International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 20-s, 2025
https://www.theaspd.com/ijes.php

Five-Year Epidemiological Trends Of Gram-Negative ESKAPE Infections At Two Tertiary Hospitals In Kwazulu-Natal, South Africa: Insights From The COVID-19 Era

AP Chiliza[1*], PM Makhoahle[2]

\[1*] *National Health Laboratory Service KwaZulu-Natal* pmakhoahle@cut.ac.za
[2] *Department of Health Sciences, Faculty of Health and Environmental Sciences Central University of Technology Free State, South Africa*

Received -29/07/2025 *Acceptance- 02/08/2025*

Abstract
Background: Gram-negative ESKAPE pathogens contribute significantly to hospital-acquired infections. The COVID-19 pandemic disrupted healthcare delivery, potentially altering infection patterns.
Aim: To assess the influence of age, gender, and healthcare facility on infections caused by gram-negative ESKAPE pathogens.
Methods: A retrospective analysis of 4,781 patient records from Inkosi Albert Luthuli Central Hospital and Mahatma Gandhi Memorial Hospital (2018–2022) was conducted using Excel 365. Chi-square tests and Pearson correlation were used to assess associations.
Results: Infections were most common in the 19–30-year group (27.51%), with a negative correlation between age and infection rates ($r = -0.991$, $p < 0.001$). Females accounted for 55.33% of cases. Klebsiella pneumoniae was the most prevalent pathogen. Significant associations were found between pathogen types and both hospitals ($p = 0.009$) and gender ($p < 0.001$).
Conclusion: Contrary to global trends, infections predominantly affected younger adults in this cohort. Gender and hospital differences in pathogen prevalence were statistically significant. COVID-19 may have contributed to shifting infection demographics.

Keywords: *ESKAPE, COVID-19, KwaZulu Natal, Epidemiology, Gender*

INTRODUCTION

The world was shaken by the SARS-CO2 virus during the sunset of 2019 in Huwan at China (Chen *et al.*, 2020). The SARS-CO2 famously known as COVID-19 changed the global completion leading to introduction of strict measures in an attempt to curb its spreading globally (Bolikas *et al.*, 2023). No age group was safe as the global population witnessed high rate of deaths daily with a lot of people being hospitalised (Ioannidis *et al.*, 2020). Even though the world was not ready, nonetheless transmission interventions measures played a major role in cubbing the infections and South Africa was not immune to the pandemic as it observed a high number of hospitalizations (Jassat *et al.*, 2021). The spread of COVID-19 and other bacterial diseases were cautioned based age, commodities as some of the factors associated with susceptibility to infection during the COVID-19 era and most hospitals couldn't handle the demand at that time. Priorities were giving to COVID-19 patients and this study aimed to determine the distribution of age, and gender to the high number of hospitalisations in patients with bacterial co-infections between 2019-2022.

Almost all human diseases are sexually dimorphic with regards to prevalence, severity and cause of infection, although genetic, immunity, and social roles do also contribute to the differences in disease risk (Ober *et al.*, 2008). Acquiring infections such as viral, fungal and bacterial leading to individuals being hospitalised can be influenced by several factors such as gender inequality, social norms, occupational activities, social roles, lifestyle changes and access to healthcare (Dias *et al.*, 2022; Fowler *et al.*, 2007).

Gender inequality plays a vital contribution to social and health outcomes which include but not limited to violence against women, men being breadwinners, and women as caregivers leading to stress and risk of being unable to fight infections (Shannon *et al.*, 2019). Gender also influences susceptibility to infections, immune response, pathophysiology and clinical presentation as they tend to differ in males and females respectively (Kroll *et al.*, 2015).

There are several studies that have been conducted to assess the influence of gender differences in hospitalised patients. Galligan noted that females have an increased ability to detect pathogens than males due to the expression of pathogen associated molecular receptors when compared to males (Galligan and Fish 2015). Whereas according to Klein, females also possess a stronger innate and adaptive response than males which allows better pathogen elimination and response to vaccination but consequently makes them more prone to inflammatory autoimmune diseases (Klein and Flanagan 2016). Furthermore, females are said to have higher neutrophil counts which are the first immune cells that respond to infections caused by microorganisms (Brain and England 1975).

