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# A comparative computational genomics of Ebola Virus Disease strains: *In-silico* Insight for Ebola control

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ABSTRACT

Ebola Virus Disease (EVD), is a national epidemic in Countries affected. It is also a potential global public health pandemic. The menace of the disease outbreak among West and Central African nations, in recent years, has resulted in the death of many unsuspecting victims. The present study was conducted to present a systematic review of the literature, focusing on the control of Ebola Virus Disease (EVD), among human subjects. It also centered on a bioinformatics analysis of five different strains of Ebola virus.

Research articles published between 2008 and 2018, on EVD control studies, were systematically reviewed. Four online databases were searched for the purpose of this review. These include: Science Direct, Google Scholar, SpringerLink and PubMed. Study outcomes were extracted. The outcomes were summarized and categorized. Five different strains of Ebola virus were obtained from the NCBI database, specifically the Entrez Genome database. Bioinformatics analysis was performed using Muscle software, RawXL, Treview, iTOL and Clustal X. Bioinformatics analysis was performed on five selected strains of Ebola virus (Reston, Bundingbugyo, Zaire, Sudan and Tai forest). Evaluation of the phylogenetic tree was performed by using MEGA X and PHYLIP software.

237,498 publications were identified, out of which 104 research articles, from different regions of the world, fulfilled our inclusion criteria. Insight was gained for the control of EVD from these studies. Of the studies reviewed, 23 articles focused on vaccines/vaccination-related Ebola control research, 12 studies on modeling and simulation-related Ebola control research, 41 on drugs and therapeutics-related Ebola control research, and 28 focused on other experimental studies (such as biological experiments, bioinformatics experiments, travel border control measures, educational campaign measures, hand and environmental sanitization, amongst others). Very few modeling and simulation studies have been conducted on the control of EVD in the last 10 years. Thus, there is the need for more modeling and simulation-related ebola control research. Comparative computational genomics of the five Ebola virus strains produced phylogenetic trees in different shapes. An evaluation of the phylogenetic tree was performed. Results showed that *Taiforest Ebola virus* and *Bundibugyo Ebola virus* are closely related. The results also revealed that *Sudan and Reston Ebola virus* are closely related. *Zaire Ebola virus* stood out from all the others. It may be possible to adopt similar Ebola control measures against Ebola virus strains that are closely related.

Insight from these results, can facilitate the development and production of multi-protective, multi-treatment drugs, multi-protective vaccines and antivirals, against these ebola virus disease strains.

The results of the evaluations of the phylogenetic tree can be assistive in providing insight into the origin, evolution, and possible structural and genetic mutations of the Ebola virus. It can also provide insight for inferring the structural and functional properties of each Ebola virus. The knowledge of such inference can be useful for EVD control. This can bring about a radical transformation in control efforts for disease.

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## 1. Introduction

Ebola Virus Disease (EVD, henceforth), is a national epidemic in affected countries. It is also a potential global public health pandemic. Particularly disturbing, is the resurgence and re-emergence of the disease in some African countries. The menace of the disease outbreak among West and Central African nations, in recent years, has resulted in the death of many unsuspecting victims [1,2,3,4]. In 2014, the spate of EVD in West African countries spurred untold hardships, many cases of fatalities, discrimination, stigmatization, isolation, and mockery of affected countries [5,6]. After curtailing the disease, a few years later, EVD re-emerged and it was confirmed in DR Congo on the 11th of May 2017. The disease killed some inhabitants of a remote village in the Northeastern region of DR Congo. It has been reported that delayed diagnosis and lack of prompt reporting of new cases of EVD affects control efforts, especially in rural areas [2]. Similarly, in a recent development, the DR Congo government recently confirmed a new outbreak of EVD on the 8th of May 2018. There were two 2 confirmed cases of EVD incidence [7]. Some of the pertinent questions that are readily evinced are: (i) what are the various efforts in Ebola research that focus on controlling EVD transmissions among human subjects? (ii) What kind of research has been conducted, that can provide insight or *in-silico* analysis for control of Ebola? (iii) How much of each kind of EVD control research has been conducted in the last decade? (iv) Is it possible to gain insight on the control of EVD from the bioinformatics analysis of different Ebola virus strains?

In order to address these pertinent questions, our study focused on a 10-year systematic review of previous studies, which centered on the control of EVD. Our study was conducted with a view to obtain insight in the control of the disease. We performed bioinformatics analysis (Multiple Sequence Alignment (MSA) and phylogenetic analysis) on five different strains of Ebola virus. We also evaluated the results of the bioinformatics analysis.

The aim of this study was to conduct a comprehensive systematic review on investigations that have determined potential control measures against EVD transmission. It was also to perform a bioinformatics analysis on five different strains of Ebola virus. The significance of performing bioinformatics analysis was to understand the relationship (s) between the five different strains of Ebola virus. It was also to gain insight toward the control and prevention of the spread of the disease. The paper is structured as follows: firstly there is a methodology of the literature review, then a bioinformatics analyses, results, discussion, recommendations and conclusion.

## 2. Methodology of literature review

### 2.1. Strategy of searching

Databases of the scientific literature such as ScienceDirect, SpringerLink, PubMed, and Google Scholar, were searched between the period of January 1st, 2008 and February 28th, 2018. Relevant subject heading and keywords were used. The databases, search terms, and number of articles found, are provided in Table 1. Multiple keywords were chosen, based on their respective relevance to identify studies on 'Ebola control', 'reduction of Ebola transmissions', 'bioinformatics analyses', 'phylogenetic analyses', 'comparative genomics', 'control'. The combination of the keywords, was used for conducting search through each scientific database. Scientific articles that relate to empirical studies, only on humans (human subjects), and published in the English language, were considered for the systematic review.

