          | -             | -                | -          | -        | -         | 77    |
| Nsofor et al., 2016 [29]| 4          | 3           | -             | -                | -          | -        | -         | 7     |
| Ekuma et al., 2016 [22]| 3          | -           | 9             | 1                | -          | -        | -         | 13    |
| Adesida et al., 2017 [23]| 6          | 3           | -             | -                | -          | -        | -         | 9     |
| David et al., 2017 [24]| -          | 27          | -             | -                | -          | -        | -         | 27    |
| Enenya et al., 2017 [35]| 2          | -           | 1             | 1                | -          | -        | -         | 4     |
| Ndubuisi et al., 2017 [26]| 12         | 10          | 1             | -                | 9          | 1        | 1         | 34    |
| Igbinosa & Beshiru., 2019 [33]| 13 | 8           | 1             | -                | -          | -        | -         | 22    |
| Igbinosa & Raje, 2019 [34]| 7          | 8           | -             | 2                | -          | 3        | 3         | 23    |
| Shettima & Iregbu, 2019 [27]| 3          | -           | 2             | -                | 1          | -        | -         | 6     |

|                  | 51 (21.7%) | 148 (62.98%) | 14 (5.96%) | 5 (2.13%) | 9 (3.83%) | 4 (1.70%) | 4 (1.70%) | 235 |
2.3. The Pooled Prevalence of VRE

The pooled prevalence of VRE in Nigeria was estimated at 25.3% (95% CI; 19.8–30.8%; \( I^2 = 96.26\% \); \( p < 0.001 \)) (Figure 3). Random-effects meta-analyses were carried out using the total sample size and number of positives (effect size, standard error of effect size) to estimate the prevalence of VRE in Nigeria. Between-study variability was high (\( t^2 = 0.011 \); heterogeneity \( I^2 = 96.26\% \) with heterogeneity chi-square (\( Q \)) = 480.667, degrees of freedom (df) = 18, and \( p = 0.001 \)).

![Figure 2. Spatial distribution and number of studies of VRE in Nigeria based on data extracted from eligible studies.](image-url)

![Figure 3. Forest plot showing the pooled prevalence of VRE in Nigeria.](image-url)
Sensitivity analysis using the leave-one-out forest plot revealed that no single study significantly influenced the heterogeneity and pooled prevalence of VRE (25.3%; 95% CI; 19.8–30.8%; \(p < 0.001\)) (Figure 4). The presence of publication bias was observed from the drawn asymmetric funnel plot (Figure 5) which indicates no publication bias.

2.4. Subgroup Meta-Analysis

Since this meta-analysis showed substantial heterogeneity, subgroup analysis was done using the study period, study area, isolate sources, and detection method to identify the possible sources of heterogeneity among the studies. The result of subgroup meta-analysis by study region revealed overall large variability in studies reporting the prevalence of VRE (the Higgins \(I^2\) statistic = 96.26% with heterogeneity chi-square (\(Q\)) = 480.667, degrees of freedom = 18, and \(p < 0.001\)). The Southeast

![Figure 4. Leave-one-out forest plot of VRE in Nigeria.](image)

![Figure 5. Funnel plot showing no publication bias.](image)
region was the only region with moderate heterogeneity, though not significant ($I^2 = 51.15\%$, $p = 0.129$), revealing a probable cause of heterogeneity. The overall statistics are shown in Table 3.

Table 3. Subgroup analysis for comparisons of the prevalence of VRE across study regions.

| Study Region      | Number of Studies | Prevalence (%) | 95% CI | $I^2$ (%) | $Q$     | Heterogeneity Test |
|-------------------|-------------------|----------------|--------|-----------|---------|--------------------|
| South-West        | 8                 | 20.7           | 13.1–28.2 | 95.5      | 155.404 | 7                  |
| North-Central     | 3                 | 22.4           | −3.6–48.3 | 97.81     | 91.227  | 2                  |
| South-East        | 3                 | 10.2           | 2.7–17.8  | 51.15     | 4.094   | 2                  |
| North-West        | 1                 | 25.0           | 3.8–46.2  | NA        | -       | -                  |
| South-South       | 4                 | 56.2           | 33.5–79.0 | 88.37     | 25.802  | 3                  |
| Overall           | 19                | 25.3           | 19.8–30.8 | 96.26     | 480.667 | 18                 |

Similarly, the result of subgroup meta-analysis by isolate source revealed the highest variability in isolates from clinical ($I^2 = 195.18\%$), followed by the environment ($I^2 = 95.33\%$), and animal sources ($I^2 = 96.37\%$). Isolates from environmental sources had the highest prevalence (27.2%, CI 17.3–13.2%). The overall statistics are shown in Table 4.

Table 4. Subgroup analysis for comparison of prevalence of VRE among isolate sources.

| Isolate Source  | Number of Studies | Prevalence (%) | 95% CI | $I^2$ (%) | $Q$     | Heterogeneity Test |
|-----------------|-------------------|----------------|--------|-----------|---------|--------------------|
| Clinical        | 8                 | 19.9           | 12.5–27.2 | 195.18    | 145.362 | 7                  |
| Environmental   | 7                 | 27.2           | 17.3–37.2 | 95.33     | 128.519 | 6                  |
| Animal          | 4                 | 32.9           | 5.1–60.7  | 96.37     | 82.535  | 3                  |
| Overall         | 19                | 25.3           | 19.8–30.8 | 96.26     | 480.667 | 18                 |

Further, the result of subgroup meta-analysis by the detection method revealed that 16 of the studies utilised the disc diffusion method in their antimicrobial susceptibility test accounting for a prevalence of 33.8% with a CI of 24.3–43.4% and $I^2$ of 93.84%. The overall statistics are shown in Table 5.

