ANTIBIOTIC RESISTANCE INDUCED BY EXTENDED-SPECTRUM BETA-LACTAMASES AND COVID-19

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ABSTRACT

Antibacterial resistance, particularly that resulted from by extended-spectrum beta-lactamases (ESBLs), is increasing at an alarming pace as a direct consequence of extensive antibiotic usage, leading to an increase in the number of infections that are difficult to be eradicated.. Klebsiella pneumoniae and Staphylococcus epidermidis were the most common pathogens grown from 156 (18.5%) samples. Escherichia coli AmpC-producing ESBL due to worldwide Escherichia coli proliferation, researchers tested 10,780 clinical strains for decreased susceptibility. Nevertheless, genes and multilocus sequences varied widely among nations. CTX-M enzymes caused ESBL to rise 53% from 2012 to 2017. Levofloxacin, cefepime, piperacillin-tazobactam, and meropenem may detect ESBL-E bacteremia risk. During the COVID-19 pandemic, Acinetobacter baumannii had the most resistant strains, followed by Klebsiella pneumonia, Escherichia coli, and Pseudomonas aeruginosa. To combat the epidemic's spread, a statewide community lockdown was implemented, confining nursing home patients and prohibiting outside contact and movement. This study found that donor screening for fecal microbiota transplantation is likely to fail due to a high frequency of extended-spectrum beta-lactamase positive bacteria in feces, poor adherence to regular fecal donation, increased social isolation, travel restrictions, and decreased antibiotic use. Conventional lactamase antagonists may decrease ESBLs, which cause cephalosporin resistance in certain bacteria. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae strains are increasing, and the COVID-19 pandemic triggered a critical care unit pandemic. This study found that gram-negative antibiotic resistance was 1.11-fold higher among those without documented attempts to improve infection prevention, treatment, or prescription safety. More efforts need to be made to prevent infections, offer treatments, and monitor medication resistance. These activities are all vital.

Keywords: *ESBL, COVID-19, antibiotic resistance*

I. INTRODUCTION

Antibacterial resistance is a growing issue all over the world. Because of the widespread use of antibiotics, many kinds of bacteria have become resistant to treatment, which has led to a rise in the number of illnesses that are difficult to cure. Antibiotic-resistant microorganisms kill approximately 33,000 people in Europe each year. If there is no effective method, it is anticipated that by 2050, 10 million people per year would be at risk owing to the growth of drug resistant illnesses. This problem is serious and complex, requiring a multi-faceted approach that includes better education about proper antibiotic use, greater investment in research to find new treatments, and a shift away from overprescribing of antibiotics [1], [2].

II. CONTENT

2.1. Antibiotic and antibiotic resistance

The prospective cross-sectional study, which was carried out at the Arsho Advanced Medical Laboratory in Addis Ababa, Ethiopia, between January 2019 and July 2020, revealed that infections of the bloodstream and medication resistance in blood-borne microorganisms are a significant global health concern. In the present investigation, the researchers wanted to determine the microbiological spectrum of bacteremia patients, as well as the extent of ESBL production and the pattern of antibiotic resistance. The blood of the patients was injected into blood-collection containers, which were thereafter appropriately maintained. Verification of identification, testing for antimicrobial susceptibility, and generation of ESBL were all accomplished with the use of the VITEK 2 compact equipment. 156 of the total materials received (about 18.5%) tested positive for culture. Both *Klebsiella pneumoniae* and *Staphylococcus epidermidis* were found to be the most common of the isolated bacteria. Among gram-negative bacteria, the incidence of antibiotic resistance was highest against ampicillin (80.8%), while it was lowest against imipenem (5.2%) Clindamycin resistance was shown to be the highest among gram-positive bacteria, whereas resistance to vancomycin and daptomycin was the lowest. It was shown that 41.6% of gram-negative bacteria exhibited multidrug resistance, whereas 34.2% of gram-negative bacteria exhibited ESBL production. 18.5% of patients had some kind of infection in their bloodstream. The most dangerous life-threatening infections were *Staphylococcus aureus (S. aureus), Klebsiella pneumoniae (K. pneumoniae), Acinetobacter baumannii (A. baumannii), Pseudomonas aeruginosa, Escherichia coli (E. coli),* and several species of Enterobacter. Although carbapenem resistance was uncommon, multi-drug resistance and ESBL production were common in both gram-positive and gram-negative bacteria. In clinical settings, each of these conditions necessitates the installation of efficient infection control procedures, a pharmaceutical regulatory system, and antibiotic management [3].

