Vancomycin Resistance Enterococcus in Africa in Onehealth approach: A systematic review and meta-analysis

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SUBJECT AREAS
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Vancomycin resistance enterococci, Onehealth, Meta-analysis, Africa
Abstract
Background Vancomycin resistance enterococci are enterococci that cannot be cured with vancomycin treatment. To combat this resistance, an integrated disciplinary action is mandatory. Therefore, this study aimed to show the prevalence of these agents with the concept of one health approach.

Methods Literature search was conducted on PubMed, Google scholar and Hinari with the term “Vancomycin resistance enterococcus in Africa” in august 1-3, 2019. All available articles exported to “Endnote version 7.1” then to Microsoft word. All the articles checked to meet our criteria for the review. Those articles reported the prevalence of vancomycin resistance Enterococcus and published from 2010 to present in the English language was included for the review. There were 151 articles from the databases; of this, 37 articles included after extensive review with two independent authors.

Result Out of 4112 samples collected, 1527 isolates identified with overall magnitude of VRE as 28.8% (12.9%-44.7%) in Africa with a one-health perspective. The meta-analysis indicates that there was substantial heterogeneity among the articles with consistency index ($I^2$) =99.9%. A higher rate of Vancomycin resistance enterococci was identified from South Africa 74.8%, followed by Egypt 37. 2%. Laboratory method employed for identification showed that a higher rate was from BacTec 98.8%, followed by PCR 59.2%. It is also a non-human sample source was with higher rates of VRE i.e. 32.5%.

Conclusion This meta-analysis indicates there was a high rate of Vancomycin resistance enterococcus in African continent. A lot should be done to prevent and control the transmition of this resistance gene circulating in the environment.

Introduction
Vancomycin-resistant enterococci an enterococci (VRE) that acquired resistance to the antibiotic vancomycin used to treat infection caused by these bacteria [1]. VRE emerged as important nosocomial pathogens since 1987, and there is concern that they may be, or become, endemic in the non-hospital setting, both in human and animal carriers and in the general environment [2]. It advanced to inoffensive colonizer of the gut of humans and animals, ranging from insects to reptiles, birds, and mammals. Whilst they are ubiquitous, they represent a minority population of the healthy
human microbiome [3]. Outside the gut, they can disseminate in the environment where they survive in wastewater, slurry and soil contaminated by manure and hence used as indicators of faecal contamination in recreational or drinking water [4].

Members of the genus Enterococcus are well-documented pathogens associated with various clinical manifestations, including bacteremia, infective endocarditis, intra-abdominal and pelvic infections, urinary tract infections, and, in rare cases, central nervous system infections [5–7]. Infection with VREs associated with an increased mortality rate, illustrated by a 2.5-fold increase in mortality for patients suffering from VRE bacteremia [8].

The ‘One Health’ concept recognizes that the health of people connected to the health of animals and the environment. Humans, animals, plants, food of animal origin and our environment all potentially constitute overlapping reservoirs of antimicrobial resistance (AMR). Given the serious health threat, a common understanding of AMR, and of the need for a One Health approach to tackle it, are of fundamental importance [9].

VRE is one of this multidrug resistance that needs comprehensive data that indicates the magnitude of VRE in Africa. Therefore, the aim of this study was to compile available data of vancomycin resistance enterococci in Africa in one health perspective.

Methods
Literature Search Strategy
A literature search conducted on PubMed, Google scholar and Hinari with the term “Vancomycin resistance enterococcus in Africa” in august 1–3, 2019. All available articles exported to “Endnote version 7.1” then to Microsoft word. All the articles checked to meet our criteria for the review. Those articles reported the prevalence of vancomycin resistance Enterococcus and published from 2010 to present in the English language was included for the review. There were 151 articles from the databases; of this, 37 articles included after extensive review with two independent authors. Articles failed to fulfill the criteria excluded as presented in Figure 1 according to the PRISMA protocol 2015.

Data analysis
Excel used for data extraction and then exported to Microsoft word as presented in table 1. Meta-analysis was conducted with OpenMeta analyst software available freely and the result presented as a
forest plot in Figure 2 &3 and in Table 2.

Data Quality
The quality of the study included in the review and meta-analysis evaluated with 14 points scoring tool. NIH quality assessment tool for observational and cross-sectional studies in which studies categorized as a good, fair and poor quality based on the internal validity of each article[10].

Heterogeneity and Publication Bias
The heterogeneity of the publication was determined according to the measure of the inconsistency index ($I^2$). That measures the total variations in the articles was due to heterogeneity rather than by chance with a value of <30%, 30-60%, 61-75% and >75% suggestive of low, moderate, substantial and considerable heterogeneity, respectively [11]. No need for conducting publication bias as the study is considerably heterogeneous as recommended by Hak T. et al [12].

Study features
As presented in table 1 studies that conducted in African countries that reported the prevalence of enterococcus and resistance rate for vancomycin, published after 2010. Whatever the sample type and laboratory method employed captured for the review and meta-analysis. The author name, year of publication, country of origin, source of sample (human vs non-human), laboratory method used (culture & polymerase chain reaction (PCR), PCR only, BacTec, culture only, number of enterococcus isolated and the proportion of vancomycin resistance enterococci isolated was extracted from each articles.