Age also contributes vastly to the ability of individuals capabilities to fight infections leading to high hospitalisation rates in the older population as compared to younger population of female patients (Pandey *et al.*, 2017). It has been noted that the median age of hospitalisation reported in India was 47 years while the median age of 68 years of deceased patients was reported in China when compared to a median age of 51 years of male patients who recovered from the COVID-19 (Wan *et al.*, 2020; Chen *et al.*, 2020). On the contrary a 56% hospitalisation rate for various diseases for females with age range 15 to 59 years which the now includes the younger age group (Naser *et al.*, 2023). Furthermore, the influence of gender and age to the infectivity still remains an area of active investigation (Kopel *et al.*, 2020)

South African has embarked on the introduction of national health insurance (NHI) with the plan to optimised health care services to majority of the population (Louw *et al.*, 2023). Before and during the COVID-19 pandemic globally including South Africa, healthcare facilities experienced challenges when it comes to service delivery especially the public sector thus contributing to the increase of hospital acquired infections as well as mortality rate (Jassat *et al.*, 2021). Public health facilities provide medical assistance to all citizens that are unable to afford health insurance, which is a very large population size (Louw *et al.*, 2023). This was evident during the COVID 19 pandemic where South Africa as a developing country demonstrated an enormous challenge in providing sufficient resources to cater for its citizens (Hart *et al.*, 2022). In this retrospective study, the influence of age and gender on hospitalisation will be assessed. The study focuses on the two public hospitals situated at KwaZulu-Natal province of South Africa namely- Inkosi Alber Luthuli Central Hospital and Mahatma Gandhi Memorial Hospital.

ESKAPE pathogens namely, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* were named as the global priority pathogens by the World Health Organization because of their ability to develop resistance to antimicrobial agents (WHO, 2017). The Gram-negative ESKAPE pathogens are members of Enterobacteriaceae and are the leading cause of hospital acquired infections although they can also be community acquired (Shakibaie *et al.*, 2014). They produce enzyme called beta-lactamase's and carbapenemase's which enable them to destroy the chemical structure of beta lactam antimicrobial agents (Gasink *et al.*, 2009).

To assess the trends for the isolation rates of ESKAPE pathogens, several studies were conducted worldwide, and Iran reported 8% *Klebsiella pneumoniae (K. pneumoniae)* and 1.81% Enterobacter species isolated from 2011 to 2012 (Shakibaie *et al.*, 2014). In a 10-year resistance trend study done in Saudi Arabia on pathogens causing hospital acquired infections, Gram-negative pathogens accounted for 63% of the infections, with specifically the *Klebsiella* infection rate higher than *Acinetobacter* (Balkhy *et al.,* 2020). On the contrary, China reported a rather less isolation rate for *K. pneumoniae* (26.2%), being the second-most isolated organism in 2021 (Yang *et al.*, 2023). Similarly, in a recent European study, *Enterobacter cloacae (E. cloacae)* complex (44.8%) was the most prevalent organism isolated (Boattini *et al.*, 2024).

Birru found that out of 225 blood samples, only 22 had confirmed bloodstream infections, with 40.9% caused by Gram-negative bacteria in a general South Ethiopia hospital (Birru *et al.*, 2021). Contrary to the worldwide study by Shakibaie and team (2014), 78% of *K. pneumoniae* was obtained in a study conducted in South Africa from 2010 to 2012, with 70% of carbapenem-resistant Enterobacteriaceae found to be hospital acquired, with a 38% mortality rate (Perovic *et al.,* 2014). *Klebsiella* species are among the leading causes of sepsis in hospital cases, and *K. pneumoniae* was the most common isolate with 77%, and only 10% *Escherichia coli* found in 36 of the patients on invasive ventilator support with 44% mortality rate from 2013 to 2014 (Fourie *et al.*, 2018; Sorsa *et al.*, 2019).

The objective of this study was to determine the influence of age and gender to the high number of hospitalisations in patients with bacterial infections caused by the gram-negative ESKAPE organisms namely *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter cloacae* for a period of 5 years including the years when the COVID-19 pandemic occurred.