Table 5. Subgroup analysis for comparison of prevalence of VRE using various detection methods.

| Detection Method | Number of Studies | Prevalence (%) | 95% CI | $I^2$ (%) | $Q$     | Heterogeneity Test |
|------------------|-------------------|----------------|--------|-----------|---------|--------------------|
| Disc diffusion   | 15                | 33.8           | 24.3–43.4 | 93.84     | 227.406 | 14                 |
| Disc diffusion   | 1                 | 4.1            | 1.6–6.5  | -         | -       | -                  |
| Agar dilution    | 1                 | 17.9           | 9.4–26.5 | -         | -       | -                  |
| E test           | 1                 | 1.9            | 1.9–6.2  | -         | -       | -                  |
| VRE chromogenic agar | 1             | 1.1            | 1.1–0.2  | -         | -       | -                  |
| Overall          | 19                | 25.3           | 19.8–30.8 | 96.26     | 480.667 | 18                 |

Finally, the result of subgroup meta-analysis by study period revealed that the years 2017 and 2018 had four studies each, and the study period ranged from 2009 to 2018. The prevalence of VRE ranged from 42.9%, CI 6.2–79.5% in 2009 to 53.6%, CI 26.5–80.7%, indicating an increase in the prevalence of VRE over 10 years. The overall statistics are shown in Table 6.
Table 6. Subgroup analysis for comparison of prevalence of VRE across study periods.

| Study Period | Number of Studies | Prevalence (%) | 95% CI      | $I^2$ (%) | Q       | Heterogeneity Test |
|--------------|------------------|----------------|-------------|----------|---------|-------------------|
|              |                  |                |             |          |         | DF    | p        |
| 2009         | 1                | 42.9           | 6.2–79.5    | -        | -       | -     | -        |
| 2010         | 1                | 17.9           | 9.4–26.5    | -        | -       | -     | -        |
| 2012         | 2                | 18.5           | -10.4–47.5  | 97.14    | 34.954  | 1     | <0.001   |
| 2013         | 2                | 7.9            | 4.0–15.3    | 95.19    | 20.806  | 1     | <0.001   |
| 2014         | 1                | 25.0           | 3.8–46.2    | -        | -       | -     | -        |
| 2015         | 3                | 23.1           | 0.7–45.5    | 98.19    | 110.342 | 2     | <0.001   |
| 2016         | 1                | 8.3            | -0.7–17.4   | -        | -       | -     | -        |
| 2017         | 4                | 30.2           | 18.0–42.3   | 82.92    | 17.560  | 3     | <0.001   |
| 2018         | 4                | 53.6           | 26.5–80.7   | 90.54    | 31.711  | 3     | <0.001   |
| Overall      | 19               | 25.3           | 19.8–30.8   | 96.26    | 480.667 | 18    | <0.001   |

2.5. Meta-Regression

Meta-regression analysis was done for each variable included in the study individually. The variables included were study region, study year, isolate sources, and detection method. Continuous variables were subjected to assessment to observe a linear relationship with the independent effect size. Variables with $p$-values $<0.25$ were used in the multivariable meta-regression analysis. Independent variables such as study region, study year, isolate sources, and detection method had a reasonably significant value and were retained in the final multivariate analysis. Most of the variables were significantly associated with the prevalence of VRE in the final multivariate meta-regression except for the animal isolate source ($p = 0.188$) and studies done in 2013 ($p = 0.219$). Interestingly, all the variables listed contributed to the heterogeneity observed in this study except for the animal isolate source and studies done in 2013. No result was computed for the study period 2016–2018. The final multivariate meta-regression is shown in Table 7 below.

Table 7. Final multivariable meta-regression model.

| Variable             | Coefficient | p-Value | 95% CI       |
|----------------------|-------------|---------|--------------|
| Study area           |             |         |              |
| South-West Reference |             |         |              |
| North-Central        | 0.175       | 0.005   | 5.2–29.8     |
| North-West           | −1.044      | <0.001  | −142.1–66.7  |
| South-East           | −0.533      | <0.001  | −65.9–40.7   |
| South-South          | −0.286      | 0.003   | −47.7–9.4    |
| Isolates source      |             |         |              |
| Clinical Reference   |             |         |              |
| Animal               | 0.273       | 0.188   | −13.3–67.9   |
| Environmental        | 0.865       | <0.001  | 38.4–134.6   |
| Detection method     |             |         |              |
| Disc diffusion       |             |         |              |
| Reference            | −1.114      | <0.001  | −143.7–79.2  |
| Agar dilution        |             |         |              |
| E test               | 0.371       | <0.001  | 16.7–57.5    |
| VRE chromogenic agar | −0.917      | <0.001  | −113.9–69.6  |
| Study period         |             |         |              |
| 2009                 | Reference   |         |              |
| 2010                 | −1.132      | <0.001  | −147.8–78.6  |
| 2012                 | −1.177      | <0.001  | −148.9–86.5  |
| 2013                 | −0.093      | 0.219   | −24.1–55.0   |
| 2014                 | −0.230      | 0.041   | −45.1–0.9    |
| 2015                 | −0.688      | <0.001  | −87.9–49.6   |
| Constant             | 0.429       | 0.022   | 6.2–79.5     |
3. Discussion

To the best of our knowledge, this is the first study to determine the prevalence of VRE in Nigeria using systematic review and meta-analysis. For interventions to be accurately formulated, the prevalence of VRE needs to be known. The NCDC has a program in collaboration with the Federal Ministries of Health, Agriculture and Rural Development and Environment designed to checkmate antimicrobial resistance (AMR) [36]. A National AMR Technical Working Group (AMR-TWG) was inaugurated with members from several sectors such as human and animal health, food animal production, and the environment. The objective of this group is to analyse the situation of AMR in Nigeria and to develop an action plan for its prevention treatment and control. This is a robust plan, but the plan did not list VRE as a priority pathogen given that VRE is one of the most common causes of nosocomial infection worldwide.