Many variables, including geographical position, population density, cleanliness, and antibiotic use, are believed to contribute to the spread of extended-spectrum beta-lactamase (ESBL)-producing bacterial infections. The frequency of ESBLs in *E. coli*, for example, is low in Europe but quite common in Southeast Asia, Africa, and Central America. The frequency of dissemination is also expected to vary among species due to changes in virulence factors. Although most ESBL-producing Enterobacteriaceae outbreaks occur in intensive care units or in people with compromised immune systems, other patient categories can also be impacted. Community-associated outbreaks, such as those due to travel or contact with food sources or water, can be linked to the spread of ESBL-producing bacteria.

Table 1. Families of ESBL

	Family	Nomenclature
1	BEL	Belgium extended β-lactamase
2	CMT	A complex mutant that was developed from TEM-1.
3	CTX-M	Cefotaxime-hydrolysing β-lactamase isolated in Munich
4	GES	Guiana-extended spectrum
5	IRT	TEM that is resistant to inhibitors
6	OXY	*Klebsiella oxytoca*
7	PER	*Pseudomonas*extended resistant

	Family	Nomenclature
8	SHV	Sulfhydryl reagents factor
9	SFO	*Serratia fonticola*
10	TEM	Temoneira was the patient who was contaminated with the TEM-1 virus when it was originally isolated.
11	TLA	Taking its name from the Tlahuica people of Mexico, from where the first isolated strain of the virus was taken.
12	VEB	Vietnam extended-spectrum β-lactamase

Table 1 shows that there are 12 families of ESBL. Gram-negative bacteria that produce ESBLs are now widespread in both hospital and community settings. While found naturally in some bacteria, beta-lactamases are becoming mobilized on chromosomes and have proliferated as a result of beta-lactam medication use and abuse. Broad-spectrum enzymes such as TEM-1 and SHV-1 emerged in gram-negative bacteria. Following that, ESBL drugs that were unable to be hydrolyzed by these enzymes were launched, such as ceftazidime and cefotaxime. This resulted in the emergence of new beta-lactamases, which hydrolyzed these novel medicines [4].

In another study, it is noted that the incidence of *E. coli* bacteria generating ESBL has increased dramatically in recent years, both in the community and in clinical settings. The purpose of this multicenter investigation was to describe the ESBLs generated by *E. coli* isolates producing hospital- and community-onset urinary tract problems and to evaluate their antibiotic susceptibility patterns, beta-lactamase levels, and chromosomal variants. After phenotypic testing for ESBLs and plasmid-mediated AmpC beta-lactamases, molecular detection of resistance genes, plasmid characterization, genotyping using pulsed-field gel electrophoresis, including whole genome sequencing were performed. The isolates carried CTX-M or TEM beta-lactamases and were resistant to expanded-spectrum cephalosporins. All six sample isolates submitted to whole genome sequencing were shown to be members of the ubiquitous clone ST131. Finally, our study demonstrated the spread of group 1 CTX-M positive *E. coli* in various geographic regions of Croatia, as well as in various components of the health-care system (hospitals, nursing homes, and the community), and confirmed the shift from suprahydril variant 2 and 5 ESBLs to group 1 CTX-M beta-lactamases as the country primacy. Various plasmids were found to be connected with the spread of blaCTX-M genes in various areas of Croatia [5].

It is recorded in the research of Epp Sepp et al. that gram-negative bacteria resistance (such as Enterobacterales) is growing in numerous European nations (EARS-Net, 2018). The synthesis of ESBL, AmpC cephalosporinases, and carbapenemases is one of the key resistance mechanisms of Enterobacteriaceae. The majority of ESBLs are CTX-M, SHV, and TEM enzymes; AmpCs CMY, ACT, and DHA; and carbapenemases KPC, NDM, and OXA-48 (Bush and Jacoby, 2010; Bush, 2018). *E. coli* susceptibility to 3rd-generation cephalosporins is lower in Northern Europe and greater in Southern and Eastern Europe. According to the EARS-Net 2017 report, the proportion of invasive *E. coli* isolates resistant to third-generation cephalosporins was 5.9%, 8.8%, 16.8%, and 22% (in Norway, Estonia, Lithuania, and Latvia, respectively, EARS-Net 2018). The WHO CAESAR 2016 study includes only a few strains from Russia's western region, but it reveals that 66% of invasive *E. coli* isolates are resistant to the third-generation cephalosporin group. This highlights the disparity of resistance rates to third-generation cephalosporins across different regions.