METHODOLOGY

Population and sample

The retrospective data consisting of 4781 patients for a period of 5 years obtained from CDW AARMS system respectively. This data was anonymized, except for gender and age. Data in all National Health Laboratory Services (NHLS) laboratories is stored in the laboratory information system (LIS) and controlled at the Central Data Warehouse (CDW). Permission and ethics approval to use data from the NHLS was obtained from the NHLS Academic Affairs and Research Management System (AARMS) and ethics from Health Science Research Ethics Committee (HSREC) from the university of the Free State respectively. The requested data was for patients with infections caused by Gram-negative ESKAPE organism. Since NHLS is the data owner, no approval from KwaZulu Natal Department of Health (DOH) was needed.

Study location

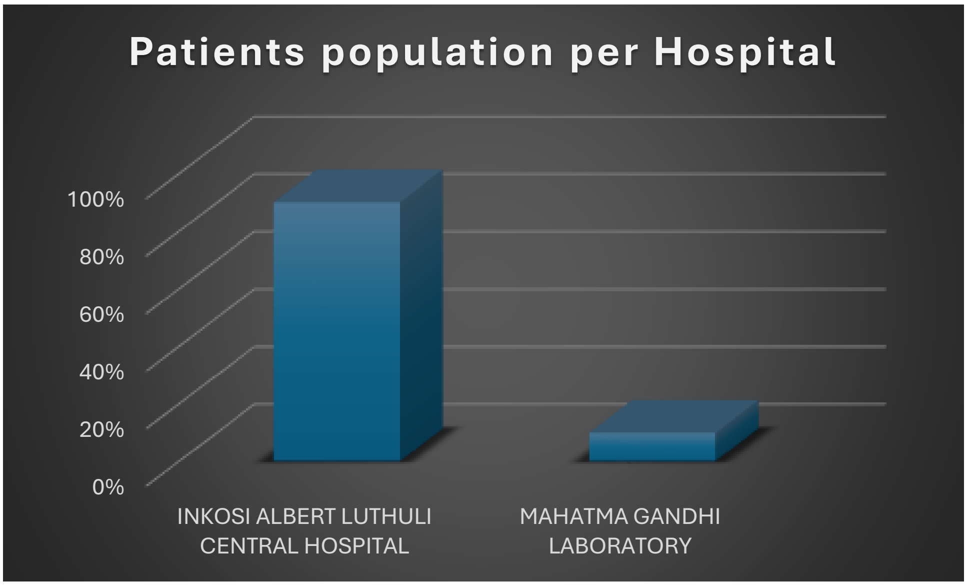
The study was conducted with data from Mahatma Gandhi Memorial Hospital at the NHLS in KwaZulu-Natal Durban Phoenix and Inkosi Albert Luthuli Central Hospital NHLS situated in KZN Bellair Durban.

Data collection

The extracted data was for the period from 1 January 2018 to 31 December 2022, to obtain the demographic picture before and during the pandemic. Data were obtained from the NHLS CDW for samples processed on the Vitek®2 automated system (bioMérieux, Marcy I'Etoile, France). A systemic investigation was conducted on quantifiable data and statistical descriptive analysis was performed using Microsoft Excel 365.

Results

Demographic profile of patients presenting to hospital from 2018 to 2022 The data was analysed using a descriptive analysis on Microsoft Excel 365 for the demographic profiling of patients presenting to healthcare facilities with bacterial infection according to facility name or laboratory, age and gender using frequency tables.



Graph 1: Distribution of patients in Inkosi Albert Luthuli Central Hospital laboratory and Mahatma Gandhi Memorial Hospital laboratory from 2019 to 2022

Graph 1 illustrates the distribution of patients who were treated at Inkosi Albert Luthuli Central Hospital (IALCH) and Mahatma Gandhi Memorial Hospital (MGMH) respectively between 2018 to 2022. The majority of patients were treated at IALCH (90.09%) as it is a referral academic hospital when compared to MGMH, a district hospital with 9.91%.

Table 1: Age Group Distribution

Age Group	% of patients
19–30	27.51%
31–40	20.86%
41–50	18.00%
51–60	14.98%
61–70	11.40%
71+	7.34%

Table 1 indicates that most patients presenting to the hospitals range from the age of 19-30 years old, accounting for 27.51%, followed by the age group 31-40 years old with 20.86%. The median age of patients presenting to either hospital is 42 years old.