The results presented in this report were from the analysis of data obtained through a systematic review of scientific publications on the prevalence of VRE at the country level between the years of 2009–2019, and the literature was heterogeneous. This review did not only take into consideration VRE in clinical settings but also in animals and the environment to get a holistic picture of VRE in Nigeria. The final meta-analysis of the prevalence was done only on 19 articles.

The random effect meta-analysis result showed high variability with Higgin’s $I^2$, which indicates that the variability between studies was not as a result of chance alone. The detection method, study region, study period, and clinical and environmental isolate source were highly significant predictors of the prevalence of VRE, indicating that these variables explain a substantial portion of the variability between studies. However, the animal isolate source and studies done in 2013 retained in the final meta-regression seem statistically insignificant in explaining the study variability.

Although considerable methodological differences between studies existed, these differences were pooled for this review. Therefore, the pooled prevalence of VRE in Nigeria was estimated at 25.3%. This indirectly indicates the potential existence of VRE, not only in health care settings but in in the environment as well as animals in Nigeria, and its likely spread to communities unless properly contained. Our estimate is comparable with reports from Malaysia 25% [37] but higher than those reported in Ethiopia 14.8% [16], Iran 14%, 18.75% [38,39], North America (21%), Asia (24%), Europe (20%) [40], Germany (9.8%) [41], Iran (9.4%) [42], the United Kingdom (9.2%) [43], and Singapore (9.3%) [44]. Our estimate was probably higher because our studies included animal and environmental sources in addition to clinical settings unlike all the studies listed above where they largely centred on clinical settings. This high prevalence could be as a result of various risk factors such as contact with VRE patients, infected animals, surfaces and objects, underlying conditions, serious illness, prior hospitalization, use of catheters, and improper antibiotic usage [45]. Camins et al. [46] stated that health care contacts were the likely source of VRE colonization and infection, and this is plausible in situations where infection control knowledge, attitudes, and practices among healthcare workers, farmworkers, and the general population are poor in third-world countries [47–50] and Nigeria [26].

The antimicrobial susceptibility testing mainly relied on the disc diffusion method and was interpreted according to the Clinical and Laboratory Standard Institute (CLSI) guideline. However, agar dilution and VRE chromogenic agar were also used. Another study in Iran by Shokoohizadeh et al. [51] reported a 48.9% higher prevalence in patients hospitalised than this study estimate. Adams et al. [52] stated that the prevalence of VRE tends to be higher in critically ill and hospitalised patients than non-hospitalised patients, unlike this present study where isolate sources were diverse. Another probable reason might be the study period as these studies were mostly done in the 1990s and 2000’s following the first reports of VRE [53,54], while the oldest study from our analysis was in 2009 and the earliest in 2019 where a ban was already placed on the indiscriminate use of vancomycin [55].

Results obtained from this review indicate that E. faecalis is the most reported VRE and this might be because most enterococcal infections are caused by E. faecalis [56] and can be treated with aminoglycosides and beta lactams. Because resistance to vancomycin is more regular in homogenous E. faecalis, administering of beta lactams should be at the forefront before the use of conventional
culture [56]. Arias and Murray [57] and Davis et al. [58] stated that most VRE infections were caused by \textit{E. faecalis}. This has changed as more VRE caused by \textit{E. faecium} are increasingly being reported [59–61] because of their resistance to different group of antibiotics which are mostly expensive [62,63]. In \textit{E. faecalis}, however, there is a marked difference in the occurrence and nature of resistance [64,65] even though \textit{E. faecalis} exhibit some level of acquired resistance.

Prevalence of VRE based on study area or region was also estimated. The highest estimated prevalence was in the South-South (56.2%) which is more than twice that estimated in the South-West (20.7%), North-Central (22.4%), South-East (10.2%) and North-West (25.0%). These regional differences could be ascribed to the type of environment and animal samples obtained, study period, the disparity in antibiotic use, detection method, and specimen type. No study or estimate was reported in the North-East of Nigeria. This is probably because this region has been plagued by insecurity as a result of insurgency which could deter researchers from conducting research [66].

According to data analyses for the isolate source, VRE prevalence was high in clinical, animal, and environmental sources and this is worrisome. These estimates indicate the depth of the spread of VRE in Nigeria and is one of the strengths of this study. Conducting these studies in different regions and isolates sources has provided a subtle picture of the prevalence in Nigeria. This does not give an in-depth explanation of the status of VRE in Nigeria, but it can be used as baseline information in its control.