### 2.2. Selection and exclusion criteria of study

The initial search resulted in the identification of 237,498 articles (See Fig. 1 and Table 1). The next stage was the title review stage. This was conducted by adopting the inclusion criteria. 234,830 articles were

**Table 1**
Databases, number of articles synthesized and integrated to the system.

| s/n | Scientific Databases | Search terms | Initial Results | Articles Synthesized& integrated |
|---|---|---|---|---|
| 1 | Science Direct Database https://www.sciencedirect.com/ | (multiple sequence alignment* OR 'Ebola virus') OR (Phylogenetic analyses* OR 'Ebola virus') OR (Comparative genomics* OR 'Ebola virus') OR (Bioinformatics analysis* OR 'Ebola virus') AND (Ebola control) OR (Ebola transmission) OR (reduction) | 6000 articles | **6** |
| 2 | Google Scholar https://scholar.google.com | (multiple sequence alignment* OR 'Ebola virus') OR (Phylogenetic analyses *OR 'Ebola virus') OR (Comparative genomics* OR 'Ebola virus') OR (Bioinformatics analysis* OR 'Ebola virus') AND (Ebola control) OR (Ebola transmission) OR (reduction) | 940 articles | **12** |
| 3 | Springer Link https://link.springer.com/ | (multiple sequence alignment* OR 'Ebola virus') OR (Phylogenetic analyses* OR 'Ebola virus') OR (Comparative genomics* OR 'Ebola virus') OR (Bioinformatics analysis* OR 'Ebola virus') AND (Ebola control) OR (Ebola transmission) OR (reduction) | 950 articles | **6** |
| 4 | PubMed [MEDLINE DATABASE] PubMed https://www.ncbi.nlm.nih.gov/pubmed/ | (multiple sequence alignment* OR 'Ebola virus') OR (Phylogenetic analyses* OR 'Ebola virus') OR (Comparative genomics* OR 'Ebola virus') OR (Bioinformatics analysis* OR 'Ebola virus') AND (Ebola control) OR (Ebola transmission) OR (reduction) | 229,608 articles | **80** |
| | | | Total Articles Reviewed = 237,498 | **104** |

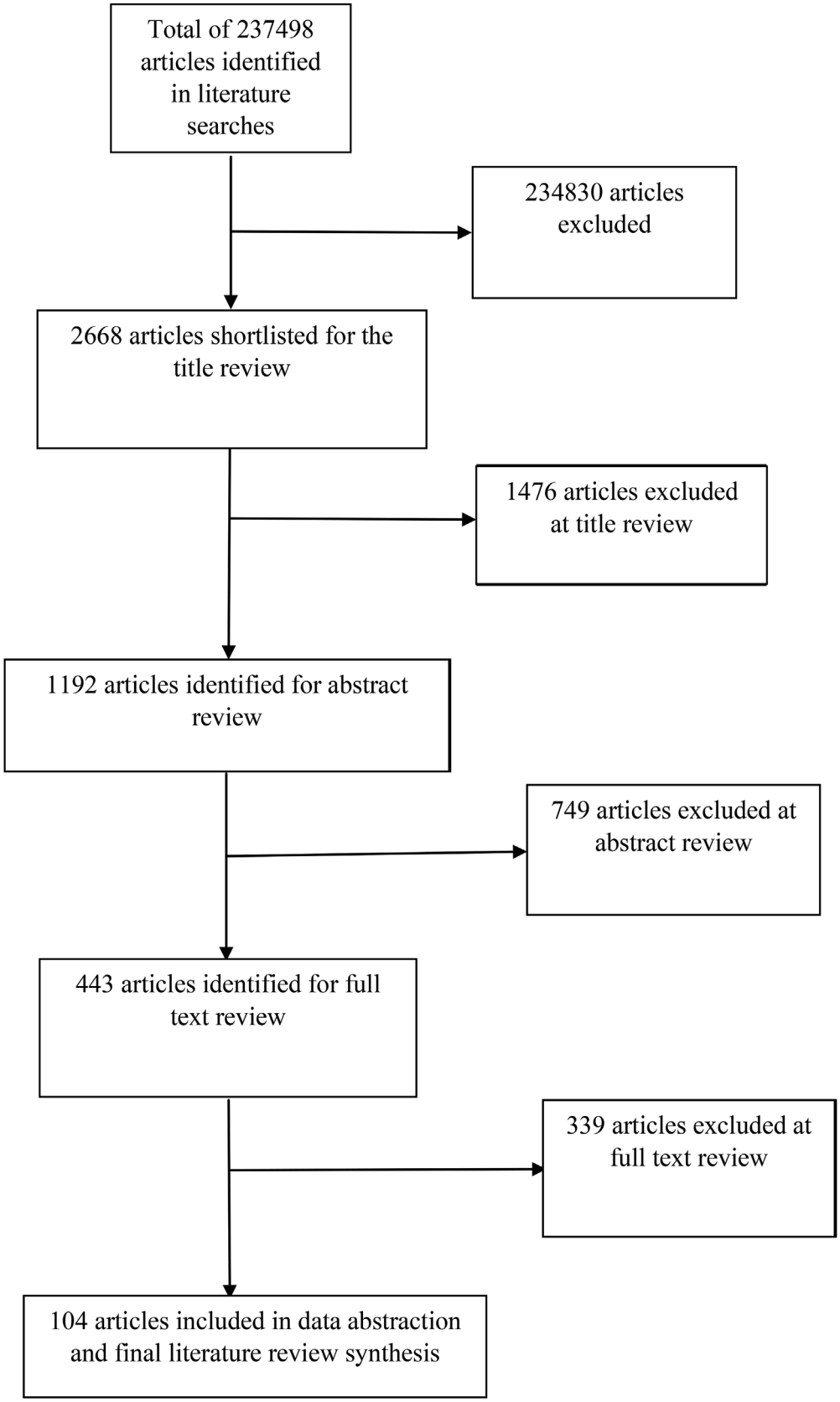


**Fig. 1.** The literature review process with the number of studies identified, excluded and included.

excluded after specifically reviewing each of the articles for the title review. At the title review stage, 2668 articles were shortlisted. The next stage was the abstract review stage. 1476 articles were excluded. At the abstract review stage, 1192 articles were identified for abstract reviews. Following the exclusion of 749 articles based on prior specified inclusion criteria, the full text of 443 articles were reviewed and studied

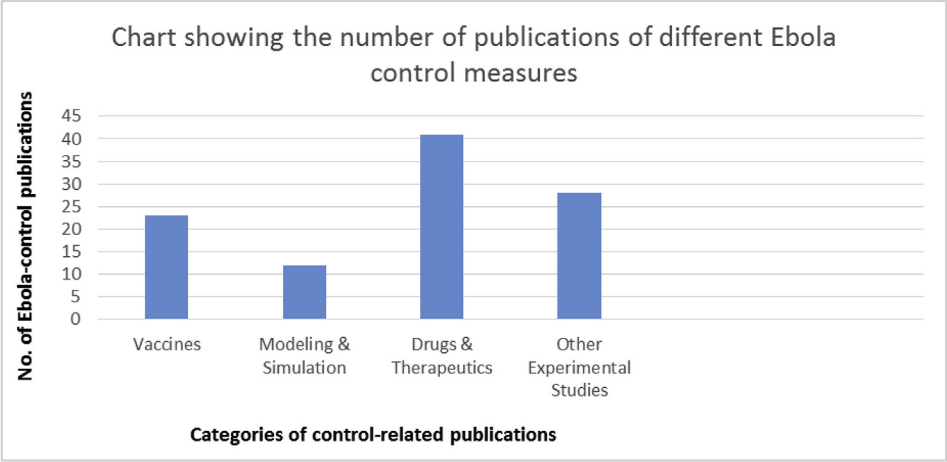


**Fig. 2.** Bar charts showing the classification of synthesized EVD control studies into Potential Control/intervention groups.

in details. Subsequently, 339 articles were excluded from the review. Finally, 104 articles met the inclusion criteria. These 104 articles were integrated and synthesized into the review [Reference [8–50][51–90][91–112]] (See Fig. 1 and Supporting material 1).