Table 2: Gender Distribution

Gender	% of patients
Female	55.33%
Male	44.34%
Unknown	0.33%

Table 2 indicates that the majority of patients presenting to IALCH and MGMH for 5 years are females at 55.33%. Males only accounted for 44.34% which is not too different from females, indicating that both genders are almost equally affected by infections caused by Gram-negative ESKAPE pathogens.

Table 3: Pathogen Distribution by Hospital

Pathogen	MGMH (%)	IALCH (%)
Acinetobacter baumannii	17.30	20.18
Enterobacter cloacae complex	8.02	5.29
Klebsiella pneumoniae	65.82	48.80
Pseudomonas aeruginosa	8.86	25.73

The most isolated pathogen is *K. pneumoniae*, with 65.82% and 48.80% at MGMH and IALCH, respectively, as illustrated in Table 3. *Pseudomonas aeruginosa* (25.73%) was the second most isolated pathogen at IALCH, but at MGMH, *A. baumannii* complex (17.30%) was the second most isolated pathogen. A chi-square test of independence was performed using Microsoft Excel 365, yielding a p-value of 0.0316. Since $p < 0.05$, this indicates a statistically significant association between the pathogen type and the healthcare facilities

Table 4: Pathogen Distribution by Gender

Pathogen	Female (%)	Male (%)	Unknown (%)
Acinetobacter baumannii	17.20	23.32	12.50
Enterobacter cloacae complex	5.30	5.90	6.25

Pathogen	Female (%)	Male (%)	Unknown (%)
Klebsiella pneumoniae	55.65	45.81	75.00
Pseudomonas aeruginosa	21.85	26.96	6.25

Table 4 illustrates the pathogens isolated in patients against their gender to evaluate the relationship between the two. *A. baumanni* complex isolated from females was 17.20% and 23.32% from males. *K. pneumoniae* isolated from females was 55.65% and 45.81 from males. *P. aeruginosa* isolated from females was 21.85% and 26.96% from males, all with a difference that is less than 10% which indicates the insignificance of gender against infections caused by these pathogens.

Table 5: Summary of Key Statistical Tests

Test	Statistic	P-value	Significance
Pearson r (Age vs %)	−0.991	0.00013	Significant
Chi-square (Hospitals)	11.54	0.00915	Significant
Chi-square (Gender)	23.55	0.00063	Highly Significant

Insights from statistical results

A total of 4,781 patients were included in the study. The largest proportion of infections occurred in the 19–30-year age group (27.51%), with a progressive decline in older age groups (Pearson r = −0.991, $p < 0.001$). Females accounted for 55.33% of cases, males for 44.34%, and unknown gender 0.33% (Table 2). Table 5 shows that chi-square analysis revealed a significant association between pathogen types and hospitals ($\chi^2 = 11.54$, $p = 0.009$), as well as between pathogen types and gender ($\chi^2 = 23.55$, $p < 0.001$). *Klebsiella pneumoniae* was the most frequently isolated pathogen, accounting for 65.82% at Mahatma Gandhi Memorial Hospital (MGMH) and 48.80% at IALCH. *Pseudomonas aeruginosa* was more prevalent at IALCH (25.73%) compared to MGMH (8.86%). Gender distribution for *Klebsiella pneumoniae* infections showed higher prevalence in females (55.65%) compared to males (45.81%), while *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were more prevalent in males.

Table 6: Comparative correlation with few global studies

Study Reference	Main Findings	Correlation to Current Study
Al-Hasan *et al.*, 2008 (USA)	*P. aeruginosa* bacteraemia higher in elderly and males.	This study shows *P. aeruginosa* is higher in males but predominant in younger adults, indicating a possible shift during the COVID-19 era.
Zhongzhi Liang *et al.*, 2015–2023 (China)	*A. baumannii* more frequent in elderly males.	This data shows *A. baumannii* slightly higher in males, but predominant age is younger (contrast to global trends). COVID-19 disruptions may explain younger patient profile.
Joshaline *et al.*, 2023 (India)	*K. pneumoniae* prevalent in post-COVID cases, especially in younger adults.	These results align closely, *K. pneumoniae* is dominant, especially in patients aged 19–30, supporting post-COVID-19 shifts in bacterial epidemiology.