In addition to obtaining isolates from different sources as strength of our study, our study also included a rigorous search with precise inclusion and exclusion criteria and we also observed frequently used specimens and methods of susceptibility testing. Several limitations also existed and these were our inability to report pooled estimates of VRE at the species level due to the limited number of included studies reporting enterococci at the species level, unavailability of studies from the Northeast region of Nigeria, which throws more question on the exact status of VRE in Nigeria, non-use of unpublished reports, and finally, the protocol of our study was not registered in PROSPERO.

4. Materials and Methods

4.1. Study Design and Protocol

The protocol of this study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P 2015) guidelines [67] (Supplementary file S1). The risk of bias across studies and the risk of bias graph are presented in Supplementary file S2.

4.2. Literature Review

A systematic review and meta-analysis were performed first by searching the PROSPERO database and database of abstracts of reviews of effects (DARE) (http://www.library.UCSF.edu) to check whether published or ongoing projects exist related to the topic. The literature search strategy, selection of studies, data extraction, and result reporting were done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. International databases MedLib, PubMed, ISI, Web of Science, Scopus, Google Scholar, and African journals online (AJOL) for published studies about the prevalence of VRE were also searched. PubMed was searched using the search strategy (“enterococcus”[MeSH Terms] OR “enterococcus”[All Fields]) AND (“nigeria”[MeSH Terms] OR “nigeria”[All Fields]), VRE [All Fields] AND (“nigeria”[MeSH Terms] OR “nigeria”[All Fields]), (“epidemiology”[Subheading] OR “epidemiology”[All Fields] OR “prevalence”[All Fields] OR “prevalence”[MeSH Terms]) AND (“vancomycin-resistant enterococci”[MeSH Terms] OR (“vancomycin-resistant”[All Fields] AND “enterococci”[All Fields]) OR “vancomycin-resistant enterococci”[All Fields] OR (“vancomycin”[All Fields] AND “resistant”[All Fields] AND “enterococci”[All Fields]) OR “vancomycin resistant enterococci”[All Fields] AND (“nigeria”[MeSH Terms] OR “nigeria”[All Fields]). Another search was also performed using keywords and their English equivalent (clinical infections, environmental
VRE, VRE in poultry and farm animals, Gram-positive bacteria, enterococci, antibiotic resistance, glycopeptide, vancomycin, and Nigeria) with all possible combinations. Also, the titles and references from selected articles were an additional search tool. To reduce bias, the search process was conducted independently by two authors.

4.3. Inclusion and Exclusion Criteria for Studies

We considered all cross-sectional or cohort studies that reported the prevalence of vancomycin resistance in Enterococcus isolates or numbers of VRE and total enterococci isolates in patients suspected of having clinical infection, in poultry, poultry/animal product, farmworkers, and the environment in Nigeria. We also included studies in which the standard method was used to detect VRE and were published or reported in English.

Exclusion criteria for the analysis were as follows: studies with insufficient information; studies on antimicrobial susceptibility tests other than vancomycin (studies that did not include VRE), studies having fewer than two isolates, studies not reporting enterococcal isolates separately (no population denominator), reviews, comments and duplications, case report studies, and studies that did not report the prevalence of VRE.

4.4. Data Extraction

After studies were identified based on their eligibility criteria, the first author’s name, the publication year, the date of the study, the study location, the number of cases involved in the studies, the study method, the source of isolates, the sample size, and the prevalence of VRE infections were extracted from the manuscripts. Two independent reviewers extracted all data from the articles included, and the results were reviewed by the third reviewer. Inconsistencies between the reviewers were decided by a consensus. The published studies were examined in three steps: title, abstract, and full text.

4.5. Data Analysis

Prevalence of VRE was calculated and subgroup analyses were done according to the study region, isolate sources, and detection method. Considering the existence of heterogeneity in observational studies conducted in diverse settings, the random-effects model was used in determining the pooled prevalence of VRE which prompted the use of the DerSimonian and Laird method of meta-analysis [68,69].

4.6. Bias and Heterogeneity Analysis

The qualities of the study methods (study area, isolate source, and detection method) were used to assess the within-study biases. The across-study bias (small study effects) was examined by funnel plots. The heterogeneities of study-level estimates were assessed by Cochran’s Q test. Non-significant heterogeneity was accepted if the ratio of Q and the degrees of freedom (Q/df) was less than one. The percentage of the variation in prevalence estimates attributable to heterogeneity was measured by the inverse variance index ($I^2$), and $I^2$ values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively [69]. In this meta-analysis, the $I^2$ value was high (96.26%) which is >75% an indication of significant heterogeneity. Due to this reason, the analysis was conducted using a random-effects model at 95% CI instead of the fixed-effects model. Funnel plot subgroup analyses were done if the heterogeneities were moderate to high. The sources of heterogeneity were analysed using the sensitivity analysis (leave-one-out meta-analysis), subgroup analysis, and meta-regression. Meta-analysis was performed using OpenMeta Analyst software version 10.10 [70].
5. Conclusions

We designed this study to obtain the pooled prevalence of VRE in Nigeria to provide baseline information to the National AMR Technical Working Group. The pooled prevalence of VRE in Nigeria was estimated at 25.3% (95% CI; 19.8–30.8%; $I^2 = 96.26%$; $p < 0.001$) and *E. faecalis* is the most reported VRE. The prevalence of VRE is on the rise in Nigeria seeing the trend from the oldest to the earliest studies. High variability between studies may influence the estimate pooled prevalence at the national level. This can be overcome by using advanced diagnostic techniques in the detection of VRE and the implementation of a nationwide survey to estimate the true prevalence of VRE in Nigeria. This report indicates that a program directly targeting VRE nationally be in place and VRE be listed as a priority pathogen to reduce the burden of the infection. Adherence to proper and accurate antimicrobial usage, comprehensive testing and ongoing surveillance of VRE infections in the health care, community and environmental settings are required.