### 2.3. Extraction of data and synthesis

For each paper reviewed that met our inclusion criteria, the following data were extracted: Authors, year, study method, study design, study site/region/country, data used/data collection methods/specimen/population involved/type of participants, key discoveries, title/issue/product investigated and *in-silico* insight/insight derived for EVD control. Results, titles, key discoveries and study methods were stated or in some cases paraphrased (see supporting material 1).

### 2.4. Bioinformatics analysis

The purpose of the bioinformatics analysis was to understand the relationships among the five Ebola virus strains. It was also to gain insight into control measures against EVD. The updated versions of the completely sequenced genomes of Ebola virus, was obtained from the NCBI database. Five different strains of Ebola virus genome data were obtained from the source: https://www.ncbi.nlm.nih.gov/genomes/GenomesGroup.cgi?taxid=186536. The authors obtained the sequences from the Entrez Genome database. The summary of the data is shown in Table 2. The Ebola virus genome data were obtained from isolates of Ebola virus from Zaire (now DR Congo), Tai Forest (in the present Cote d'ivoire), Sudan, Reston (in the USA), and Bundibugyo (a town in Western Uganda). A bioinformatics analysis (multiple sequence alignment and phylogenetic analyses) was conducted.

Complete genomes of five Ebola virus isolates were downloaded from the NCBI website. The *Bundibugyo Ebola virus* genome data has accession number NC_014373; the *Reston Ebola virus* updated genome data has an accession number NC_004161; the *Sudan Ebola virus* genome data is a recently updated data with accession number NC_006432; the *Tai Forest Ebola virus* updated genome data has accession NC_004161. Finally, the *Zaire Ebola virus* has an accession number of NC_002549. More information about these data can be found in Table 2.

### 2.5. Multiple sequence alignment and phylogenetic analyses

During analysis, the complete genome of Ebola virus isolates were downloaded. The genomes were in the FASTA file format (genomes_ebov.fasta). These are respectively *Bundibugyo Ebola virus* complete genomes, *Reston Ebola virus* complete genomes, *Sudan Ebola virus* complete genomes, *Tai forest Ebola virus* complete genomes, and *Zaire Ebola virus* complete genomes. These five *Ebola virus* species are cRNA molecules. This means that they are RNA viruses, with a length of about 19,000 nucleotides each. A Multiple Sequence Alignment (MSA) of all Ebola genomes was performed, using Muscle version 3.8.3.1 [113,114]. An aligned FASTA file format was created with it (genomes_Ebola_5.afasta). A

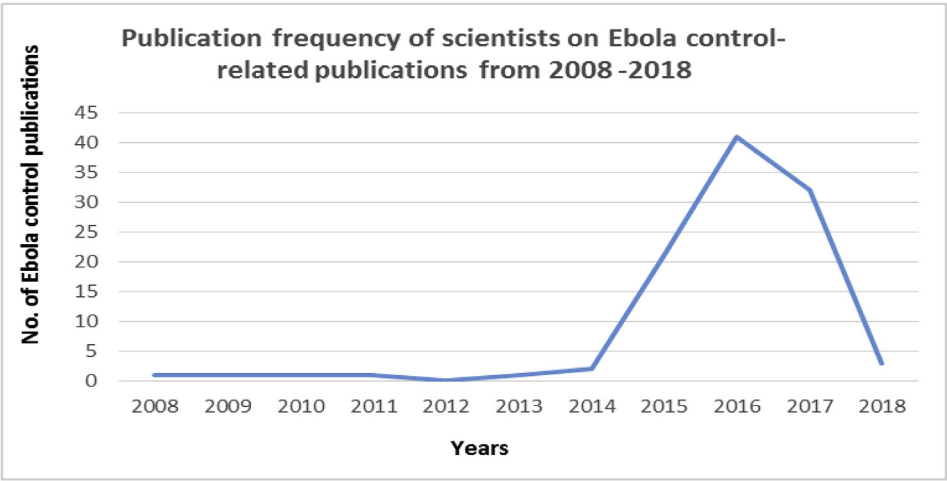


**Fig. 3.** Graph depicting the publication frequency of scientists on EVD control-related publications from 2008 to 2018.

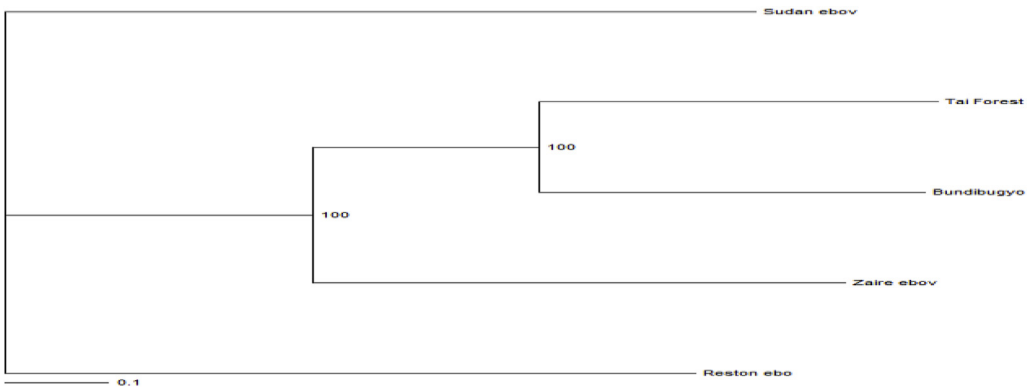


**Fig. 4.** Phylogram depicting the relationships among the five different strains of Ebola virus.

visualization tool, Seaview4 [115], was used to view the aligned output. Clustal X [116], was utilized to convert our aligned fasta file into phylip format. This contains 5 sequences and 20,308 base pairs.