ESBLs and AmpC-producing *E. coli* have spread around the world. The researchers tested 10,780 clinical *E. coli* strains for decreased susceptibility to third-generation cephalosporins over a five-month period in 2012. They were gathered from 21 hospitals (in Estonia, Latvia, Lithuania, Norway, and St. Petersburg). By phenotypic test, the total prevalence of ESBL/AmpC strains was 4.7%, and by sequencing, it was 3.9%. In essence, the study discovered a low incidence of ESBL, AmpC, and carbapenemase in *E. coli* strains obtained in Northern and Eastern Europe. However, there were notable inter-country disparities in the prevalence of certain genes and multilocus sequence patterns. The study concluded that further studies should be conducted in order to confirm the results obtained and to determine the impact of national antibiotic prescription policies on the selection of resistant microorganisms [1].

Even though the incidence of ESBL in Enterobacterales has increased over time, the prevalence of ESBL may vary according to the species, hospital allocation, source of infection, nosocomial or population acquisitions, and geographic locations. The predominant forms of the Enterobacter cloacae complex were SHV-type ESBLs (SHV-5 and SHV-12), although *Serratia marcescens, Proteus mirabilis, E. coli*, and *K. pneumoniae* were much more likely to have CTX-M-type ESBLs (CTX-M-3 and CTX-M-14). Furthermore, a clonal sequence type of O25b-ST131 has emerged among urine or bloodstream *E. coli* isolates in the Taiwanese community, and this clone has been linked to toxicity, ESBL (CTX-M-15) expression, ciprofloxacin resistance, and fatality. [6] Reports from the early 2000s revealed that CTX-M-producing strains were spreading throughout Europe, Latin America, and the Asia-Pacific region. TEM- and SHV-type enzymes were once the most common ESBLs globally. CTX-M group 1 and CTX-M group 9 genes were the most prevalent. Since the year 2000, the overall occurrence of ESBL infectious agents has increased in the United States, with a 53% growth from 2012 to 2017. Generally, this increase is largely attributed to the spread of CTX-M enzymes, which have surpassed TEM and SHV types in frequency.

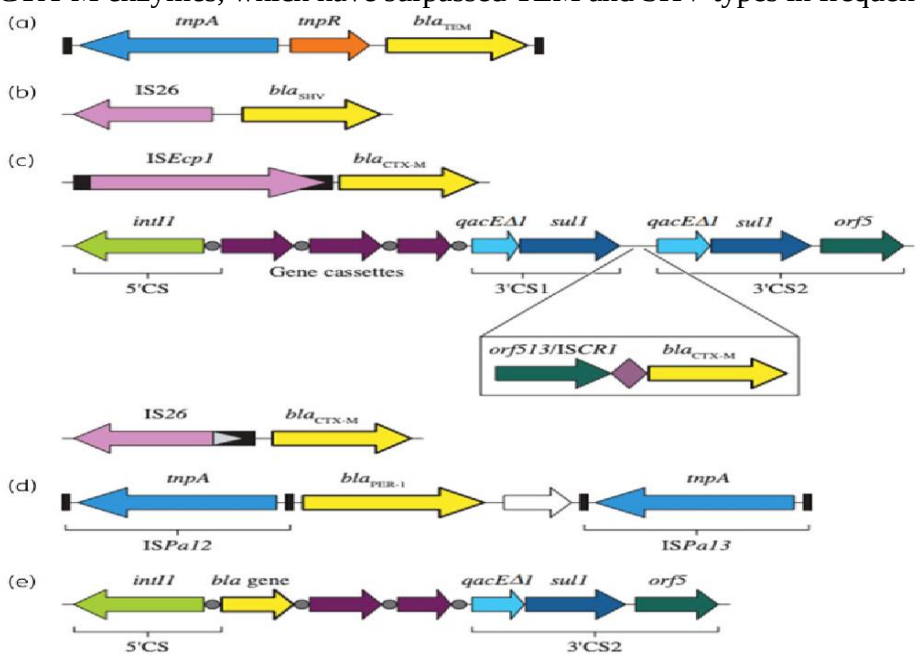

Figure 1. Genetic structures harboring genes encoding ESBLs.

