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Research Article

Surveillance of Antimicrobial Resistance in Emerging and Reemerging Infectious Diseases in Nigeria

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Abstract

Antimicrobial agents play vital roles in decreasing human morbidity and mortality resulting from infectious diseases. However, the advent of resistance to many of these agents are significantly declining their efficacy. Most of the emerging and reemerging diseases are increasingly becoming resistant to a number of antibiotics that have previously been used in their treatment by developing mechanisms of resistance through target protection, target substitution, antibiotic detoxification and blockage of intracellular antibiotic accumulation thereby posing serious health threat in the public health all over the world. This review was conducted to ascertain the surveillance of AMR in emerging and reemerging infectious disease in Nigeria using extensive literature search through Google scholar, PubMed, Scopus and Wikipedia. From the reviewed data, laboratory-based surveillance of AMR system in Nigeria is limited as most research institutes, hospitals and laboratories have poor AMR system for organisms that are linked to multidrug resistance. This therefore recommends urgent intervention of researchers, health practitioners, Nigerian Government and the global society to ensure protection of these life-saving drugs for future value. Detection of resistant strains, its mechanisms of resistance and monitoring its spread using molecular techniques as well as implementing effective antimicrobial stewardship and infection control programs that will aid in curbing emerging and reemerging diseases that are becoming resistant should be prioritized.

Keywords: *Surveillance; Antimicrobial Resistance; Emerging and Reemerging; Infectious Diseases; Nigeria*

Introduction

The use of antimicrobial agents in the treatment of infectious diseases plays vital roles in reducing the morbidity and mortality rate in global population that result from infectious and communicable diseases however, the advent of microbial resistance to many of these agents are opposing their effectiveness thereby posing health threats to public health. According to WHO [1], emerging infectious diseases such as Acquired Immune Deficiency Syndrome (AIDS), Ebola haemorrhagic fever, Lassa haemorrhagic fever, Lyme disease, Severe Acute Respiratory Syndrome (SARS), and West Nile Virus are consistently becoming epidemic while previously treated diseases outbreaks such as cholera, tuberculosis, Influenza (flu), hepatitis and staphylococcus infections are re-emerging. WHO (2013), reported that Antimicrobial resistance (AMR) challenges and its magnitude within African Region including Nigeria are hampered by surveillance of drug resistance. After many years of widespread of antibiotic use, microbial pathogens of human and animal origin are becoming increasingly resistant to many antimicrobial agents which constitute a major health threat around the globe in the present. WHO (2015), reported that

Resistant microbes become increasingly difficult to treat, requiring alternative medications or higher doses, both of which may be more costly or constitute toxicity. Centers for Disease Control and Prevention (CDC) defined surveillance as the consistent collection, analysis and interpretation of health data crucial to the planning, implementation and evaluation of public health practice, closely integrated with the timely distribution of these data to the needed parties [2]. The increase of resistance by disease causing pathogens such as *E. coli*, *M. tuberculosis, S. aureus,* HIV and nosocomial infection imposes the focal burden of this problem on developing countries 3 Despite the burden of AMR occurring from emerging and reemerging diseases, its surveillance resistance is derailed. This research therefore aimed at determining AMR and its surveillance system in Nigeria with the hope of providing promising recommendations that could help in curbing AMR for a sustainable society.

Antimicrobial resistance (AMR)

Antimicrobial resistance (AMR), including antibiotic resistance, is the resistance of a microbe to an antimicrobial agent (medication) that is effective in treating or preventing an infection caused by that microbe (WHO 2015); this is a serious health problem (Wiley., *et al.* 2008) as it poses a major threat to clinical medicine and public health, not only in developing countries but global society as a whole. According to World Health Organization [1], antibiotics are not only essential for the treatment of classical infections such as bacterial pneumonia, sepsis or meningitis, tuberculosis (TB) or gonorrhea, but also opportunistic infections that may occur in patients predisposed to infection, particularly in hospital. According to Anzaku., *et al.* [4] resistance of organisms to some antibiotics has increased and it has been observed that frequent use of these antibiotics have caused a visible increase in the development of resistance of third generation Cephalosporin's with aminoglycosides, Quoninoles that are used to treat acute Urinary Tract Infections (UTIs). In spite of the preceding and the continuous scrutiny of improved pathogenicity of microorganisms and their associated resistance to antimicrobial agents, relatively few documented report on its incidence and antimicrobial resistance mechanisms are available in Nigeria [4].