Availability of Data and Materials: The datasets used and/or analyzed during the current study are included in the manuscript.

Supplementary Materials: The following are available online at http://www.mdpi.com/2079-6382/9/9/565/s1,
File S1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P 2015) guidelines
File S2: The risk of bias across studies and the risk of bias graph.

Author Contributions: Y.W. Conceived and designed the study; Y.W., C.Y.Y. select and assess quality of studies; extracted and analyzed data; Y.W., A.B.H. interpreted results; and drafted the manuscript. Y.W., A.R.Z. select and assess quality of studies; extracted data and interpret results. A.R.Z. interpret results and review the manuscript. All authors have read and agreed to the published version of the manuscript.

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References

1. Wada, Y.; Harun, A.B.; Yean, C.Y.; Zaidah, A.R.; Wada, Y. Vancomycin-Resistant Enterococcus: Issues in Human Health, Animal Health, Resistant Mechanisms and the Malaysian Paradox. *Adv. Anim. Vetern.-Sci.* 2019, 7, 1021–1034. [CrossRef]
2. Iseppi, R.; Di Cerbo, A.; Messi, P.; Sabia, C. Antibiotic Resistance and Virulence Traits in Vancomycin-Resistant Enterococci (VRE) and Extended-Spectrum β-Lactamase/AmpC-producing (ESBL/AmpC) Enterobacteriaceae from Humans and Pets. *Antibiotics* 2020, 9, 152. [CrossRef] [PubMed]
3. Adapa, S.; Naramala, S.; Boken, D.; Moreno, A.; Konala, V.M. Peritonitis from Anaerobic Gram-positive Cocci Likely Due to Translocation of Bacteria from Gut in a Patient Undergoing Peritoneal Dialysis. *Cureus* 2019, 11. [CrossRef] [PubMed]
4. Argudín, M. Ángeles; Deplano, A.; Meghraoui, A.; Dodémont, M.; Heinrichs, A.; Denis, O.; Nonhoff, C.; Roisin, S. Bacteria from Animals as a Pool of Antimicrobial Resistance Genes. *Antibiotics* 2017, 6, 12. [CrossRef]
5. Rostkowska, O.M.; Kuthan, R.; Burban, A.; Salińśka, J.; Ciebiera, M.; Mlynarczyk, G.; Durlik, M. Analysis of Susceptibility to Selected Antibiotics in Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis and Enterococcus faecium Causing Urinary Tract Infections in Kidney Transplant Recipients over 8 Years: Single-Center Study. *Antibiotics* 2020, 9, 284. [CrossRef]
6. Folliero, V.; Caputo, P.; Della Rocca, M.T.; Chianese, A.; Galdiero, M.; Iovene, M.R.; Hay, C.; Franci, G.; Galdiero, M. Prevalence and Antimicrobial Susceptibility Patterns of Bacterial Pathogens in Urinary Tract Infections in University Hospital of Campania “Luigi Vanvitelli” between 2017 and 2018. *Antibiotics* 2020, 9, 215. [CrossRef]
7. Banik, A.; Halder, S.K.; Ghosh, C.; Mondal, K.C. *Enterococcal Infections, Drug Resistance, and Application of Nanotechnology*, Springer Science and Business Media LLC: New York, NY, USA, 2020; pp. 417–445.
8. Bhardwaj, S.B. Enterococci: An Important Nosocomial Pathogen. In *Pathogenic Bacteria [Working Title]*; IntechOpen: Rijeka, Croatia, 2019.
9. Bender, J.K.; Cattoir, V.; Hegstad, K.; Sadowey, E.; Coque, T.M.; Westh, H.; Hammerum, A.M.; Schaffer, K.; Burns, K.; Murchan, S.; et al. Update on prevalence and mechanisms of resistance to linezolid, tigecycline and daptomycin in enterococci in Europe: Towards a common nomenclature. Drug Resist. Updat. 2018, 40, 25–39. [CrossRef]

10. Wada, Y.H.; Harun, A.; Yean, C.; Nasir, N.M.; Zaidah, A.R.; Wada, Y. Vancomycin-resistant enterococcus, obesity and antibiotics: Is there a possible link? Obes. Med. 2020, 18, 100226. [CrossRef]

11. Freitas, A.R.; Tedim, A.P.; Coque, T.M.; Jensen, L.; Novais, C.; Peixe, L.; Sánchez-Valenzuela, A.; Sundsfjord, A.; Hegstad, K.; Werner, G.; et al. Multilevel population genetic analysis of vanAandvanB Enterococcus faeciumcausing nosocomial outbreaks in 27 countries (1986–2012). J. Antimicrob. Chemother. 2016, 71, 3351–3366. [CrossRef]

12. Hansen, T.A.; Pedersen, M.S.; Nielsen, L.G.; Ma, C.M.G.; Søes, L.M.; Worning, P.; Østergaard, C.; Westh, H.; Pinholt, M.; Schoenning, K. Emergence of a vancomycin-variable Enterococcus faecium ST1421 strain containing a deletion in vanX. J. Antimicrob. Chemother. 2018, 73, 2936–2940. [CrossRef]