RAxML [117] was used for the tree building and drawing process. The tree-building technique uses the Maximum Likelihood (ML, henceforth) method to build trees. RAxML [117], was utilized to perform a ML search, based on the genome sequences, and then bootstrapped 20 times. ML is a statistical technique of finding the value of one or more parameters, for given statistics, which makes the known likelihood distribution maximum [123]. Bootstrapping is another statistical technique that assists in providing allowance for assigning measures of accuracy [124]. It relies on random sampling with replacement [125,126]. The genome evolution was then modeled and the Phylip file was used to generate a newick file that produced the phylogenetic tree. A Tree Viewer [118,119,and120]] was then used to view the tree. Treeview X [ [118,119,and 120]], was mostly used for generating the trees in different formats (the slanted cladogram, rectangular cladogram, and the phylogram). These trees were confirmed with iTOL [119]. Here is the tree generated in iTOL: http://itol.embl.de/tree/1003661602829015275270 43.

### 2.6. Evaluating the phylogenetic tree

Evaluating phylogenetic trees is significant because it helps to reveal how reliable the tree is. There are several methods, studies and tools for evaluating phylogenetic trees. Some of them include phylogenetic tree evaluation tools and studies, such as can be found in the following literature [127–157,161].

Two evaluations were performed on the phylogenetic tree. In order to conduct a bootstrap (or jackknife, or permutation test), with some method in the PHYLIP package [158], these programs were used: Seqboot, Dnapars and Consense.

First, Seqboot was run to accept the original Ebola genome sequence data set, and produce a large number of bootstrapped or jackknifed data sets (with range between 100 and 1000). In our study, a value of 100 was selected.

Next, the phylogeny estimate for each of these was determined. This estimates were calculated according to the particular method of interest. For instance, to use the DNA parsimony algorithm, we first ran Seqboot, and generated a file with 100 bootstrapped data sets. The phylogeny estimate for each of the Ebola viruses was determined using the DNA parsimony algorithm. The Bundingbugyo Ebola virus was used as the outgroup. One hundred replicates were utilized for the phylip bootstrapping algorithm. A random number seed of three was employed.

The file produced was fed as input file into the Dnapars. The Dnapars was run with the Multiple Data Sets option, and informing it to expect 100 data sets.

The output from this analysis produced a large output file, as well as a tree file, with the trees from the 100 data sets. The tree file later served as the input for the Consense tree.

For DNA parsimony, 10000 number of trees were used to save. The input order of sequences were randomized using a seed of 13, and performed 10 times.

When Consense is run, this resulted in the majority rule consensus tree. This produced the outcome of the analysis: genomes_Ebola_final_phylip_output(1) and genomes_Ebola_final_phylip_output_tree (1). The evaluation results from this exercise are depicted in

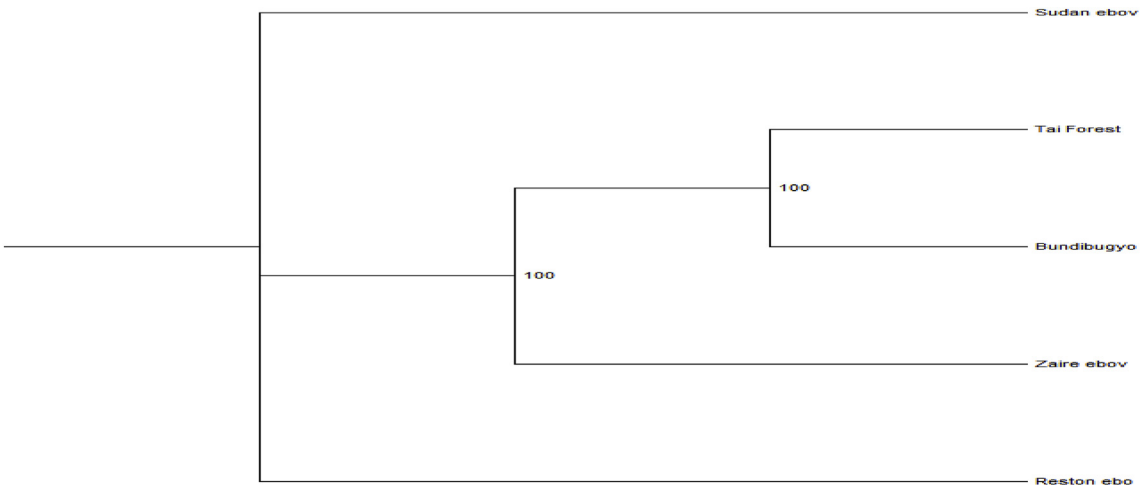


**Fig. 5.** Rectangular cladogram depicting the relationships among the five different strains of Ebola virus.

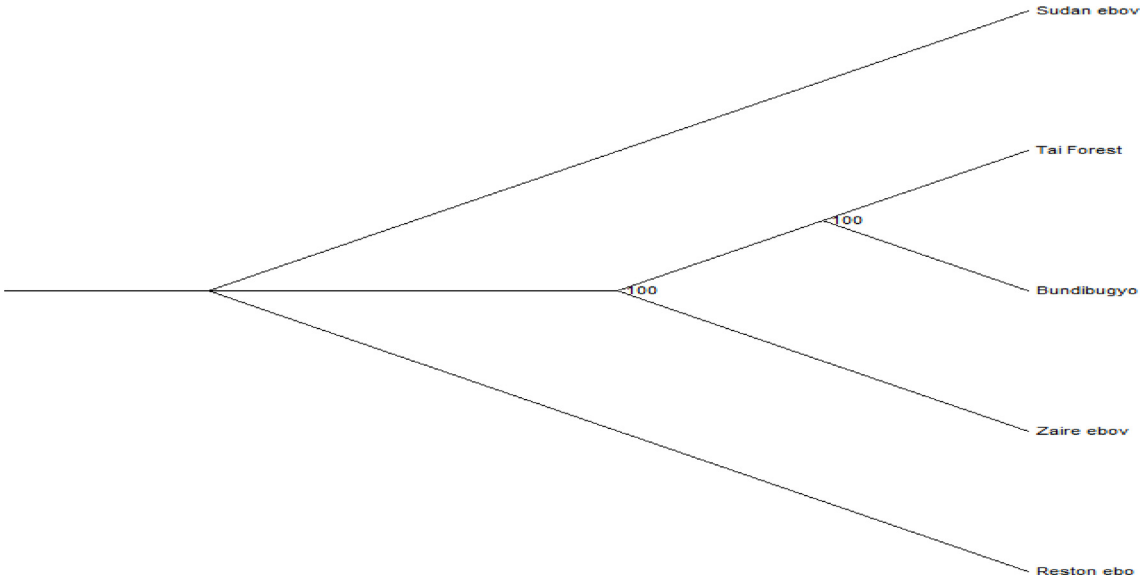


**Fig. 6.** Slanted cladogram depicting the relationships among the five Ebola virus strains.

Figs. 12 and 13. Online Tree viewer, ETE Toolkit phylogenetic tree viewer [160], was incorporated to visualize the results.