Table 6 shows the key insights from global age patterns were gram-negative infections typically rise with age due to comorbidities. Contrary this study results differs, showing more infections in younger age groups, possibly reflecting increased COVID-19 exposure, changing hospital admission patterns, or altered healthcare-seeking behaviour during the pandemic as older people were restricted from movement in South Africa as they were regarded as high-risk group. This study gender patterns is consistent with global data, males have slightly higher rates for *A. baumannii* and *P. aeruginosa*, reflecting risk factors such as occupational exposure and underlying conditions. For *K. pneumoniae*, this study showed a female predominance, which supports KZN stats male: female percentage and other factors may be due to sample composition and or healthcare access differences during

COVID-19. On hospital variation this study shows the difference in pathogen prevalence between the two hospitals which suggests differences in patient populations, hospital services, or infection control practices.

DISCUSSION

As shown in graph 1, the IALCH has the greatest number of patients with bacterial infection, which is explained by the capacity of patients this hospital can accommodate as a referral hospital. MGMH, as a district hospital, has fewer patients presenting with infections as it can accommodate a smaller number of patients over the period of 5 years. These results were also affected by the COVID-19 era that occurred from 2020 to 2022, where patients were hospitalised for extended periods and being immunocompromised and the restriction measures that were enforced.

A total of 4782 patients were admitted in both these hospitals with different bacterial infections, 27.51% of these patients were 19-30 years of age. The median age was 42 years which differs from a study which reported a median age of 47 years for patients hospitalised (Wan *et al.*, 2020). On the contrary, China reported a median age of 68 years which is expected since elderly people are more prone to infections as they have weakened immune systems (Chen *et al.*, 2020). Furthermore, India reported elderly population had a much higher rate of hospitalisation (Pandey *et al.*, 2017), but on the contrary, this study indicated young adults are mostly affected by bacterial infections, which may be further distinguished with regards to which sex is mostly affected. The age of a study in China indicated widespread age, with most patients being elderly with a median age of 47 years (Wan *et al.*, 2020; Chen *et al.*, 2020 and Pandey *et al.*, 2017). Table 1 shows right-skewed data, which could predict that the mode age range (19-30) could possibly be less than the median of the population of the study. Indeed, it is true that the average median age of the study population was found to be 42 years which is represented by adults in South Africa's life expectancy, which is currently between 60 and 65 years. Therefore, the study results correlate with Wan et al study and fairly so this could indicate that the older population were more prone to the infection.

The infection rates, including COVID-19, have been reported not to be sex- dependent but mostly associated with the underlying health status of an individual (Kopel *et al.*, 2020). China reported a mortality rate of 75%males and only 27% females during the pandemic, this was explained by the fact that males are smokers, which affects their lungs, and similarly, COVID-19 caused respiratory difficulties (Chen *et al.*, 2020). The results of the study indicated that out of 4782 patients, 55.33% were females and 44.34% were males indicating a difference of 10.99% as reflected in Table 2. On the contrary, gender does not indicate any significance when compared against the pathogen types as illustrated in Table 4 which means any gender can be infected by any of the gram-negative ESKAPE pathogens. These results correlate with the common view that infections, including COVID-19, are based on an individual's health status and not sex. Different specimen types were collected and tested to ascertain the cause of these bacterial infections, and further analysis was performed.

The most isolated pathogen for both hospitals is *K. pneumoniae,* with 48.80% and 65.82% at IALCH and MGMH, respectively, which correlates with the fact that historically this organism was one of the pathogens that led to the introduction of 3rd generation cephalosporins in the 1980's due to its prevalence and increasing resistance patterns (Deephti *et al.*, 2010). However, in this study, *K. pneumoniae* for both hospitals attributed to 57.31%, which correlates with Ballchy, who reported a 63% *K. pneumoniae* infection rate. The *P. aeruginosa*, *E. cloacae* complex and *A. baumannii* complex results were 25.73%, 5.29%, and 20.18%, respectively, at IALCH. On the contrary, in a recent European study, *Enterobacter cloacae* complex (44.8%) was the most prevalent organism isolated, which does not correlate with this study (Boattini *et al.*, 2024).