13. Lee, T.; Pang, S.; Abraham, S.; Coombs, G.W. Molecular characterization and evolution of the first outbreak of vancomycin-resistant Enterococcus faecium in Western Australia. Int. J. Antimicrob. Agents 2019, 53, 814–819. [CrossRef] [PubMed]

14. Lee, B.J.; Vu, B.N.; Seddon, A.N.; Hodgson, H.A.; Wang, S.K. Treatment Considerations for CNS Infections Caused by Vancomycin-Resistant Enterococcus faecium: A Focused Review of Linezolid and Daptomycin. Ann. Pharmacother. 2020, 106002802093251. [CrossRef]

15. Ross, J.L.; Rankin, S.; Marshik, P.; Mercier, R.-C.; Brett, M.; Walraven, C.J. Antimicrobial Stewardship Intervention and Feedback to Infectious Disease Specialists: A Case Study in High-Dose Daptomycin. Antibiotics 2015, 4, 309–320. [CrossRef] [PubMed]

16. Dagnaw, A.M.; Genet, C.; Andualem, T. Prevalence of Vancomycin resistant enterococci (VRE) in Ethiopia: A systematic review and meta-analysis. BMC Infect. Dis. 2020, 20, 1–12. [CrossRef]

17. Olawale, K.; Fadiora, S.; Taiwo, S. Prevalence of hospital acquired enterococci infections in two primary-care hospitals in Osogbo, Southwestern Nigeria. Afr. J. Infect. Dis. 2015, 2, 69. [CrossRef]

18. Oyedegi, O.; Olutio, P.O.; Owolabi, K.D.; Adeojo, K.A. Multiresistant faecal indicator bacteria in stream and well waters of Ille-ife city, southwestern Nigeria: Public health implications. J. Public Health Epidemiol. 2011. Available online: https://academicjournals.org/journal/JPHE/article-abstract/5C2D8F51666 (accessed on 22 March 2020).

19. Olawale, A.K.; Akinro, E.B.; Olawale, A.O.; Olakunle, T.P. Transmission of Antibiotic-Resistant Enterococcus faecalis through Currency Notes. Am. J. Biol. Life Sci. 2014, 2, 162–165. Available online: http://www.openscienceonline.com/journal/archive?journalId=704&pageId=1078 (accessed on 22 March 2020).

20. Olawale, A.; Salako, R.; Famurowa, O. Antibiotic-Resistant Enterococcus faecalis Isolated from Food Canteens in Osun States, Nigeria. Br. Microbiol. Res. J. 2015, 6, 196–206. [CrossRef]

21. Ayeni, F.A.; Odumosu, B.T.; Oluseyi, A.E.; Ruppitsch, W. Identification and prevalence of tetracycline resistance in enterococci isolated from poultry in Ilishan, Ogun State, Nigeria. J. Pharm. Bioallied Sci. 2016, 8, 69. [CrossRef]

22. Ekuma, A.E.; Oduyebo, O.O.; Efunsilile, A.M.; König, B. Surveillance for Vancomycin Resistant Enterococci in a Tertiary Institution in South Western Nigeria. Afr. J. Infect. Dis. 2016, 10, 121–126. [CrossRef]

23. Adesida, S.A.; Ezenta, C.C.; Adagbada, A.O.; Aladesokan, A.A.; Coker, A.O. Carriage of Multidrug Resistant Enterococcus Faecium and Enterococcus Faecalis among Apparently Healthy Humans. Afr. J. Infect. Dis. 2017, 11, 83–89. [CrossRef] [PubMed]

24. David, O.M.; Imonitie, K.; Osuntoyinbo, R.T.; Olawale, A.K. Virulence Factors and Beta-Lactamase Production among Vancomycin-Resistant Enterococcus Faecalis Isolated from Clinical Samples and Hospital Environment. Int. J. Biol. Res. 2017, 5, 1–5. [CrossRef]

25. Oguntuyinbo, F.A.; Okueso, O. Prevalence, distribution and antibiotic resistance pattern among enterococci species in two traditional fermented dairy foods. Ann. Microbiol. 2012, 63, 755–761. [CrossRef]

26. Ndubuisi, J.C.; Ononitola, O.S.; Olanyinka, A.T.; Jatau, E.D.; Iregbu, K.C. Prevalence and antibiotics susceptibility profile of Enterococcus spp. Isolated from some hospitals in Abuja, Nigeria. Afr. J. Clin. Exp. Microbiol. 2017, 18, 154. [CrossRef]

27. Shettima, S.A.; Iregbu, K.C. Antimicrobial Resistance Pattern of Enterococci Isolated from Stool Samples in a Tertiary Hospital in Nigeria. Ann. Trop. Pathol. 2019, 10, 126. [CrossRef]
28. Anyanwu, M.U.; Obetta, T.U. Prevalence and Antibiogram of Generic Enterococci in Ready-to-Slaughter Beef Cattle. *Not. Sci. Bull.* 2015, 7, 390–399. [CrossRef]

29. Nsofor, C.A. High Antibiotic Resistance Pattern Observed in Bacterial Isolates from a Tertiary Hospital in South East Nigeria. *Int. J. Res. Pharm. Biosci.* 2016, 3, 1–6.

30. Anyanwu, M.U.; Okorie-Kanu, O.J.; Ogugua, A.J.; Ezenduka, E.V.; Anidebe, C.O. Occurrence, Antibiogram and Vancomycin Resistance of Generic Enterococci in Horses in Nigeria. *Revue Méd. Vét.* 2019, 170, 46–52.