A second evaluation of the phylogenetic tree was then performed. For the second evaluation of the phylogenetic tree, MEGA X [159] and Clustal X [116], were used. Clustal X was used for bootstrapping, by incorporating the Neighbor Joining Clustering algorithm, and then a random number generator seed of 100 was used. The number of bootstrap trials was 1000.

MEGA X was employed to generate the newick tree. The newick tree was then viewed in different styles, as shown in Figs. 8–11.

## 3. Results

237,498 publications were identified. Out of these publications, 104 studies fulfilled our inclusion criteria. The studies were heterogeneous in the aspect of the study method, key discoveries, and insight gained towards control of Ebola, amongst others (see supporting material 1). The publications that fulfilled the inclusion criteria were classified into different groups - see Table 3 and Fig. 2, for the classification. The studies included were classified according to the EVD control intervention conducted. The interventions were classified into: drug & therapeutics, vaccines, modeling & simulations, and other experiments (See Table 3 and Fig. 2). Of the studies reviewed, 41 were drugs and therapeutics-related Ebola control research, 23 research publications were Ebola control vaccine-related studies, and 12 publications were EVD-control research that adopted a modeling and simulation approach [8–112]. Finally, 28 publications fell into the category of other experiments [8–112]. Other experiments include: biological experiments, bioinformatics experiments, border control measures, educational campaign measures, hand sanitation, and environmental sanitization, amongst others.

Furthermore, the trend and numbers of Ebola-control research from 2008 until 2018 were monitored. It was evident that from 2008 to 2013, there were very few publications. In 2014, the number of publications increased to 2 [87,96]. The number of publications of Ebola control-related research outputs in 2015, 2016, 2017 and 2018, were respectively, 21 research publications [60,67–80,83–85,89,93,104], 41 research publications [35–59,61–64,66,82,86,90,91,100,106–110,112], 32 research publications [8,10–34,81,88,92,94,99,105] and three research publications [9,101,103]. The results of the publishing frequency and trend, for scientists worldwide, are depicted in Table 4 and Fig. 3.

### 3.1. Phylogenetic analysis result

The phylogenetic tree results, from the comparative analysis of the five different strains of Ebola virus, is depicted in Figs. 4–7. The results showed that *Taiforest Ebola virus* and *Bundibugyo Ebola virus* are closely related. The results also showed that the *Sudan and Reston Ebola viruses* are closely related. The *Zaire Ebola virus* stood out from all.

### 3.2. Results of the evaluation of the phylogenetic tree

As an extended work, the phylogenetic tree produced from the bioinformatics analysis was evaluated. The results of the evaluation of the phylogenetic tree can be found as shown in Figs. 8–13. *Sudan Ebola virus* has a phylogenetic tree evaluation value of 0.19, the *Reston Ebola virus* value is 0.18, *Zaire Ebolarvirus has 0.17*, *Tai forest Ebola virus* has 0.15, and *Bundibugyo Ebola virus* has 0.15.

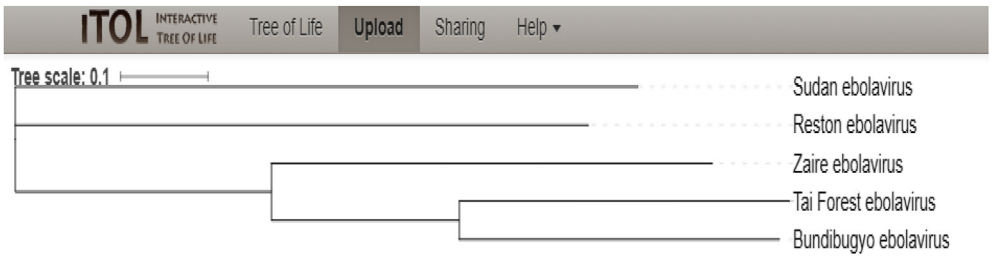


**Fig. 7.** Phylogenetic tree, depicting the relationships among the five Ebola virus strains, viewed using iTOL software.

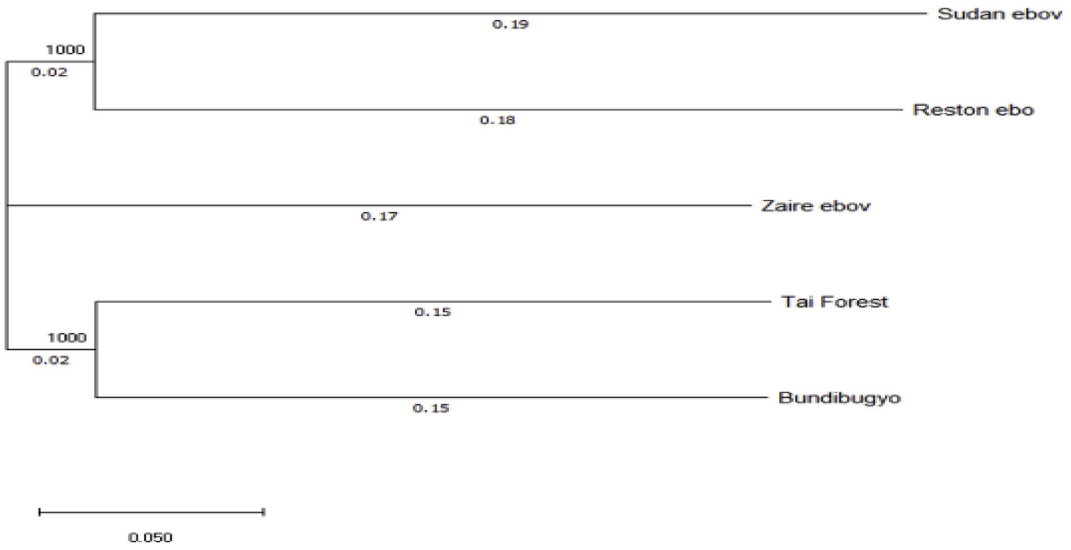


**Fig. 8.** Rectangular cladogram view of the phylogenetic tree evaluation results. This depicts the relationships among the five Ebola virus strains. It was generated via MEGA X software [159]. It was viewed in the newick version using Treeviewer [160]. The bootstrap value used during the evaluation was 1000. This is evident at the nodes of Fig. 8. This shows that the evaluation is good. The smaller numbers on the tree are phylogenetic evaluation estimates.