Genetic structures that are home to genes that code for ESBLs. The genetic structures that are most often reported to contain (a) blaTEM, (b) blaSHV, (c) blaCTX-M, (d) blaPER, or (e) class 1 integrons that are able to carry rare ESBL genes.

In 2059 (13.3%) and 836 (11.8%) K. pneumonia, an ESBL gene was noticed. Canton and Coque found a significant rise in *E. coli* isolates generating CTX-M in the mid-2000s. CTX-M-3 and CTX-M-15 became the most frequently discovered. Except for Latin America, where blaCTX-M-2 constituted the most prevalent gene, blaCTX-M-15 constituted the most prominent gene detected. Other groups that have expanded internationally include blaCTX-M-9, blaCTX-M-14, and blaCTX-M-27 [4].

Epp Sepp et al. discovered that proven ESBL genes (blaCTX-M, blaTEM-29, blaTEM-71) or AmpC genes (blaCMY-59, blaACT-12/-15/-20, blaESC-6, blaFEC-1, blaDHA-1, blaNDM-1) were present in 85% of phenotypic *E. coli* strains. All nations have blaCTX-M-1, blaCTX-M-14, and blaCTX-M-15 [1].

A study conducted in Spain noted that the proportion of TEM-producing isolates decreased from more than 19% in 2000 to 1.2% in 2006 (Spain). The researchers also emphasized the superiority of CTX-M-producing *E. coli* and found CTX-M-14 to be the most prevalent form of ESBL. Subsequent research by the same group found an increase in CTX-M-15-producing isolates, which looked to be replacing the CTX-M-14-producing population. In the meantime, when assessing Canadian isolates, Peirano and his colleagues discovered CTX-M enzymes supplementing SHV-type ESBLs, which had previously been detected in other locations. These studies show that ESBLs are complicated and change over time, with different subtypes showing up in different places.

In the late 1980s and 1990s, both TEM- and SHV-type ESBLs were found in the United States and Europe, with particular variants showing regional heterogeneity in occurrence. To illustrate this, the aforementioned types are uncommon in Europe. Nevertheless, it has been reported in the United States in outbreaks of ESBL-producing Enterobacterales. In addition, the CTX-M classification's global hegemony has lowered the appeal of both TEM- and SHV-type ESBLs. Because the presence of ESBL-E is the cause of bacteremia in HSCT recipients, in the meantime, the death rate associated with this illness is escalating. As a result, a new approach for identifying patients at increased risk from ESBL-E bacteremia must be investigated. When fever and neutropenia are present, these individuals can be treated with an antibiotic that has ESBL-E antagonist action on the spot. Furthermore, in low-risk circumstances, doctors may opt to treat it with an antipseudomonal cephalosporin or beta-lactam/beta-lactamase inhibitor. In a study of 312 individuals having HSCT, 212 allogeneic and 100 autologous HSCT responders were included. Pre-transplant ESBL-E colonization was found in 10% of cases. Levofloxacin was 25% susceptible, cefepime was 9%, piperacillin-tazobactam was 84%, and meropenem was 97%. Ten (32%) of the 31 patients infected with ESBL-E before transplantation acquired ESBL-E bacteremia throughout their transplant hospitalization, whereas only 1/281 participants weren't contaminated with ESBL-E. All the levofloxacin-resistant ESBL-E in the circulation was colonizing, and circulation specimens from different individuals showed similar profiles of genotype. It can be explained that HSCT patients were infected with levofloxacin-resistant ESBL-E before the procedure. As a result, levofloxacin prophylaxis increases the risk of bacteremia from the invading strain throughout neutropenia. Therefore, the authors

concluded that evaluating neutropenic patients for ESBL-E colonization is necessary in order to improve empirical antibiotic treatment.

To summarize, gram-negative microorganisms that produce ESBLs, including ESBL-E, will continuously and globally be a key factor in antibiotic resistance. It is critical that we exercise caution when looking for them in patient isolates as well as through monitoring investigations. Appropriate prophylactic measures should be taken to prevent the spread of ESBL-E and other gram-negative bacteria [4].