31. Foka, F.E.T.; Yah, C.S.; Bissong, M.E.A. Physico-Chemical Properties and Microbiological Quality of Borehole Water in Four Crowded Areas of Benin City, Nigeria, During Rainfalls. *Shiraz E-Med.* 2018, 19. [CrossRef]

32. Abasiubong, V.N.; Ikon, G.M.; Amadi, C.P. Enterococcus Isolates in Clinical Samples from In-Patients in Uyo, Nigeria. *Int. J. Life Sci. Res.* 2019, 7, 353–358.

33. Igbinosa, E.O.; Beshiru, A. Antimicrobial Resistance, Virulence Determinants, and Biofilm Formation of Enterococcus species from Ready-to-Eat Seafood. *Front. Microbiol.* 2019, 10, 728. [CrossRef] [PubMed]

34. Igbinosa, I.H.; Raje, O.C. Characterization of Enterococcus species isolated from abattoir environment in Benin city, Nigeria. *Ifj. Sci.* 2020, 21, 81. [CrossRef]

35. Enenya, R.P.; Yakubu, S.E.; Ado, S.A.; Ella, E.E.; Igwe, J.C. Antibiotic Resistance Profile of Enterococcus species Isolated from Drinking Water Sources in Zaria, Kaduna State, Nigeria. *J. Trop. Biosci.* 2017, 12, 20–25. Available online: https://www.researchgate.net/profile/Rufus_Enenya/publication/325688794_AntibioticResistance_Profile_of_Enterococcus_species_Isolated_from_Drinking_Water_Sources_in_Zaria_Kaduna_State_Nigeria/links/5b1e5cf745851587f29feef1/Antibiotic-Resistance-Profile-of-Enterococcus-species-Isolated-from-Drinking-Water-Sources-in-Zaria-Kaduna-State-Nigeria.pdf (accessed on 23 March 2020).

36. Federal Ministries of Agriculture, Environment and Health. In *National Action Plan for Antimicrobial Resistance 2017–2022* 2017. Available online: https://ncdc.gov.ng/themes/common/docs/protocols/77_1511368219.pdf (accessed on 8 August 2020).

37. Wada, Y.; Harun, A.B.; Chan, Y.Y.; Mohammad Nasir, N.S.; Zaidah, A.R. Prevalence of Vancomycin resistant enterococcus in Malaysia: A meta-analysis and systematic review. *Int. J. Infect. Dis.* 2020, Accepted Manuscript.

38. Ali, S.; Alemayehu, M.A.; Dagnew, M.; Gebrecherkos, T. Vancomycin-Resistant Enterococci and Its Associated Risk Factors among HIV-Positive and -Negative Clients Attending Dessie Referral Hospital, Northeast Ethiopia. *Int. J. Microbiol.* 2018, 2018, 1–9. [CrossRef]

39. Moghimbeigi, A.; Moghimbeigi, M.; Dousti, M.; Kiani, F.; Sayehmiri, F.; Sadeghifard, N.; Nazari, A. Prevalence of vancomycin resistance among isolates of enterococci in Iran: A systematic review and meta-analysis. *Adolesc. Health Med. Ther.* 2018, 9, 177–188. [CrossRef]

40. Alevizakos, M.; Gaitanidis, A.; Nasioudis, D.; Tori, K.; Flokas, M.E.; Mylonakis, E. Colonization with Vancomycin-Resistant Enterococci and Risk for Bloodstream Infection Among Patients With Malignancy: A Systematic Review and Meta-Analysis. *Open Forum Infect. Dis.* 2016, 4. [CrossRef]

41. Kramer, T.; Remschmidt, C.; Werner, S.; Behnke, M.; Schwab, F.; Werner, G.; Gastmeier, P.; Leistner, R. The importance of adjusting for enterococcus species when assessing the burden of vancomycin resistance: A cohort study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob. Resist. Infect. Control* 2018, 7, 133. [CrossRef]

42. Emaneini, M.; Hosseinkhani, F.; Jabalameli, F.; Nasiri, M.J.; Dadashi, M.; Pouriran, R.; Beigverdi, R. Prevalence of vancomycin-resistant Enterococcus in Iran: A systematic review and meta-analysis. *Eur. J. Clin. Microbiol. Infect. Dis.* 2016, 35, 1387–1392. [CrossRef]

43. Toner, L.; Papa, N.; Aliyu, S.H.; Dev, H.; Lawrentschuk, N.; Al-Hayek, S. Vancomycin resistant enterococci in urine cultures: Antibiotic susceptibility trends over a decade at a tertiary hospital in the United Kingdom. *Investig. Clin. Urol.* 2016, 57, 129–134. [CrossRef]

44. Yang, K.-S.; Fong, Y.-T.; Lee, H.-Y.; Kurup, A.; Koh, T.-H.; Koh, D.; Lim, M.-K. Predictors of vancomycin-resistant enterococcus (VRE) carriage in the first major VRE outbreak in Singapore. *Ann. Acad. Med. Singap.* 2007, 36, 379–383.