## 4. Discussion

### *4.1. Discussion on the results of the systematic review*

The results obtained from the systematic literature review, has helped identify literature that has been tailored towards controlling the spate of Ebola. The control of EVD can be achieved through useful interventions such as drug targets, vaccines, and immunotherapeutic approaches, amongst others.

Out of the initial 237,498 publications identified, only **104** articles met the inclusion criteria. It is interesting to note that drugs and therapeutics-related Ebola control research, with a total of 41, had the highest number of publications [8–112]. The second control group, classified as other experiments, ranked second, with a total of 28 research publications [8–112]. Vaccine-related Ebola control research ranked third, with a total of 23 research publications [8–112]. This was followed by modeling and simulation-related EVD control research, with a total of 12 research publications [8–112].

These results reveal that, from 2008 to 2018, there are very few modeling and simulation research articles relating to Ebola control. Modeling and simulation research exhibited the least number of publications. It is evident that no modeling and simulation research studies have been specifically conducted with regard to the impact of multi-level interventions on EVD control, reduction, and possible eradication. Such multi-level interventions include the joint application of multi-target vaccines, multi-target drugs, and multi-target therapeutics toward EVD reduction and possible eradication, on selected communities. This calls for further research. It is also evident from the results of this study, that very few modeling and simulation studies have been conducted on the control of EVD in the last 10 years. Thus, there is need for more modeling and simulation-related Ebola control research. There is a need for more studies on modeling and simulation to assess or estimate the impact of drugs targets, hybrid drugs, and hybrid therapeutic formulations on Ebola incidence, reduction, and possible eradication.

In the last decade, research on drugs or drug targets and therapeutics have contributed immensely to control measures against EVD.

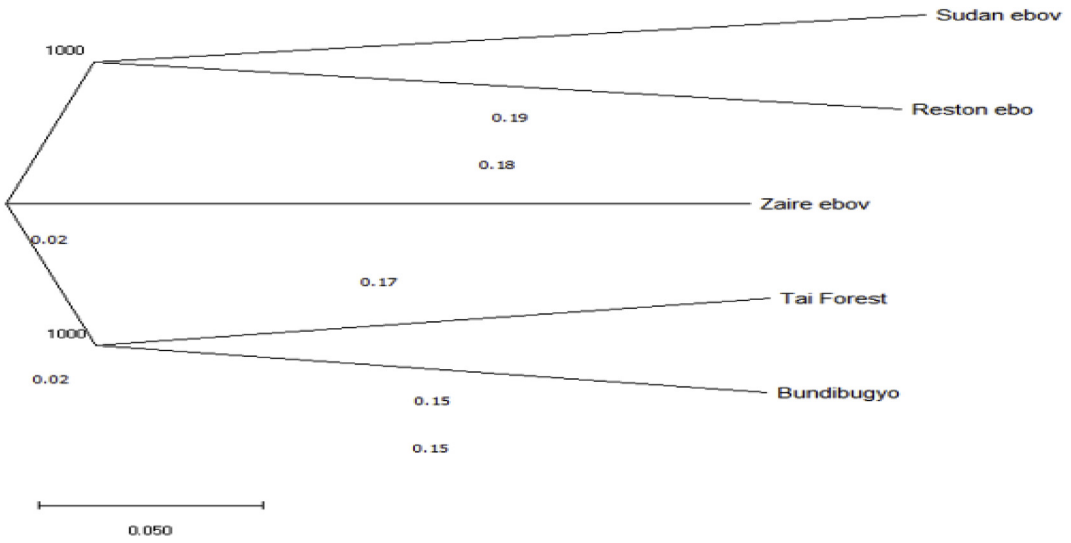


**Fig. 9.** Straight tree cladogram view of the phylogenetic tree evaluation results. This depicts the relationships among the five Ebola virus strains. It was generated by the MEGA X software [159]. It was viewed in the newick version using Treeviewer [160]. The bootstrap value used during the evaluation was 1000. This is evident at the nodes of Fig. 9. This shows that the evaluation is good. The smaller numbers on the tree are phylogenetic evaluation estimates.

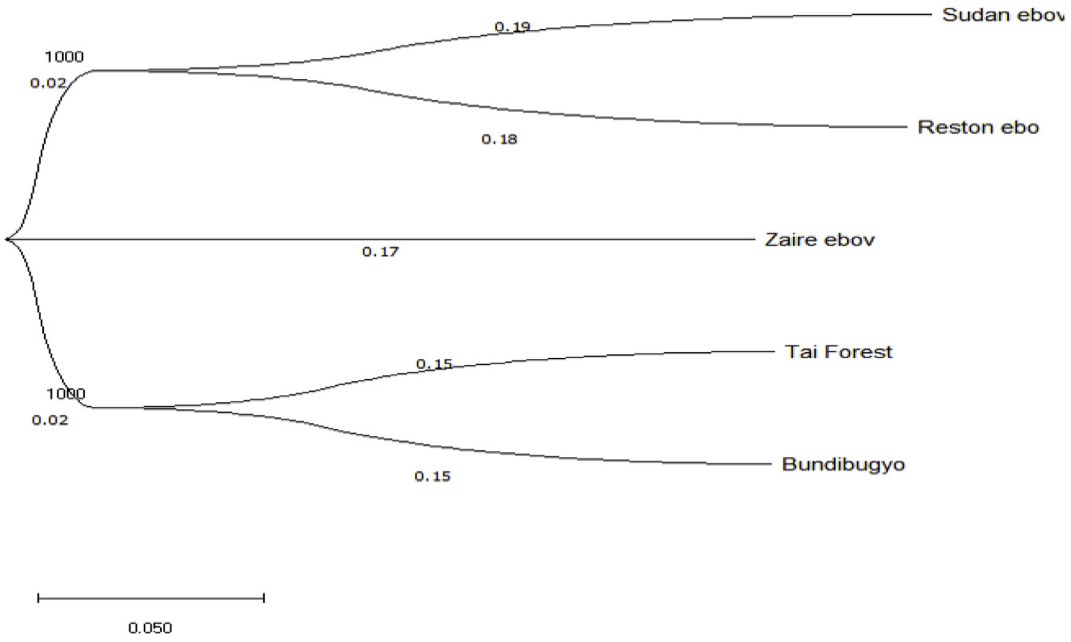


**Fig. 10.** Curved cladogram (Bow-shaped view) phylogenetic tree evaluation results. This depicts the relationships among the five Ebola virus strains. It was generated by the MEGA X software [159]. It was viewed in the newick version using Treeviewer [160]. The bootstrap value utilized during the evaluation was 1000. This is evident at the nodes of Fig. 10. This provides evidence that the evaluation is satisfactory. The smaller numbers on the tree are phylogenetic evaluation estimates.

