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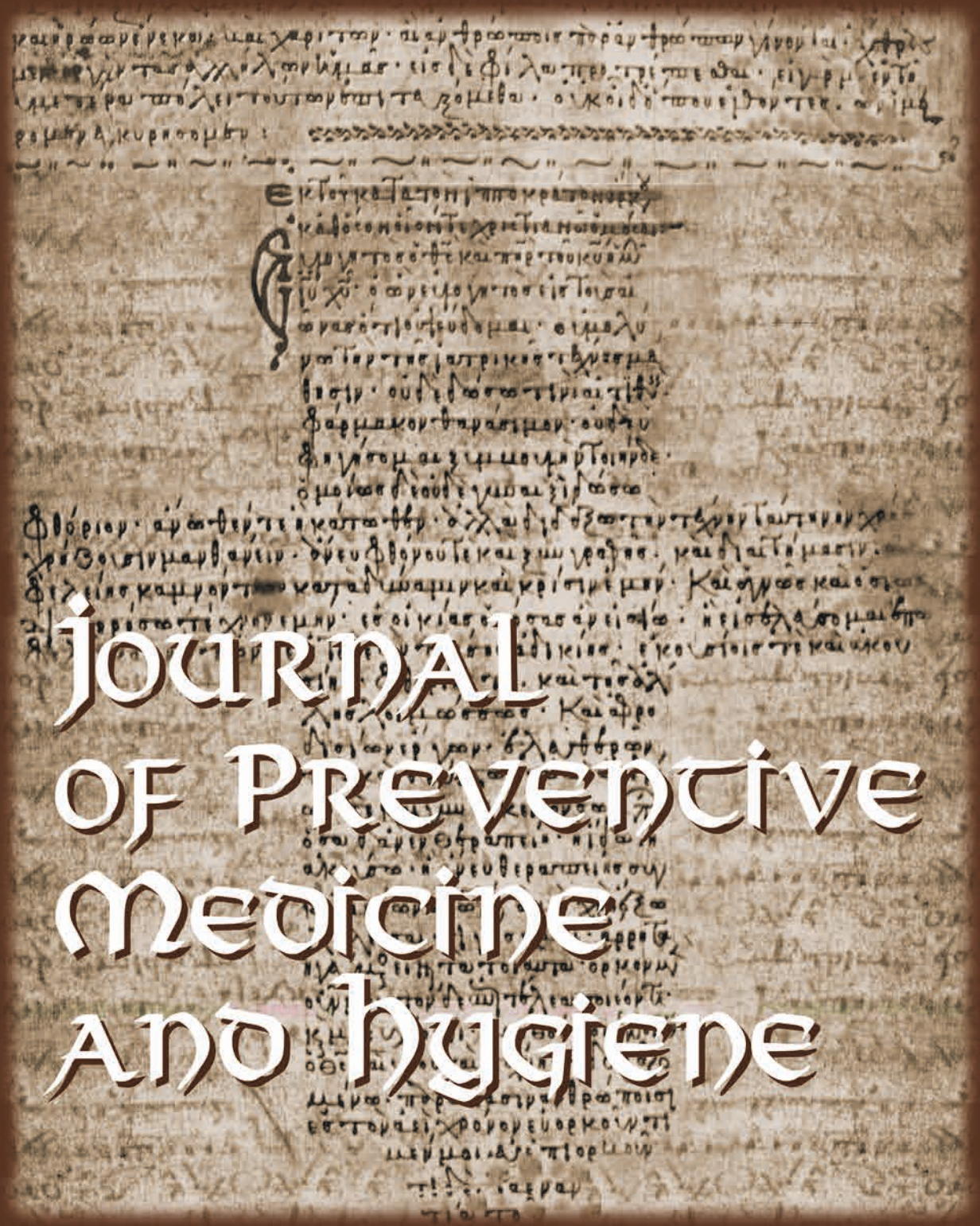

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Contents[1]

Infectious diseases

Resurgence of Measles in the United States - A Public Health Risk

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Keywords

Measles • United States • Immunization • Infectious Disease

Dear Editor,

Measles is a highly contagious respiratory illness caused by the measles virus (MeV). As per the World Health Organisation, there was a 20% rise from 2022 to 2023, with 10.34 million cases reported worldwide in 2023. Resultantly, 107,500 unvaccinated or partially vaccinated children died under the age of 5 [1]. Despite notable progress in vaccination efforts, it poses significant public health challenges globally and in the region of the Americas. Between January 1 and April 18, 2025, the region of the Americas recorded 2,318 confirmed measles cases and three deaths, an 11-fold rise from 205 cases during the same period in 2024. Cases were reported in six countries: Argentina (21), Belize (2), Brazil (5), Canada (1,069), Mexico (421, one death), and the USA (800, two deaths) [2]. This recent resurgence of measles globally and in the region of the Americas, driven by disruptions to routine vaccination services and campaigns during the COVID-19 pandemic, has heightened the risk of imported cases and outbreaks in the United States, although measles was officially declared eradicated in the United States in the year 2000. After the declaration of the COVID-19 pandemic in the United States in March 2020, there was a marked decrease in routine childhood vaccine administration due to disrupted routine immunisation services. This decline was also consistent with the enactment of stay-at-home orders in many regions [3]. The COVID-19 pandemic-related vaccine hesitancy also led to the reluctance to other routine immunisations, including Measles vaccination [4].