Emerging infectious diseases

An emerging infectious disease (EID) is an infectious disease whose has appeared in a population for the first time; this account for at least 12% of all human pathogens (Taylor, 2001). EIDs are caused by newly identified species or strains (e.g. severe acute respiratory syndrome (SARS), HIV, Ebola virus, Lassa Hemorrhagic fever virus, Zika virus and Monkey pox virus that may have evolved from a known infection (e.g. influenza) or spread to a new population (e.g. West Nile fever) or to an area undergoing ecologic transformation (e.g. Lyme disease), or be reemerging infections, like drug resistant tuberculosis. Nosocomial (hospital-acquired) infections, such as methicillin-resistant Staphylococcus aureus are emerging in hospitals, and extremely problematic in that they are resistant to many antibiotics of growing concern are adverse synergistic interactions between emerging diseases and other infectious and non-infectious conditions leading to the development of novel syndemics (Jump,1997).

Reemerging infectious diseases

Reemerging infectious diseases are diseases experienced rapid increase after a period of control e.g. cholera, malaria and tuberculosis; they are infections that have newly appeared in a population or have existed previously but are rapidly increasing in incidence or geographic range [5]. Emerging and Re-emerging infectious diseases is a clear indication that all infectious diseases are constantly changing in the interplay between pathogens, their hosts and environmental factors influencing both emerging and reemerging infections. Figure 1 below is a pictorial presentation of globally noted emerging and re-emerging infectious diseases.

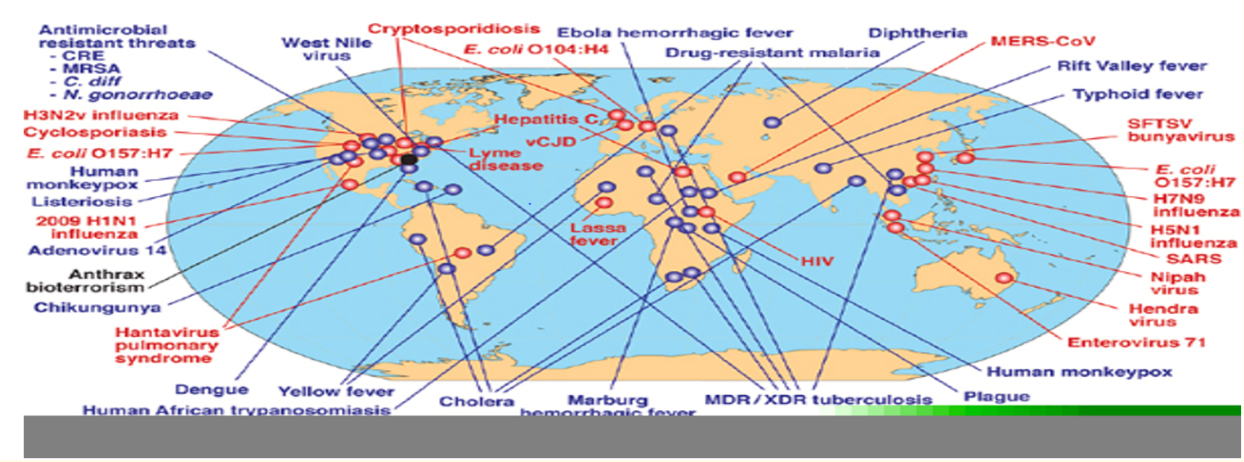

Figure 1: *Global example of emerging and reemerging infectious diseases.*
Source: (Rimer, 2016).

Ebola haemorrhagic fever outbreak in Nigeria

The Ebola outbreak in 2014 (notably in West Africa - Liberia, Sierra Leone, Senegal, Guinea and Nigeria) was supposed to be a warning of greater dangers to come, especially for countries that do not have sound healthcare systems such as Nigeria.