Vaccine-related research have also contributed meaningfully to control efforts against EVD. Modeling and simulation will likely be useful to forecast future outbreaks of EVD. It will also be useful to predict the level of future interventions needed to drastically reduce or avert future EVD outbreaks.

More research is needed to translate Ebola drug-targets, multi-drug targets, and therapeutic targets, into effective EVD drugs. Moreover, modeling and simulation studies can be used for modeling Ebola drug trial designs, therapeutic trial designs, and multi-target vaccine trial designs. Ebola drugs and therapeutic trials are essential for safety and efficacy. Modeling and simulation studies can complement this process.

Another interesting finding revealed that scientists were actively engaged in EVD-control research whenever there were incidences of Ebola Virus Disease. However, whenever there was a lack of EVD incidence, scientists engaged to a lesser extent in EVD-control research. This is evident in Fig. 3. Frequency of EVD-control scientific publications soared higher in years 2015 and 2016, when the 2014–2015 Ebola pandemic ravaged some West African countries. The pandemic caused some panic, and mortality rates were relatively high. It should be noted that research in scientific publications published in 2015 and 2016 were initially conducted in year 2014 and 2015 respectively (this was a period of Ebola pandemic and high mortality rate). The same applies to scientific publications published in 2017. There had been incidences of EVD in DR Congo in 2016 and most recently in 2017. The incidence accounted for the deaths of many people. This confirms the results obtained in Fig. 3.

### *4.2. Discussion on the results of the bioinformatics analysis - phylogenetic trees*

Fig. 4, depicts the relationship between the five EVD virus strains. It is evident that *Zaire Ebola virus* was distinct from the other four Ebola virus strains. *Zaire Ebola virus* is the most virulent of all Ebola viruses [122]. Consistent with other phylogenetic studies [48,121], our results showed that *Bundingbugyo and Tai forest Ebola virus* are closely related [See Fig. S5 in [48]; See Fig. 3 in [121]]. *Reston and Sudan Ebola virus* are also closely related from the results shown in the phylogenetic tree information. This is similar to the results obtained in prior work. An

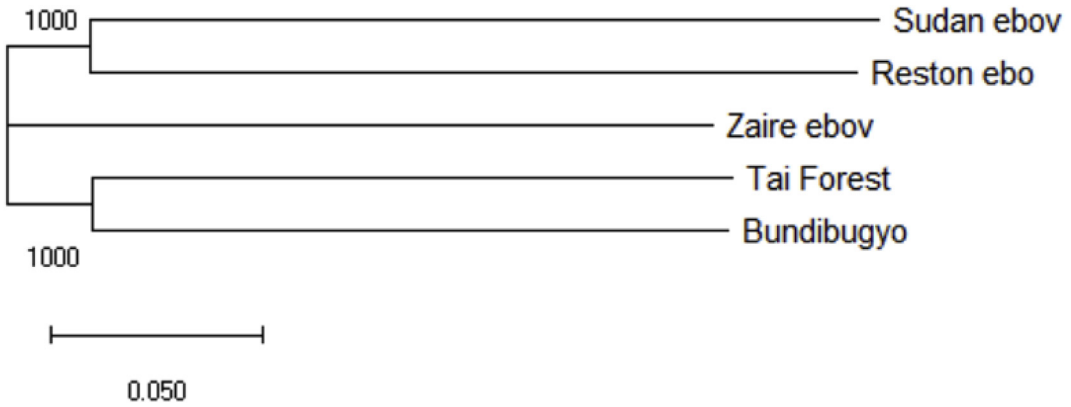


**Fig. 11.** Rectangular Cladogram (Fourth view) of phylogenetic tree evaluation results. This depicts the relationships among the five Ebola virus strains. It was generated by the MEGA X software [159]. It was viewed in the newick version using Treeviewer [160]. The bootstrap value used during the evaluation was 1000. This is evident at the nodes of Fig. 11. This provides evidence that the evaluation is satisfactory. The smaller numbers on the tree are phylogenetic evaluation estimates.

**Table 2**
Five complete genome of Ebola virus.

| Genome | Accession | Source information | Host | Genome Size | Proteins | Neighbors | Date Created | Date Updated |
|---|---|---|---|---|---|---|---|---|
| *Bundibugyo Ebola virus* | NC_014373 | isolate: Bundibugyo virus/H.sapiens-tc/UGA/2007/Butalya-811250 | Vertebrates, human | 18940 nt | 9 | 6 | 08/09/2010 | 04/24/2018 |
| *Reston Ebola virus* | NC_004161 | isolate:Reston virus/M.fascicularis-tc/USA/1989/Philippines89-Pennsylvania | Vertebrates, human | 18891 nt | 9 | 17 | 09/04/2002 | 02/16/2018 |
| *Sudan Ebola virus* | NC_006432 | isolate:Sudan virus/H.sapiens-tc/UGA/2000/Gulu-808892 | Vertebrates, human | 18875 nt | 9 | 14 | 11/15/2004 | 02/16/2018 |
| *Tai Forest Ebola virus* | NC_014372 | isolate:Tai Forest virus/H.sapiens-tc/CIV/1994/Pauleoula-CI | Vertebrates, human | 18935 nt | 9 | 1 | 08/05/2010 | 04/20/2016 |
| *Zaire Ebola virus* | NC_002549 | isolate:Ebola virus/H.sapiens-tc/COD/1976/Yambuku-Mayinga | Vertebrates, human | 18959 nt | 9 | 1382 | 02/10/1999 | 02/16/2018 |

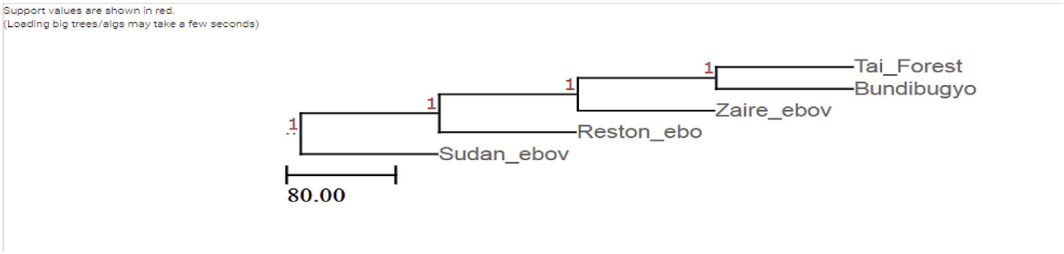


**Fig. 12.** The output from Phylip phylogenetic tree evaluation [158]. It was viewed by using the online Tree viewer [160].