45. Barger, M.; Blodget, E.; Pena, S.; Mack, W.J.; Fong, T.-L. VRE in cirrhotic patients. *BMC Infect. Dis.* 2019, 19, 1–8. [CrossRef]

46. Camins, B.C.; Farley, M.M.; Jernigan, J.J.; Ray, S.M.; Steinberg, J.P.; Blumberg, H.M. A Population-Based Investigation of Invasive Vancomycin-Resistant Enterococcus Infection in Metropolitan Atlanta, Georgia, and Predictors of Mortality. *Infect. Control Hosp. Epidemiol.* 2007, 28, 983–991. [CrossRef]
47. Jakovljevic, M.; Al Ahdab, S.; Jurisevic, M.; Mouselli, S. Antibiotic Resistance in Syria: A Local Problem Turns Into a Global Threat. *Front. Public Health* 2018, 6, 212. [CrossRef]

48. Zhussupova, G.; Skvirskaya, G.; Reshetnikov, V.A.; Dragojević-Simić, V.; Rančić, N.; Utepova, D.; Jakovljevic, M. The Evaluation of Antibiotic Consumption at the Inpatient Level in Kazakhstan from 2011 to 2018. *Antibiotics* 2020, 9, 57. [CrossRef]

49. Robertson, J.; Iwamoto, K.; Hoxha, I.; Ghazaryan, L.; Abilova, V.; Cvijanovic, A.; Pyshnik, H.; Darakhvelidze, M.; Makalkina, L.; Jakupi, A.; et al. Antimicrobial Medicines Consumption in Eastern Europe and Central Asia–An Updated Cross-National Study and Assessment of Quantitative Metrics for Policy Action. *Front. Pharmacol.* 2019, 9. [CrossRef]

50. Jakovljevic, M.; Timofeyev, Y.; Ranabhat, C.L.; Fernandes, P.O.; Teixeira, J.P.; Rancic, N.; Reshetnikov, V. Real GDP growth rates and healthcare spending – comparison between the G7 and the EM7 countries. *Glob. Health* 2020, 16, 1–13. [CrossRef]

51. Shokoohizadeh, L.; Mobarez, A.M.; Zali, M.R.; Ranjbar, R.; Alebouyeh, M.; Sakinc, T.; Ali, L. High frequency distribution of heterogeneous vancomycin resistant Enterococcous faecium (VREfm) in Iranian hospitals. *Diagn. Pathol.* 2013, 8, 163. [CrossRef]

52. Adams, D.J.; Eberly, M.D.; Goudie, A.; Nylund, C.M. Rising Vancomycin-Resistant Enterococcus Infections in Hospitalized Children in the United States. *Hosp. Pediatr.* 2016, 6, 404–411. [CrossRef]

53. Leclercq, R.; Derlot, E.; Duval, J.; Courvalin, P. Plasmid-Mediated Resistance to Vancomycin and Teicoplanin in Enterococcus Faecium. *N. Engl. J. Med.* 1988, 319, 157–161. [CrossRef]

54. Uttley, A.; Collins, C.; Naidoo, J.; George, R. vancomycin-resistant enterococci. *Lancet* 1988, 331, 57–58. [CrossRef] [PubMed]

55. Werner, G.; Coque, T.M.; Hammerum, A.M.; Hope, R.; Hryniewicz, W.; Johnson, A.; Klare, I.; Kristinsson, K.G.; Leclercq, R.; Lester, C.H.; et al. Emergence and spread of vancomycin resistance among enterococci in Europe. *Eurosurveillance* 2008, 13, 19046.

56. Levitus, M.; Rewane, A.; Perera, T.B. Vancomycin-Resistant Enterococci (VRE). In StatPearls 2020 Treasure Island (FL); StatPearls Publishing: Florida, FL, USA, 2020.

57. Arias, C.A.; Murray, B.E. The rise of the Enterococcus: Beyond vancomycin resistance. *Nat. Rev. Genet.* 2012, 10, 266–278. [CrossRef] [PubMed]

58. Davis, E.; Hicks, L.; Ali, I.; Salzman, E.; Wang, J.; Snitkin, E.; Gibson, K.; Cassone, M.; Mody, L.; Foxman, B. Epidemiology of Vancomycin-Resistant Enterococcus faecium and Enterococcus faecalis Colonization in Nursing Facilities. *Open Forum Infect. Dis.* 2020, 7, ofz553. [CrossRef]

59. Treitman, A.N.; Yarnold, P.R.; Warren, J.; Noskin, G.A. Emerging Incidence of Enterococcus faecium among Hospital Isolates (1993 to 2002). *J. Clin. Microbiol.* 2005, 43, 462–463. [CrossRef]

60. Deshpande, L.M.; Fritsche, T.R.; Moet, G.J.; Biedenbach, D.J.; Jones, R.N. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: A report from the SENTRY antimicrobial surveillance program. *Diagn. Microbiol. Infect. Dis.* 2007, 58, 163–170. [CrossRef]

61. Madu Tella, C. Insecurity in Northern Nigeria: Causes, Consequences and Resolutions. *Int. J. Peace Confl. Stud.* 2015, 2, 23–36.
67. Shamseer, L.; Moher, D.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.; the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 2015, 349, g7647. [CrossRef]
68. George, B.J.; Aban, I.B. An application of meta-analysis based on DerSimonian and Laird method. J. Nucl. Cardiol. 2015, 23, 690–692. [CrossRef] [PubMed]
69. Higgins, J.P.T.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. Stat. Med. 2002, 21, 1539–1558. [CrossRef]
70. Wallace, B.C.; Dahabreh, I.J.; Trikalinos, T.A.; Lau, J.; Trow, P.; Schmid, C.H. Closing the Gap between Methodologists and End-Users: Ras a Computational Back-End. J. Stat. Softw. 2012, 49, 1–15. [CrossRef]