2.2. Antibiotic resistance and COVID-19

The findings (2019-2022) of an analysis that included 23 separate scientific investigations demonstrated that the level of resistance has increased during the course of the COVID-19 pandemic. *A. baumannii* was the gram-negative bacterium with the highest frequency of resistance strains observed. The next three bacteria to be identified were *K. pneumonia*, *E. coli*, and *P. aeruginosa*. In addition to this, *K. pneumonia* has shown a high level of resistance to colistin. In addition, *Escherichia faecium* and *S. aureus* were the gram-positive pathogens that were found most often. The antibiotics ampicillin, erythromycin, and ciprofloxacin were ineffective against the *E. faecium* infection. During the COVID-19 study, the factors that increased one's likelihood of having a high degree of resistance were treating yourself with antibiotics, undergoing antimicrobial therapy, and having prescriptions by general practitioners [2].

A significant drop in the number of patients who got tested resulted in a perceived rise in the isolation rate established in Japan and the incidence of illnesses identified in the WHO's Global Antimicrobial Resistance and Use Surveillance System for various bacterial species and specific antimicrobial-resistant pathogens. The results indicate that surveillance data collected during the pandemic must be cautiously interpreted, in addition to monitoring isolation rates, and taking into account both the denominator and numerator of the investigations, particularly variables that influence the denominator [7].

The research's outcome by Olivier Lemenand et al revealed that the fast spread of the COVID-19 plague startled experts. COVID-19 caused 4,000 illnesses and 90,000 deaths in France during two waves of infection. The epidemic did not neglect healthcare facilities, with one out of every five institutions reporting major breakouts in 2020. The impact of COVID-19 on resistant bacteria is unknown. Before the COVID-19 epidemic, the resistance was one of the top worldwide public health objectives. The resistance, which is already a difficult issue, must now be tackled inside a shifting health sector.

In the short term, modifications to healthcare administration, pandemic-related mitigation strategies such as improved infection control practices, or the impact of the outbreak on domestic and foreign tourism may diminish antibiotic resistance pathogen recruitment and transmission. The reverse consequences may be observed if antibiotics are used more broadly if normal treatment paths fail, or if disruptions in healthcare organizations promote cross-infection in health facilities. A year after the COVID-19 epidemic began, the mechanisms of the resistance remain unknown. Data on the influence of COVID-19 on antimicrobials is becoming increasingly available.

Nevertheless, antimicrobial use is simply one of several variables driving worldwide levels of resistance. Records are desperately required to investigate the effects of COVID-19 containment initiatives taken at the national level on alterations in the resistance of

pathogens. To combat the pervasiveness of COVID-19 in France, a nationwide community shutdown was implemented. All nursing home patients were quarantined, with all exterior interactions and trips outside the institution suspended. Although the incidence decreased significantly, the highly contagious transmission continued throughout the summer of 2020 with a massive group. The most common cause of community-acquired infections of the urinary tract is *E. coli*. The resistance to most beta-lactam medicines is provided by ESBL, reducing the efficiency of first-line antibacterial drugs.

ESBL genes are often carried on plasmids that can spread horizontally alongside other resistant genes. Because of their toxicity and widespread spread throughout hospitals and communities, ESBL-*E. coli* are difficult to treat. In endemic places, they can colonize humans in the digestive tract years after exposure and spread across the population, including care facilities. So, they are a great way to measure the patterns of resistance in the population as a whole.

Using data from the national antibiotic resistance monitoring system, the researchers looked at how COVID-19 and the response to the epidemic across the country affected the number of ESBL-*E. coli* cases in general health care and nursing facilities in France.

A total of 793,954 *E. coli* specimens from 1022 clinical laboratories were examined. In March 2020 and earlier, 3.1% of *E. coli* strains from diagnostic specimens made ESBL, and 2.9% in May 2020 and after that. The percentage of ESBL-*E. coli* in urine specimens dropped considerably among females in most of the age groups. The ESBL-*E. coli* rate in care facilities has increased from 9.3% to 8.3%. Furthermore, the monthly decrease rate reached -0.4% prior to March 2020 and -0.2% beginning in May 2020 [8].