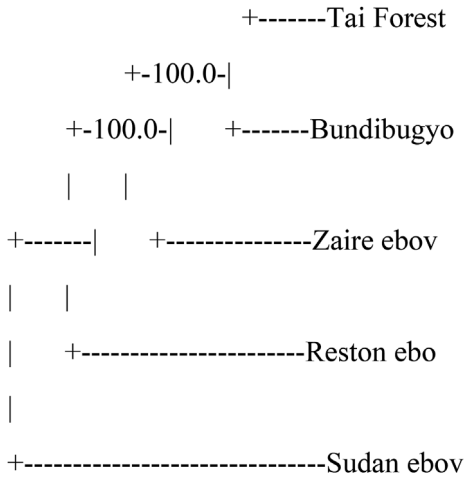


**Fig. 13.** Consensus Tree. The numbers on the branches indicate the number of times the partition of the species into the two sets which are separated by that branch occurred among the trees, out of 100.00 trees.

**Table 3**
Classification of synthesized Ebola control studies into Potential Control/intervention groups.

| Ebola Control Group | Vaccines | Modeling and Simulations | Drugs and Therapeutics | Other Experimental studies |
|---|---|---|---|---|
| Number of studies from 2008 to 2018 | 23 | 12 | 41 | 28 |

important insight for EVD control is that similar methods of control can be applied to curb the spread of *Reston and Sudan Ebola viruses*, because these viruses are closely related. Similar approaches can also be adopted and applied to *Bundingbugyo and Tai forest Ebola viruses*, since these two Ebola viruses are closely related. It may be possible to adopt similar EVD control measures, at the molecular level, against other Ebola virus strains that are closely related. Furthermore, this can facilitate the development and production of joint, multi-protective, multi-treatment drugs and vaccines against Ebola virus strains.

Zaire is the most virulent of the five Ebola viruses [122]. More intensive research efforts should be directed at preventing the transmission of *Zaire Ebola virus,* especially to assist in preventing a major Ebola pandemic from occurring. EVD-control vaccination-related research, drug target-related, and therapeutic-related research, should be encouraged and funded. One of the possible control insights from the phylogenetic analysis result is that molecular and biological experiments on Ebola virus strains that are closely related, should be funded towards discovering hybrid novel control measures against EVD transmissions. Vaccine development and trials have shown great promise in the fight against *Zaire Ebola virus* [10,18,20,23,34,47,96,106]. More research is needed to develop an effective, efficient and safe vaccine against *Zaire Ebola virus*. This current study is potentially significant in the fight against Ebola Virus Disease (EVD).

### 4.3. Discussion on the evaluation of the phylogenetic tree

Figs. 8–13, depict the results of the evaluations of the phylogenetic tree. It is evident that the outputs from the MEGA X phylogenetic tree evaluation, and the Phylip phylogenetic tree evaluations, yielded the same results. It is evident that these results can spur more research toward the control of EVD. The values obtained from the evaluation of the phylogenetic trees reveal that some of the virus strains are very

**Table 4**
Showing the frequency of publications of EVD control research between 2008 and 2018.

| Year | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Publications | 1 | 1 | 1 | 1 | 0 | 1 | 2 | 21 | 41 | 32 | 3 |

closely related. Such results can provide a platform for further research into the evolutionary analysis of the five different Ebola viruses. Such analysis may produce novel results. The results may then be useful to ultimately eradicate EVD. Furthermore, the results obtained from the evaluation of the phylogenetic tree, can help provide insight into the origins and evolution of these Ebola viruses. The evaluation can also provide insight into the possible structural and genetic mutations that each Ebola virus may undergo. Finally, the structural and functional properties of the genetic make-up of the genes of each Ebola virus can be inferred. Knowledge from such inference can be channeled toward the control of EVD.

## 5. Recommendations

Proper partnership with relevant health organizations can be assistive in future surveillance efforts. This will help in the fight against EVD. Prompt response to an EVD outbreak, will help in reducing the transmission of the disease. Isolation and treatment of EVD infected individuals, will help in curtailing the spread of the disease. Investment and adequate funding for biological computation, bioinformatics and molecular research on EVD, will assist scientists to develop novel disease treatments. Regulation on the consumption of bush meat can also help to reduce the transmission of EVD. Implementation strategies, computational models and computational systems that can send early signals and predict possible future outbreaks of EVD should be implemented. Educating and sensitizing the public, both rural and urban dwellers, concerning the prevention of Ebola Virus Disease would be a substantiative progress. Effective border control and health screening at various ports of entry for all African countries, as well as other nations, should be implemented. All of these recommendations, if fully implemented, can play a major role in the effective control of EVD.

## 6. Conclusion

This study has provided generalized and in-silico insight for the control of EVD from the studies identified according to inclusion criteria. To the best of our knowledge, the investigation has extensively reviewed the Ebola control-related literature. Insight for Ebola control was gained from the reviewed studies. Insight for EVD control was also obtained from the bioinformatics analyses performed on five different strains of Ebola virus. Evaluation of the phylogenetic tree provided further insight for EVD control. We recommend that scientists should continue these efforts toward EVD control. Investigators should consistently engage in active research toward EVD control and possible eradication.

## Conflicts of interest

The authors declare that there are no competing interests.

## Author contribution

Olugbenga Oluwagbemi conceived of the research and designed the overall study. Awe Olaitan and Olugbenga Oluwagbemi performed the bioinformatics analysis; Olugbenga Oluwagbemi wrote the manuscript. Olugbenga Oluwagbemi conducted the systematic review and rewrote the revised version of the manuscript. All authors read and approved the final manuscript.

## Ethical statement

The names of authors that contributed to the paper have been included. We have conducted plagiarism check on the manuscript. We used the turnitin plagiarism checker for this purpose. The result was OK. The paper has not been submitted to any other journal for consideration. All references have been duly cited.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.imu.2018.07.004.

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