Lassa haemorrhagic fever outbreak in Nigeria

The experience of Lassa outbreak in Nigeria has uncovered the ineffectiveness of the health system to grapple emerging and reemerging disease outbreaks all over the globe, where diseases can quickly spread from remote villages to cities. Nigeria has four documented incidents of Lassa fever occurrences with the first emergence in 1969 in Lassa village (Borno State, North East Nigeria) but was isolated from the blood sample of a missionary nurse who had sought treatment in Jos, Plateau State (North Central region of Nigeria) [7]. Since the re - emergence of Lassa fever in Nigeria 2015, it has showed no significant reduction as first quarter of 2018 has claimed over 450 life.

Emergence of Antimicrobial Resistance (AMR)

Antimicrobial resistance emergence is determined by a multifaceted interaction of epidemiological, clinical, environmental, and behavioural factors while overuse of antibiotics has been a powerful elector of resistance (Coast and Smith, 2003). Okeke., *et al.* [8], stated that while antimicrobial resistance emerge primarily as a result of excessive and often unnecessary use of antibiotics in humans and animals, it has also been exacerbated by multiple factors such as the human source problem in the health sector in sub-Saharan Africa. The cells containing resistance gene grow in the presence of an antibiotic and rapidly increase in the numbers at the expense of susceptible cells once a resistance gene or mutational gene is present and is recognized [9]. Resistance of microbial strains to antibiotics is a major public health concern that requires multidisciplinary approach towards curbing it [10].

Spread of antimicrobial resistance (AMR)

The spread of transportable genetic elements such as plasmids, transposons, and integrons has significantly contributed to the rapid dispersion of AMR among several bacterial species of human. According to Harbottle., *et al.* [11], AMR genes have been shown to accumulate on mobile elements, leading to a situation where multidrug resistance phenotypes can be transferred to a susceptible recipient via a single genetic event and the increasing prevalence of antimicrobial resistant bacterial pathogens has severe implications for the future

treatment and prevention of infectious diseases in both humans and animals. The most common mechanisms sustaining AMR is horizontal gene transfer between a resistant bacterium and a susceptible one which frequently occurs in the absence of selection [12].

Common AMR pathogens in Nigeria

According to Okesola and Oni [13], most Nigerian microbial isolates indicated high resistance in both Gram-positive and Gram-negative organisms through examination of antimicrobial susceptibility assay. Resistance to Ampicillin allegedly increased from 70% to 90%, Co-trimoxazole from 77% to 85%, Chloramphenicol from 71% to 77%, Streptomycin from 71% to 79%, and Nalidixic acid from 0% to 11.3% during 1990 - 2000 root-cause analysis of antimicrobial resistance in Africa [14]. Methicillin resistant *Staphylococcus aureus* (MRSA), Vancomycin Resistant *Staphylococcus aureus* (VRSA) and *Enterococci*, Multidrug resistant gram negative bacteria such as those with Extended Spectrum Beta Lactamase (ESBL) resistance and carbapenem resistant Enterobacteriaceae, Multi drug and extensive-drug resistant *Mycobacterium tuberculosis* (MDR-TB and XDR-TB) [15].

Drug resistant among HIV/AIDS patients in Nigeria

Kanki [16], stated most HIV/AIDS infected mothers in Nigeria are developing resistance to nevirapine (NVP) whereas14% of HIV infected babies have developed resistance to no-nucleotide reverse transcriptase inhibitors (NNRTI) which could be attributed to genetic diversity among HIV patients in Nigeria, a situation that may be responsible for the resistance. Booth and Geratti [17] asserted that transmission of drug-resistant HIV-1 variants from antiretroviral treatment-experienced persons has occurred through multiple routes including sexual intercourse, intravenous drug use and vertical transmission from mother to child.

Drug resistant tuberculosis in Nigeria

The control efforts and the burden of drug resistant tuberculosis (TB) is poorly comprehended in resource-limited settings. According to WHO (2017), out of the global rate of 10.4 million incident cases of TB, 3.9% are estimated to have had rifampicin-or Drug resistant tuberculosis whereas 21% treated TB cases were estimated to have had MDR/RR-TB in the same year. Nigeria is one of the leading countries in the high burden countries for TB/HIV, DR-TB and TB and the estimated incidence of TB in Nigeria is 322 per 100 000 population with only 15% of the total burden of the disease in the country being reformed in 2015 (WHO, 2017). The WHO estimated the proportion of patients with MDR/RR-TB as 4.3% among new cases and 25% among previously treated cases in Nigeria [18].