CONCLUSION

Age and gender differences in terms of infection have been observed in several clinical and epidemiological studies although several factors contribute to the observations in these studies, which include genetic differences in humans, underlying disorders, lifestyle habits, population size as well as our immune systems. In this study contrary to global trend, the age group of 19-30 years was mostly hospitalised, which can be explained by that people of this age group travel thus standing a greater chance of contracting infections when compared to elderly people who are mostly confided in their homes. COVID-19 may have contributed to shifting infection demographics due to stricter measures against the elderly. In terms of gender, females were mostly hospitalised due to the population size of females when compared to males. There is not enough data available in South Africa to distinguish age and gender differences in terms of contracting bacterial infections but according to this study there is no significant contribution of gender towards the increasing infection rates caused by these pathogens. The most isolated gram-negative ESKAPE pathogen is *K. pneumoniae* and the infection rates over the five-year period have increased for most pathogens concluding that infections caused by ESKAPE pathogens is increasing.

ACKNOWLEDGMENT
A special gratitude to the late Miss A van der Spoel van Dijk and Prof Mashele for participating on the previous publication and master's work. I also thank NHLS for funding this study and granting me the permission to conduct this research.

Ethics:
The study was ethically approved by University of the Free state ethics committee with the HSREC clearance number: UFS-HSD2023/0400/2908 and National Health Laboratory Service (NHLS)with the AARMS number: PR2232466

Funding
This study was supported financially by the NHLS.

Conflict of interest
We declare no conflict of interest

REFERENCES

1. Al-Hasan, M. N., Wilson, J. W., Lahr, B. D., Eckel-Passow, J. E., & Baddour, L. M. (2008). Incidence of *Pseudomonas aeruginosa* bacteremia: A population-based study. *The American Journal of Medicine*, *121*(8), 702–708. https://doi.org/10.1016/j.amjmed.2008.03.029
2. Bain, B. J., & England, J. M. (1975). Normal haematological values: Sex difference in neutrophil count. *British Medical Journal*, *1*(5953), 306–309.
3. Balkhy, H. H., El-Saed, A., Alshamrani, M. M., Alsaedi, A., Al Nasser, W., El Gammal, A., ... & Bonnie, H. B. (2020). Ten-year resistance trends in pathogens causing healthcare-associated infections: Reflection of infection control interventions at a multi-hospital healthcare system in Saudi Arabia, 2007–2016. *Antimicrobial Resistance & Infection Control*, *9*(1), 1–12.
4. Birru, M., Woldemariam, M., Manilal, A., Aklilu, A., Tsalla, T., Mitiku, A., & Gezmu, T. (2021). Bacterial profile, antimicrobial susceptibility patterns, and associated factors among bloodstream infection suspected patients attending Arba Minch General Hospital, Ethiopia. *Scientific Reports*, *11*, 15882.
5. Boattini, M., Bianco, G., Llorente, L. I., Acero, L. A., Nunes, D., Seruca, M., ... & Gascón, A. G. (2024). Enterobacterales carrying chromosomal AmpC β-lactamases in Europe (EuESCPM): Epidemiology and antimicrobial resistance burden from a cohort of 27 hospitals, 2020–2022. *International Journal of Antimicrobial Agents*, *63*(5), 107115.
6. Bolikas, E., Astrinaki, E., Panagiotaki, E., Vitsaxaki, E., Saplamidou, S., Drositis, I., Stafylaki, D., Chamilos, G., Gikas, A., Kofteridis, D. P., & Kritsotakis, E. I. (2023). Impact of SARS-CoV-2 Preventive Measures against Healthcare-Associated Infections from Antibiotic-Resistant ESKAPEE Pathogens: A Two-Center, Natural Quasi-Experimental Study in Greece. *Antibiotics (Basel, Switzerland)*, *12*(7), 1088. https://doi.org/10.3390/antibiotics12071088
7. Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qui, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, Z., Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *The Lancet*, *395*(10223), 507–513.
8. Chen, T., Wu, D. I., Chen, H., Yan, W., Yang, D., Chen, G., Ma, K., Xu, D., Yu, H., Wang, H., Wang, T., Guo, W., Chen, J., Ding, C., Zhang, X., Huang, J., Han, M., Li, S., Luo, X., Zhao, J., Ning, Q. (2020). Clinical

characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. (2020). *BMJ (Clinical research ed.)*, *368*, m1295. https://doi.org/10.1136/bmj.m1295