Country of origin for the articles
The country in which the articles originated is indicated as follows, eight (8) articles from each countries, Ethiopia [13–20], and South Africa, [20–28], four (4) articles in each countries Egypt [29–32], and Tunisia [33–36]. Another three articles (3) from each of these countries Morocco [37–39], Tanzania [40–42] and Uganda, [43–45]), two (2) articles from Nigeria, [46, 47] and one (1) article from Algeria [48] were included for the review as presented in Table 1.

Results
The magnitude of vancomycin resistance Enterococci
Out of 4112 samples collected, 1527 isolates identified with overall magnitude of VRE 28.8% (12.9%–44.7%) in Africa in a one-health perspective. The meta-analysis indicates that there was substantial
heterogeneity among the articles with a consistency index ($I^2 = 99.9\%$).

**Subgroup analysis**

**Country level**

The subgroup analysis performed at country level indicates that a high rate of VRE in South Africa 74.8% and the least was from Algeria and Nigeria 2.8% each even if only one article captured from Algeria as presented in *Figure 2*.

**Laboratory method**

Subgroup analysis of VRE based on the laboratory method in presented in *Table 2* that grouped into culture & polymerase chain reaction (PCR), PCR only, BacTec, culture only. It indicates that the highest rates of VRE even if a single study conducted using BacTec was 98.8 %, followed by using only PCR 59.2%, that conducted using both culture & PCR 38.9% and identified using culture only 7.3 %, chronologically.

**Sample Source**

As tried to present in *Figure 3* subgroup analysis based on the source of sample conducted by categorizing as non- human and human source. It indicates that a higher rate of VRE was detected from non-human sample sources 32.5% vs 23.3 % human source.

**Discussion**

Vancomycin is one of the few antibiotics that can be used to treat infections resulting from Gram-positive multidrug-resistant organisms (MDRO) including such as enterococci [49]. In the late 1980s, the emergence of VRE in European hospitals and the isolation of a few years later of VRE from Danish raw minced pork and frozen poultry generated global concern [50]. One Health is the concept that the optimum health for people, animals and the environment can best ensured through the ongoing cooperative efforts of scientists and practitioners in a variety of discipline [51].

Our study based on data available in Africa on VRE in one health perspective in which animal, human, avian and environmental source of samples analyzed to determine the pooled prevalence of VRE. The overall prevalence of VRE was 28.8 % in Africa from different sample source in a one-health approach. Which is higher than study systematic review and meta-analysis which was conducted in Iran that is 14 % VRE [52]. This difference may be due to the source of the sample we used for the analysis is
from different sources. The high rates of this VRE are may be due to the nature of enterococci, which is highly resistant for environmental conditions and different antibiotics [53, 54]. There is no data of systematic review and meta-analysis from other parts of the world including Africa to compare and contrast more with our finding, but the subgroup analysis at country level showed that there is a pronounced difference of VRE in different countries, which ranged from 74.8 % from South Africa to 2.8 % in Algeria.

Our study also performed a subgroup meta-analysis based on the laboratory method used for isolation and identification of Enterococcus & VRE. It showed that the higher the technique used the more sensitive for detection of VRE in which studies conducted with BacTec and PCR leads for isolation of more VRE, whereas those conducted with conventional culture less likely detect VRE. Some studies reported in comparison of PCR and Culture indicates that PCR is more sensitive and specific than later [55, 56].

Sample source in which we categorized in human & non-human source for the sake of subgroup meta-analysis showed that higher rates of VRE were isolated from non-human as compared to a human source. This may be due to most of the articles included based on our inclusion criteria is from non-human sources as different wild & domestic animal wastes or byproducts, poultry, birds, and environmental sample was compiled for analysis. This part of the study strained the one health approach, which is an important way of combating antibiotics resistance which worsens the world know a day’s [57].

Conclusion
Our meta-analysis finding from one health perspective showed that there is a high rate of Vancomycin resistance enterococci circulating in Africa based on the available articles. Thus, a means of prevention and control targeting human, animal, avian and environment should be practiced in the continent.

Abbreviations/acronyms
VRE Vancomycin-resistant enterococci
AMRAntimicrobial resistance
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

NIH National Heart, Lung, and Blood Institute

PCR Polymerase chain reaction

MDRO multidrug-resistant organisms

Declarations

Ethical Clearance: Not applicable

Consent for publication: Not applicable

Availability of data and material: All the data supporting the findings can be obtained from the corresponding author.

Competing of interest: The authors declare that they have no competing interests

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Authors’ contribution: TA: conceived the idea, develop the study plan, extracted data, analyzed the data and prepared the manuscript. MH: Extracted data and revised the manuscript.