Extended spectrum beta lactamase producing bacteria

Extended spectrum β-lactamases (ESBLs) producing bacteria are etiological agents of nosocomial infections and can have severe clinical implications with a consistent multiple antibiotic resistances [19]. During resistance reaction, the β-lactamases deactivate the molecular antibacterial properties of β-lactam antibiotics by flouting and opening the β-lactam ring Maina., *et al.* [20], reported that β-lactamase bacteria are not just resistant to β-lactam antibiotics but also to antibiotics from other classes thereby posing a therapeutic challenges to clinicians. According to Oluduro., *et al.* [21], ESBLs enzymes are carried in and transferred by bacterial plasmid and are responsible for bacteria resistance to β-lactam antibiotics but are inhibited by β-lactamase inhibitors [22].

Mechanisms of Antimicrobial Resistance

Bacteria develop the following three vital mechanisms of antimicrobial resistance which are: (1) enzymatic degradation of antibacterial drugs, (2) alteration of bacterial proteins that are antimicrobial targets, and (3) changes in membrane permeability to antibiotics [23]. AMR can either be plasmid mediated or maintenance of bacterial chromosome. The expression of chromosomal beta-lactamase can either be induced or stably depressed by exposure to beta-lactam drugs [24]. According to Semenitz (2013), resistance to methicillin which is stable to gram-positive beta-lactamase such as Methicillin Resistant *Staphylococcus aureus* (MRSA), occurs through the alteration of an antibiotic target protein, penicillin-binding protein.

Horizontal transposon (Gene) transfer (HTT)

Microorganisms also may acquire genes from each other including genes that make the microbe drug resistant. Transposon also known as jumping gene is a mobile segment of DNA that can pick up a resistance gene and insert it into a plasmid or chromosome, thereby inducing horizontal gene transfer of antibiotic resistance [25]. Horizontal transposon transfer (HTT) passes a pieces of DNA that are characterized by their ability to move from one locus to another between genomes by means rather than parent-to-offspring inheritance. HTT is critical to not only prokaryotic evolution also to widespread phenomenon in eukaryote evolution as well [26]. Spreading between genomes via HTT at the transposon side is a strategic way of escaping purging due to purifying selection, mutational decay and host defense mechanisms for example; *E. coli* 0104 which is an emerging disease causing bacterium is associated to bloody diarrhea as well as potentially fatal kidney damage [27].

Plasmid encoded antimicrobial resistance

Bacterial plasmids are elements that move many bacterial genes from one bacterial cell to another, while horizontal gene transfer are bacterial plasmids specifically conjugative plasmids that promote their own transfer and the transfer of other plasmids from one bacterial cell to another [28]. Plasmid-encoded antibiotic resistance encompasses most of antibiotics currently in clinical use and includes resistance to many that are at the forefront of antibiotic therapy [28].

Mutational resistance

During mutational resistance, a detachment of bacterial cells derived from a susceptible population develop mutations in genes that affect the activity of the drug, resulting in preserved cell survival in the presence of the antimicrobial molecule; once a resistant mutant emerges, the antibiotic eliminates the susceptible population thereby creating way for resistant bacteria to predominate [29]. Mutations resulting in antimicrobial resistance alter the antibiotic action via one of the following mechanisms, i) modifications of the antimicrobial target a decrease in the drug uptake, ii) activation of efflux mechanisms to extrude the harmful molecule, or iv) global changes in important metabolic pathways via modulation of regulatory networks [30].

Other resistance mechanisms

Microorganisms of various species evolve over time with main function of reproducing, thriving and spreading quickly with high efficiency as a result of the following [24].

Natural (Biological) causes: Microbes are pressurized in the presence of antimicrobial agents as they are either being killed or survive if they harbor resistance genes. These survivors will replicate, and their progeny will quickly become the dominant type throughout the microbial population.

Societal pressures: Antimicrobials usage creates selective pressure for resistant organisms such as the societal pressures which act to accelerate the increase of antimicrobial resistance.

Inappropriate use: improper use of antibiotics can induce antimicrobial resistance. This act past following inappropriate prescription of drugs by healthcare providers and some quacks in the field who illegally acquired such skills, wishing to placate an insistent patient who has a viral infection or an as-yet undiagnosed condition.