9. Deepthi, N., & Deepti, R. (2010). Extended spectrum beta lactamases in gram-negative bacteria. *Journal of Global Infectious Diseases*, *2*(3), 263–274.
10. Dias, S. P., Brouwer, M. C., & van de Beek, D. (2022). Sex and gender differences in bacterial infections. *Infection and Immunity*, *90*(10), e00283-22.
11. Fourie, T., Schellack, N., Bronkhorst, E., Coetzee, J., & Godman, B. (2018). Antibiotic prescribing practices in the presence of extended-spectrum β-lactamase (ESBL) positive organisms in an adult intensive care unit in South Africa: A pilot study. *Alexandria Journal of Medicine*, *54*(4), 541–547.
12. Fowler, R. A., Sabur, N., Li, P., Juurlink, D. N., Pinto, R., Hladunewich, M. A., Adhikari, N. K., Sibbald, W. J., & Martin, C. M. (2007). Sex-and age-based differences in the delivery and outcomes of critical care. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, *177*(12), 1513–1519. https://doi.org/10.1503/cmaj.071112
13. Galligan, C. L., & Fish, E. N. (2015). Sex differences in the immune response. In *Sex and gender differences in infection and treatments for infectious diseases* (pp. 1–29). Cham: Springer.
14. Gasink, L. B., Edelstein, P. H., Lautenbach, E., Synnestvedt, M., & Fishman, N. O. (2009). Risk factors and clinical impact of Klebsiella pneumoniae carbapenemase-producing *K. pneumoniae*. *Infection Control & Hospital Epidemiology*, *30*(12), 1180–1185.
15. Giefing-Kröll, C., Berger, P., Lepperdinger, G., & Grubeck-Loebenstein, B. (2015). How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging Cell*, *14*(3), 309–321.
16. Hart, T. G., Davids, Y. D., Rule, S., Tirivanhu, P., & Mtyingizane, S. (2022). The COVID-19 pandemic reveals an unprecedented rise in hunger: The South African government was ill-prepared to meet the challenge. *Scientific African*, *16*, e01169.
17. Ioannidis, J. P., Axfors, C., & Contopoulos-Ioannidis, D. G. (2020). Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environmental Research*, *188*, 109890.
18. Jassat, W., Abdool Karim, S. S., Mudara, C., Welch, R., Ozougwu, L., Groome, M. J., Govender, N., von Gottberg, A., Wolter, N., Wolmarans, M., Rousseau, P., DATCOV author group, Blumberg, L., & Cohen, C. (2022). Clinical severity of COVID-19 in patients admitted to hospital during the omicron wave in South Africa: a retrospective observational study. *The Lancet. Global health*, *10*(7), e961–e969. https://doi.org/10.1016/S2214-109X(22)00114-0
19. Joshaline, C. M., Sri Rajalakshmi, R., & Panneer Selvam, K. (2022). A study on the impact of age and gender on post-COVID-19 epidemiology of *Klebsiella pneumoniae* from COVID-19 recovered cases. *IJFANS International Journal of Food and Nutritional Sciences*, *11*(9). [UGC CARE Listed (Group I)].
20. Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. *Nature Reviews Immunology*, *16*(10), 626–638.
21. Knothe, H., Shah, P., Krcmery, V., Antal, M., & Mitsuhashi, S. (1983). Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens*. *Infection*, *11*(6), 315–317.
22. Liang, Z., Tian, D., Huang, Y., Dou, S., Yang, A., & Chen, Z. (2025). Epidemiology of *Acinetobacter baumannii*: Analysis of hazard factors associated with positivity cases in Guizhou Province, China, from 2015 to 2023. *Frontiers in Public Health*, *13*, 1592783. https://doi.org/10.3389/fpubh.2025.1592783
23. Livermore, D. M., & Paterson, D. L. (2006). Pocket guide to extended-spectrum beta-lactamases in resistance. *Journal of Antimicrobial Chemotherapy*, *58*(2), 231–237.
24. Louw, Q. A., Conradie, T., Xuma-Soyizwapi, N., Davis-Ferguson, M., White, J., Stols, M., Masipa, A., Mhlabane, P., Mdaka, L., Manzini, C., Kekana, I., Schutte, M., Rabothata, S., & Kleinitz, P. (2023). Rehabilitation Capacity in South Africa-A Situational Analysis. *International journal of environmental research and public health*, *20*(4), 3579. https://doi.org/10.3390/ijerph20043579.
25. Miyadera, T., Sugimura, Y., Hashimoto, T., Tanaka, T., Iino, K., Shibata, T., & Sugawara, S. (1983). Synthesis and in vitro activity of a new carbapenem, RS-533. *The Journal of Antibiotics*, *36*(8), 1034–1039.