Antibiotic resistance may have increased as a result of events that took place in hospitals during the COVID-19 epidemic. These events include an increase in infectious diseases, an increase in the use of drugs in hospitals, an increase in the number of people who were hospitalized in intensive care units, an increase in the number of people who needed care, and HCWs who were tired as a result of the COVID-19 spike.

In this investigation, the actual and predicted quarterly carbapenemase-producing Enterobacteriaceae index incidences per 100,000 hospitalization days in 2020 were compared and contrasted. It found a linear, exponential rise of +0.34 fatalities per 100,000 hospitalization days each quarter that were caused by carbapenemase-producing Enterobacteriaceae. Moreover, it found a predictor variable with more of an impact in the third quarter. The lower threshold for the number of carbapenemase-producing Enterobacteriaceae was lower than what the 95% prediction intervals stated would happen during the second quarter. This was the case despite the fact that the 95% prediction intervals were accurate.

Cases of Carbapenemase-producing Enterobacteriaceae that occurred during a recent overseas trip exhibited a large growing trend and periodicity but lacked a characteristic that could predict them. The forecast for carbapenemase-producing Enterobacteriaceae cases that did not include a foreign stay stayed true in the year 2020, according to the 95% prediction range. 399 secondary cases for 2131 episodes were stable during period 1, and 84 secondary cases for 380 episodes were stable throughout the year 2020. The leading public health organization in France reported a significant decrease in instances of index carbapenemase-producing Enterobacteriaceae in the year 2020, but incidences of other Enterobacteriaceae grew as they often do. According to these findings, during the COVID-19 outbreak, there was a reduction in the number of illnesses caused by

carbapenemase-producing Enterobacteriaceae in France, which suggests that worldwide interactions decreased.

Even though epidemic control has cut down on the number of cases, tourists from other countries are still the main source of carbapenemase-producing Enterobacteriaceae in countries with low rates. While efforts to improve hygiene in both the general population and institutions did not result in an increase in the incidence slope, hospital improvements did. The accuracy of the research as well as a decline in the identification of carbapenemase-producing Enterobacteriaceae in 2020 due to congestion in critical care units and swab shortages are both disadvantages of the study. Despite this, the number of patients who had previously traveled outside their country fell, which helped to buffer the effects of these limitations [9].

In relation to ESBLs and COVID-19, some of the research described above discovered that the number of ESBLs was decreasing, but other studies discovered that the number of ESBLs was increasing.

According to the findings of the study that was conducted in 2021 and published in 2021, in addition to the SARS-CoV-2 infection, the present scenario of the COVID-19 pandemic is threatened by an increase in the prevalence of antibiotic resistance. Pathogens that are resistant to several drugs include *A. baumannii*, methicillin-resistant *S. aureus, Candida glabrata*, which is resistant to pan-echinocandin, and *Aspergillus fumigatus*, which is resistant to multiple triazoles. The pathogenesis is complicated, but one key component is an increased consumption of antibiotic drugs in COVID-19 patients who have a low probability of being contaminated by secondary or tertiary sources. The scientists came to the conclusion that correct evaluations and effective disease control measures, together with appropriate prescription and antibiotic management practices, may all contribute to the prevention of the epidemic. Pathogens that are resistant to several drugs include *A. baumannii*, methicillin-resistant *S. aureus, Candida glabrata*, which is resistant to pan-echinocandin, and Aspergillus fumigatus, which is resistant to multiple triazoles. The pathogenesis is complicated, but one key component is an increased consumption of antibiotic drugs among COVID-19 patients who had a low probability of being contaminated by secondary or tertiary sources. The authors came to the conclusion that accurate evaluations and effective disease control approaches, in addition to good prescription and antibiotic management practices, may assist in preventing the onset of these conditions [10].

The researchers Yuk Kam Yau and colleagues claimed in their paper on the COVID-19 outbreak and the elevated risk of ESBL bacteria affecting donor selection for gut microbiome transplant in Hong Kong that there is a strong demand for acceptable feces donations as the number of research studies and practices of gut microbiome transplanting develop. There is a relatively high probability of failure associated with the donor screening process for fecal microbiota transplantation. In addition, a high frequency of ESBL positive bacteria in feces, as well as poor adherence to regular fecal donation, lead to a greater donor enrollment failure rate. Both of these factors contribute to a higher donor enrollment failure rate. To be more exact, there were 119 potential donors who were examined (from 2017 to 2020), and 75 of them did not pass the prescreening. Inability to return for frequent and continuous donating, having a high body mass index (BMI), having an underlying chronic illness; using drugs over an extended period of time; being a medical specialist; using antibiotics within three months or less; and other factors could all lead to rejection. Of the remaining 33 potential donors who underwent bowel and blood testing, 21 of the stool

investigations failed (19 ESBL organisms, 1 *Clostridioides difficile, Clostridioides difficile* plus methicillin-resistant *S. aureus*), one required long-term therapy, and nine withdrew their approval and/or were lost to posttreatment. Just one out of 119 prospective donors (0.8% of the total) was successfully registered as a regular basis [11].