Inadequate diagnostics: Healthcare providers uses partial or imperfect information to diagnose an infection and thus prescribe an antibiotics just-in-case or prescribe a broad-spectrum antimicrobial when a specific antibiotic is the preferred option.

Hospital use: Patients who are critically ill are more prone to infections and often require the aid of antimicrobial sensitivity assay. However, the heavier use of antimicrobial agents in these patients can worsen the problem by selecting for antimicrobial-resistant microorganisms.

Agricultural use: Adding antibiotics to agricultural feed has been reported to promote drug resistance.

Challenges Affecting AMR Surveillance in Nigeria

Despite efforts made to gather AMR data in TB for surveillance, challenges still persist. Frean., *et al.* (2012), identified some major challenges affecting AMR surveillance system in Nigeria which includes lack of a comprehensive policy and plan to address AMR, feeble medicines regulatory capacity and circulation of substandard/counterfeit antibiotics, lack of strategic AMR surveillance, poor laboratory capacity on AMR testing and reporting, lack of essential laboratory reagents and consumables and limited quality assurance and control protocols. According to Center for Disease Control and Prevention [31] that lack of inter-laboratory framework for collaborative AMR surveillance seriously impedes efforts to track emerging and reemerging diseases challenges in Nigeria.

Inappropriate use of antibiotics

Antibiotics are some of the most overused and misused medications due to their low cost, high effectiveness and low level of side effects. Beitha [32] estimated that about 60% of antibiotics prescribed by general practitioners are used inappropriately. High levels of antimicrobial use are also found in animals and plants and have been linked to transmission of resistant pathogens to humans through environmental contamination and direct contact with animals or animal products [33].

Geographical location

AMR is the outcome of a 'race' between natural selection and human ingenuity. The more antimicrobials are used, the less effective they become. Continuous innovation must take place to keep pace with evolving pathogens. Rising levels of AMR are a sign that natural selection is taking place more rapidly than is innovation in the development of new antimicrobials.

Lack of access to antibiotics

While many countries are working to decrease inappropriate use of antimicrobials to limit the growth in resistance, lack of access is still an issue in many Low and Middle Income Countries (LMICs). Hope., *et al.* [34] reported that ensuring timely access to antibiotics would prevent an estimated 445,000 pneumonia deaths in children living in LMICs as limited access may promote AMR through inappropriate treatment regimes.

Necessity for Antibiotic Resistance Surveillance

Successful treatment of serious infections requires timely administration of effective chemotherapeutic agents. While some infections (e.g. TB, whooping cough and gonorrhea) are caused by a single pathogen, the majority of infections, such as those affecting the skin and soft tissues, the upper and lower respiratory tracts, the urinary tract, meningitis and sepsis are caused by a range of pathogens (Shahan., *et al*. 2013).

Roles of microbiology laboratory in AMR surveillance

Microbiology laboratory is the key partner in the surveillance of Antimicrobial resistance. Healthcare workers and public health authorities rely on the work of the microbiologist to determine what organism is causing infection in a patient and the antimicrobials that would be effective treatment options. Surveillance system for AMR is driven by laboratory data [23]. To ensure that data is comparable, two approaches are taken namely: (1) Send isolates to a limited number of reference laboratories for analysis and reporting (2) Standardize protocols across the participating laboratories and enforce participation in external quality assurance programs (MLSC, 2014).

Antimicrobial susceptibility assay (ASA)

This test is conducted mainly to determine the susceptibility and resistance pattern of microorganisms to antimicrobial agents and it can be achieved through (1) Dilution susceptibility tests (2) Disk diffusion tests (Kirby Bauer and Stokes method) (3) E-test and E-test based automated testing systems (Vitek analysers) (4) Molecular techniques. It has been encouraged that laboratory surveillance should rely mainly on molecular and sequence-based typing data [35].

Way-Forward

The following action steps have to be taken in order to curb antimicrobial resistance in both Nigeria, Africa and the world as a whole.

Develop and implement strategic policies

In order to prevent and combat AMR, comprehensive national AMR policies, strategies and plans should be developed and implemented involving researchers, policy-makers, partners and stakeholders in public health. Targeted capacity building activities in various fields including AMR surveillance, laboratory based surveillance, quality control of test reagents and protocols, effective medicines regulation and rational use of medicines are urgently needed [35].