26. Naser, A. Y. (2023). Hospitalisation profile in England and Wales, 1999 to 2019: An ecological study. *BMJ Open*, *13*(4), e068393.
27. Ober, C., Loisel, D. A., & Gilad, Y. (2008). Sex-specific genetic architecture of human disease. *Nature Reviews Genetics*, *9*(12), 911–922.
28. Pandey, A., Ploubidis, G. B., Clarke, L., & Dandona, L. (2017). Hospitalisation trends in India from serial cross-sectional nationwide surveys: 1995 to 2014. *BMJ Open*, *7*(12), e014188.
29. Perovic, O., Singh-Moodley, A., Dusé, A., Bamford, C., Elliott, G., Swe-Han, K. S., ... & Wadula, J. (2014). National sentinel site surveillance for antimicrobial resistance in *Klebsiella pneumoniae* isolates in South Africa, 2010–2012. *South African Medical Journal*, *104*(8), 563–568.
30. Shakibaie, M. R., Adeli, S., & Salehi, M. H. (2014). Antimicrobial susceptibility pattern and ESBL production among uropathogenic *Escherichia coli* isolated from UTI children in the pediatric unit of a hospital in Kerman, Iran. *British Microbiology Research Journal*, *4*(3), 262–271.
31. Shannon, G., Jansen, M., Williams, K., Cáceres, C., Motta, A., Odhiambo, A., Eleveld, A., & Mannell, J. (2019). Gender equality in science, medicine, and global health: where are we at and why does it matter?. *Lancet (London, England)*, *393*(10171), 560–569. https://doi.org/10.1016/S0140-6736(18)33135-0
32. Sorsa, A., Früh, J., Stötter, L., & Abdissa, S. (2019). Blood culture result profile and antimicrobial resistance pattern: A report from neonatal intensive care unit (NICU), Asella Teaching and Referral Hospital, Asella, southeast Ethiopia. *Antimicrobial Resistance & Infection Control*, *8*, 1–6.
33. Wan, S., Xiang, Y., Fang, W., Zheng, Y., Li, B., Hu, Y., Lang, C., Huang, D., Sun, Q., Xiong, Y., Huang, X., Lv, J., Luo, Y., Shen, L., Yang, H., Huang, G., & Yang, R. (2020). Clinical features and treatment of COVID-19 patients in northeast Chongqing. *Journal of medical virology*, *92*(7), 797–806. https://doi.org/10.1002/jmv.25783.
34. World Health Organization. (2017). *Prioritisation of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis* (No. WHO/EMP/IAU/2017.12). World Health Organization.
35. Yang, W., Ding, L., Han, R., Yin, D., Wu, S., Yang, Y., Zhu, D., Guo, Y., Hu, F and on behalf of the China Antimicrobial Surveillance Network (CHINET) Study Group. (2023). Current status and trends of antimicrobial resistance among clinical isolates in China: A retrospective study of CHINET from 2018 to 2022. *One Health Advances*, *1*(1), 8.
36. Yigit, H., Queenan, A. M., Anderson, G. J., Domenech-Sanchez, A., Biddle, J. W., Steward, C. D., Alberti, S., Bush, K., Tenover, F. C. (2001). Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. *Antimicrobial agents and chemotherapy*, *45*(4), 1151–1161. https://doi.org/10.1128/AAC.45.4.1151-1161.2001