A study was conducted in Ontario, Canada, to investigate whether or not the COVID-19 outbreak caused increased social isolation, travel restrictions, and decreased antibiotic usage, and whether or not these factors affected the frequency of ESBLs in urine samples taken from communities and other types of healthcare facilities. Between 2016 and 2021, 8,600,000 urine samples were examined by LifeLabs Ontario. Patterns were determined using an interrupted time series regression. The COVID-19 investigation found that the prevalence of ESBL-producing *K. pneumoniae* in long-term care facilities did not change at any point over the duration of the research. Similar trends were seen throughout the subgroup analysis of genders, age categories, and local health integration network units, with the exception of a few densely populated local health integration network regions, in which rate variations were not found to be statistically significant. Urinary tract infections are a serious public health problem because they are widespread and may be caused by ESBL-producing Enterobacterales, most often *E. coli* and *K. pneumoniae*. These infections can occur anywhere in the population. The goal of this study was to evaluate the impact that COVID-19 has on the prevalence of ESBLs discovered in urine cultures collected in Ontario, Canada. Specifically, this investigation was focused on the province of Ontario in Canada. The data show the present prevalence and incidence of ESBL-producing Enterobacterales in urine collected from both the community and long-term-care facilities in Ontario, Canada. They also indicate the influence of COVID-19 limits on ESBL patterns for the whole area as well as for different sub-units of the residents depending on historical and geographic factors. The findings could have a significant impact on people's quality of life, especially given the ongoing relaxation of restrictions surrounding COVID-19 [12].

This study looked at confirmed cases at regional hospitals in northern Thailand in order to have a better understanding of the prevalence of ESBL-producing Enterobacterales and their rising resistance to antibiotics. Examples of ESBL-producing Enterobacterales include *E. coli* and *K. pneumoniae* (2016-2020). This suggests that this timeframe includes the period during which the COVID-19 virus is circulating in the population. According to the findings of the research, out of a total of 384,001 clinical specimens, 11,065 (2.9%) tested positive for *E. coli*, while 5,617 (1.5%) tested positive for *K. pneumoniae*. The vast majority of ESBL-producing bacteria were found in phlegm and urine, and these bacteria exhibited an exceptionally high level of resistance to fluoroquinolones, ampicillin, cefazolin, cefotaxime, and trimethoprim/sulfamethoxazole. The highest incidence of infections caused by ESBL-positive microorganisms was seen among patients residing in care wards [13].

K. pneumoniae is an important bacterium that has been linked to the development of a wide range of disorders, most notably infectious infections that are associated with critical care units. By contributing to the production of ESBL and carbapenemases, it is a primary factor in the global dissemination of diseases that are resistant to the treatment provided by a number of different medications. Ambler class A enzymes known as ESBLs are able to hydrolyze cephalosporins of the third generation and aztreonam, but they are inactive against cephamycins. ESBLs are responsible for the resistance of certain bacteria to cephalosporins (cefoxitin). Lactamase activity may be effectively inhibited by traditional

lactamase antagonists as well as newly discovered lactamase antagonists, such as clavulanate, sulbactam, and tazobactam.