Develop comprehensive national policies and plans to combat AMR

Within the context of national health and medicine policies, governments should develop and implement comprehensive AMR policies and strategies that take into consideration the AMR threat to public health so as to limit the emergence and spread of resistant germs [36].

The development of AMR surveillance techniques

The traditional passive surveillance refers to the health authorities' receipt of the reports of diseases or conditions which were submitted by physicians, laboratories, and other healthcare providers as was required by the public health legislation. However, the reportable diseases are often underreported to the health departments [37].

Establish AMR management platforms around the globe

Countries and health systems differ and the various barriers must be tackled in a contextualized manner. In establishing a multi- disease drug resistance surveillance network, the regional health community can build on a range of existing efforts.

Construction of clinical microbiology laboratory capacity

The vast majority of surveillance programmes are laboratory based. Strategies for ensuring and maintaining the quality of laboratory test results are critical to the value of surveillance initiatives. All facilities should have procedures for ongoing assessment of the quality of test reagents and test performance by clinical laboratory technicians.

Improvement of antimicrobial surveillance system across the country

Surveillance is the primary strategy for tracking emerging drug resistance in the population, and thus allowing for early and appropriate action. Countries should therefore strengthen their capacity for early detection and identification of resistant germs that cause diseases of public health importance.

Regional framework for collaborative surveillance of AMR

The regional framework collaborative surveillance of AMR provides a standardized overview of the prevalence of AMR in many countries in a given region. According to FAO [38], the lack of this regional framework for collaborative surveillance of AMR is a key problem hindering information sharing for decision-making both at country and regional level.

Supporting the Development of new antimicrobial Agents

Because of the limited return on investment, companies face challenges in finding capital to invest in basic research and to move promising compounds to the clinical phase.

Essential funding for clinical trials

Adequate funding for clinical trials should be provided for researchers as this stand the greatest challenges affecting researches and this could target project developers in the field of infectious diseases that successfully completed the pre-clinical stage and would now require validation through clinical trials.

Embark on Antimicrobial stewardship campaign

Prudent use of antimicrobials which is also referred to as "antimicrobial stewardship" is the optimal selection of drug, dose and duration of antimicrobial treatment, along with reduction of the inappropriate and excessive use as a means of slowing the emergence of antimicrobial resistance [39]. This therefore seek the need to embark on antimicrobial stewardship campaign since the opposite can result to multiple resistance in emerging and reemerging diseases.

Developing and implement national action plans

According to WHO [40,41], Developing national action plans (NAPs) is an integral and initial step for countries to establish an effective response to combat AMR. At the Sixty-eighth World Health Assembly in 2015, Member States committed to have NAPs in place by May 2017.

Monitoring and evaluation of surveillance of AMR

Locally relevant information is necessary for planning, prioritization, management and evaluation at country, regional and global levels. WHO (2014) global report on surveillance of antimicrobial resistance revealed that there are many parts of the world in which the scope or scale of the problem is unknown [42-49].

Conclusion and Recommendations

This study concluded that surveillance of AMR is very essential as most of the emerging and reemerging infectious diseases in Nigeria develop resistance to a good number of antibiotics. This study therefore recommends that: Since the mainstream of surveillance programs are laboratory-based, maintaining the quality of laboratory test results are critical to the value of surveillance initiatives. All facilities should have procedures for assessment of the quality of test reagents and test performance by microbiologists and laboratory scientists respectively. In addition to internal quality control practices, laboratories should also participate in national and international quality assurance programs. Building clinical laboratory capacity will enable the generation of adequate and reliable AMR data that can guide policy actions to combat AMR. Nigeria should therefore strengthen their capacity for early detection and identification of resistant bacteria that cause diseases of public health importance using molecular techniques. Finally there is an urgent need to embark on antimicrobial stewardship campaign in order to curb AMR as resistant strains are emerging and remerging.

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Ethical Consideration

This study relied on documented secondary data and as such, all sourced information were properly cited and referenced to avoid plagiarism as regards to ethical issues in research.

Competing Interest

All authors have declared 100% that no competing interest as regards to the publication of this manuscript exist.

Authors Contribution

All authors contributed immensely to the writing of the manuscripts. Anzaku AA did about 70% of the work while other authors proofread the manuscript.

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