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Tables

Table 1 articles that are selected for systematic review and meta-analysis of VRE in Africa

| Author                  | Year | Country     | Source of sample                      | Lab.         |
|-------------------------|------|-------------|---------------------------------------|--------------|
| Bouamama et al [13]     | 2010 | Morocco     | Flies & cockroaches                   | Cult         |
| Djahmi et al [14]       | 2012 | Algeria     | Clinical specimen                     | Cult         |
| Ateba et al [15]        | 2013 | South Africa| Ground water                          | PCR          |
| Kateete et al [16]      | 2013 | Uganda      | Milkmen & Cows mastitis               | Cult         |
| Moemen et al [17]       | 2014 | Egypt       | Clinical specimen                     | Cult         |
| Abebe et al [18]        | 2014 | Ethiopia    | Stool sample                          | Cult         |
| Katakweba et al [19]    | 2014 | Tanzania    | Buffalo, Zebra, Cattle & wildebeest faecal | Cult        |
| Naouel et al [20]       | 2014 | Tunisia     | Feces of birds                        | Cult         |
| Anyanwu et al [21]      | 2015 | Nigeria     | Cattle rectal swab                    | Cult         |
| Iweriebor et al [22]    | 2015 | South Africa| Pig feaces                            | Cult         |
| Amadot et al [23]       | 2015 | Tanzania    | Blood                                 | Cult         |
| Hammad et al [24]       | 2015 | Egypt       | Milk cheese                           | Cult         |
| Benson et al [25]       | 2015 | South Africa| Hospital waste water                  | Cult         |
| Abamecha et al [26]     | 2015 | Ethiopia    | Patients faeces                       | Cult         |
| Iweriebor et al [27]    | 2016 | South Africa| Cattles                               | Cult         |
| Dziri et al [28]        | 2016 | Tunisia     | Env’t sample                          | Cult         |
| Ben Said et al [29]     | 2016 | Tunisia     | Vegetable, soil & water               | Cult         |
| Nadjette et al [30]     | 2016 | Algeria     | Clinical specimen                     | Cult         |
| Hannau et al [31]       | 2016 | Morocco     | Faecal specimen                       | Cult         |
| Molale1&Cornelis [32]   | 2016 | South Africa| Surface water                         | Cult         |
| Emmanuel et al [33]     | 2016 | Nigeria     | Rectal swab & manure of poultry & cattle | Cult        |
| Yilema et al [34]       | 2017 | Ethiopia    | Clinical specimen                     | Cult         |
| Solomon et al [35]      | 2017 | Ethiopia    | Indoor air sample                     | Cult         |
| Katakweba et al [36]    | 2017 | Tanzania    | Feces of livestock, poultry & human   | Cult         |
| Ferede et al [37]       | 2018 | Ethiopia    | Clinical specimen                     | Cult         |
| Seid et al [38]         | 2018 | Ethiopia    | Stool sample                          | Cult         |
| Joseph et al [39]       | 2018 | Uganda      | Vaginal swab                          | Cult         |
| Manamenot et al [40]    | 2018 | Ethiopia    | Stool sample                          | Cult         |
| Aziz et al [41]         | 2018 | Morocco     | Cow milk                              | Cult         |
| Hassan et al [42]       | 2018 | Egypt       | Clinical specimen                     | PCR          |
| Houssem et al [43]      | 2018 | Tunisia     | Wild birds feces                      | Cult         |
| Toru et al [44]         | 2018 | Ethiopia    | Clinical specimen                     | Cult         |
| Molechan et al [45]     | 2019 | South Africa| Poultry                               | Cult         |
| Daniel et al [46]       | 2019 | South Africa| Water                                 | Cult         |
| Osman et al [47]        | 2019 | Egypt       | Poultry                               | Cult         |
| Kateete et al [48]      | 2019 | Uganda      | Clinical specimen                     | Cult         |
| Frank et al [49]        | 2019 | South Africa| Feaces, water & soil                  | Cult         |

Table 2-subgroup analysis of VRE based on laboratory methods used employed
| Subgroups        | Studies | Estimate | Lower-upper bound | Std. error | p-Val | z-Val | Heterogeneity |
|------------------|---------|----------|-------------------|------------|-------|-------|---------------|
| Culture & PCR    | 17      | 0.389    | 0.161-0.616       | 0.116      | <0.001| 3.35  | 84591.2(16)   |
| Culture          | 17      | 0.073    | 0.048-0.098       | 0.013      | <0.001| 5.76  | 57.5(16)      |
| PCR              | 2       | 0.592    | 0.068-1.253       | 0.337      | 0.079 | 1.76  | 141.7(1)      |
| BacTec           | 1       | 0.988    | 0.953-1.022       | 0.018      | NA    | NA    | NA            |
| Overall          | 37      | 0.288    | 0.129-0.447       | 0.081      | <0.001| NA    | 100478.6 (36) |

Figures
Figure 1

the flow diagram for the article selection of vancomycin resistance entrococcus in Africa

with a onehealth approach: a systematic review and meta-analysis
Figure 2 shows that the subgroup analysis of VRE at country level
Figure 3

shows the subgroup analysis based on the source of the sample for VRE in Africa

Supplementary Files

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