Up until the middle of the 1990s, the ESBLs that were produced by *K. pneumoniae* isolates were virtually invariably distinct TEM and SHV enzyme variants. CTX-M enzymes were the most frequent kind of ESBL in a number of European nations, replacing TEM and SHV mutants as the predominant type. On the basis of the sequences of their constituent amino acids, CTX-M biomolecules may be separated into the following five unique categories: CTX-M-1, 2, 8, 9, and 25. The CTX-M-8 and CTX-M-9 enzymes are more similar to Kluyvera georgiana's chromosome-encoded-lactamase, whereas Types 1 and 2 were initially linked to Kluyvera ascorbata's chromosome-encoded-lactamase. There are 246 distinct types of enzymes that belong to the CTX-M family. At the beginning, the majority of CTX-M enzymes were discovered in several strains of *E. coli*. The proliferation of these enzymes has now had an effect on all strains of the Enterobacterales family, including *K. pneumoniae*. At the present time, the CTX-M enzyme that is used all over the globe in the greatest quantity is CTX-M-15. The CTX-M-1 group includes this kind in its classification. One of the amino acids at position 240 has been altered from its CTX-M-3 counterpart, which results in a stronger catalytic impact on ceftazidime. This change distinguishes it from the CTX-M-3 type.

Many epidemics have been attributed to *K. pneumoniae*, which produces CTX-M-15. Some of the countries affected by these outbreaks include France, Hungary, and Russia. Across all of France, it was found that the strain had a 160-kb plasmid that also included the blaOXA-1, blaTEM-1, and aac6'-Ib-cr genes. This was the case throughout the country. As a result of the widespread dissemination of SARS-CoV-2 in March 2020, there was a significant increase in the number of patients admitted to intensive care units (ICUs), and numerous institutions responded by establishing COVID-specific wards to assist in the treatment of these patients. In light of these circumstances, it was hypothesized that the possibility of a nosocomial outbreak was at its lowest point. Nevertheless, between March and June of the year 2020, there was a major outbreak in the critical care unit that was reserved exclusively for COVID-19 patients.

Infections caused by *K. pneumoniae* strains that produce ESBL are on the rise all over the world, and they are frequently blamed for incidents that occur in intensive care units. Because of the increased focus on hygiene precautions and preventative measures, it was believed that bacterial cross-transmission would not occur during the initial wave of the COVID-19 pandemic. This was due to the fact that there was a greater emphasis placed on preventing the spread of the disease. Even so, the authors of the study found an ESBL-producing *K. pneumoniae* (ST394) isolate that caused a pandemic of hospital-acquired infections in an intensive care unit for COVID-19 patients [14].

The authors of a research that was conducted in 2022 disclosed, in general, that the findings of the investigations were quite diverse from one another. They emphasized the significance of both of the prerequisites. The spread of the COVID-19 virus over the world and the development of antimicrobial resistance (AMR) are two issues affecting global public health that are connected with one another. This study aimed to evaluate the impact that the COVID-19 pandemic had on AMR in a range of hospital settings in order to better understand the implications of this phenomenon. Just 28 out of the 6036 publications that were investigated in the beginning were suitable for inclusion, and only 23 of those studies

supplied sufficient data for a meta-analysis to be performed. The majority of the study, which accounted for 89% of the total, focused on events that took place in medical facilities. There was no link between COVID-19 and an increase in the incidence density (with an incidence rate ratio of 0.99) or percentage (with a risk ratio of 0.91) of cases involving methicillin-resistant *S. aureus* or vancomycin-resistant Enterococci.

On the other hand, an absence of documented steps to improve the prevention and treatment of infections and/or prescription safety regimes was associated with a risk ratio of 1.11 for a rise in gram-negative antibiotic resistance. According to the outcomes of a test that looked for disparities between the various groupings, there was not a statistically significant difference between making these efforts and not making them at all. Inequalities were looked for as part of the exam. When taken in the context of the pandemic, our results suggest that further efforts are needed to prevent infections, deliver treatments, and monitor antibiotic resistance [15].

III. PROSPECTS FOR RESEARCH/CLINICAL APPLICATION

Notwithstanding this, the findings of the investigations show that the frequencies of antibiotic resistance are decreasing in a non-uniform manner. In order to have a comprehensive understanding of the resistance situation, it is important to undertake study at each location. In particular, the COVID-19 epidemic has affected both sexes. In-depth research on populations with a higher post-epidemic resistance ratio compared to pre-epilepsy. The outcomes of the study will then inform the development of particular remedies.

IV. CONCLUSION

In conclusion, COVID-19 and antibiotic resistance caused by ESBLs are two extremely prominent disorders. Following the outbreak, antibiotic resistance tends to grow more complex, according to the majority of research. Despite our test results showing no statistically significant difference between making and not making efforts to address inequalities, it is clear that further measures must be taken in order to effectively combat the effects of the pandemic.

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