Of all the 2,280 confirmed measles cases in 2025 across 49 outbreaks (89% outbreak-associated) age distribution was as follows: 26% (582 cases) < 5 years, 44% (1,014 cases) 5-19 years, 29% (671 cases) ≥ 20 years while 93% cases occurred in unvaccinated individuals [5]. These patterns indicates increased vulnerability in children and teenagers, supporting seroepidemiological screening to identify susceptible individuals so they can get the MMR vaccine quickly after possible exposure during outbreaks. NHANES 2009-2010 national seroprevalence data showed declining measles IgG seropositivity, reaching 93.3% in adults aged 20- 29 years, pointing to potential waning of immunity provided by the vaccine over time.[6] Data from the 2025 U.S. measles outbreaks revealed that 29% of cases (671) occurred in adults ≥ 20 years, indicating possible waning MMR immunity [5]. Control via MMR could be beneficial, especially in regions with consistently low vaccination coverage or sustained transmission risks. Although the routine two-dose MMR schedule provides approximately 97% effectiveness against measles, outbreak data shows that a third dose offers additional protection which includes higher seroprotection rates and reduced antibody waning over time [7].

All unprotected healthcare workers must get the MMR vaccine to achieve presumptive immunity and lower the measles transmission risk in healthcare settings. As per CDC guidelines, healthcare workers are required to show measles immunity (2 MMR doses or lab evidence); those without protection must be vaccinated and excluded from work during any measles exposures [8].

For 2025, 2,280 cases of measles were reported in the USA across 45 states. The situation is more alarming in states such as Texas, South Carolina, Arizona, Utah and New Mexico. Alarmingly, 89% of confirmed measles cases are linked to outbreaks as compared to 69% in 2024. Forty-nine outbreaks have occurred in 2025, and 11% of the patients required hospitalisation [5].

Currently, several preventive steps are being taken to reduce the resurgence of vaccine-preventable diseases despite the severe reduction in vaccination coverage throughout the United States. The importance of sustaining elevated vaccination levels remains critical as shown by a study conducted by Mathew V et al., which shows that even a mere 5% spike in measles-mumps-rubella (MMR) vaccination coverage might substantially lower measles incidence over a 25-year period [9].

Health experts are now focusing on culturally appropriate vaccine promotion to deal with under-immunised groups that have trouble because of language and mistrust. Health officials in central Ohio use messages that fit the local culture and make sure vaccine information is given in various languages. None of these strategies works without support from reliable community leaders and local influencers who help remove fears and misconceptions about vaccines. Many vaccination centers can be found in popular community hubs to

improve access and make things more convenient for these groups [10].

Risk is higher, especially when USA travelers contact measles abroad and return while still contagious [11]. In the United States, imports accounted for 19% of measles cases reported between 2001 and 2019 [12]. Unvaccinated foreign visitors are the source of measles cases in the US. Measles vaccinations should be received at least two weeks before to overseas travel [13].

Between 2013 and 2018, measles susceptibility was primarily driven by waning immunity after vaccination, undervaccination, and primary vaccine failure. From 2021 to 2024, the immunity gap between vaccinated and unvaccinated children widened, highlighting the accumulation of susceptible individuals over time [14].

Despite these efforts and the availability of an effective vaccine, resurgence has been noticed in many states of the USA [15]. Moreover, recent policies have also been criticised for their detrimental impact on measles control in the U.S. Measures like reducing the vaccination schedule, reforming advisory committees, modifying official information, and resisting mandatory vaccinations pose a further risk of increasing measles cases among the American population. Whereas CDC recommends a more than 95% vaccination rate for measles to ensure herd immunity. This goal is affected by policy changes and hence increases the probability of outbreak and the number of susceptible individuals.

This calls for the need of effective measures to be taken to increase the vaccination coverage in the region. Moreover, the use of the Supplementary Activities (SIA), like those which are used by Kenya, especially the use of auto-disable syringes, can reduce the risk of transmission of disease [16]. A method by which access of laymen to vaccines can be increased, which may also facilitate measles eradication by increasing vaccination coverage, is the use of microarray patches, which are easily accessible and easy to use. Point-of-care diagnostic tests can help to assess measle outbreak so that immediate preventive measures can be taken, also point of contact IgG antibody tests can help to identify the population that is susceptible to measles so that their vaccination can be done. Measles is one of the diseases the eradication of which cannot be done without global commitment and coordination. So, there is a need to raise awareness and to encourage the stakeholders, including local and national health authorities, to make efforts to devise new tools that can help to achieve measles eradication [17].

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Not applicable. This report is based solely on publicly available data and does not involve human participants or identifiable individual information.

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Data availability

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Authors' contributions

MT: Review the work critically; MT, ZF, ZK: Conception of the work; MT, ZF, ZK, S: Final approval of the version to be published; Agreement to be accountable; ZF, ZK, S: Drafting the work.

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Infectious diseases

Infodemics management in the digital world: The implications for Public Health in Sub-Saharan Africa

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Keywords

Infodemic • Misinformation and disinformation • Risk communication • Public health preparedness • Digital health communication • Health systems strengthening • Sub-Saharan Africa

Dear Editor,

Digital technology has profoundly transformed modern society, effectively turning the world into a global village. Advances in information and communication technologies have removed many traditional barriers to communication, education, commerce, and healthcare delivery, including those associated with telemedicine. Individuals can now communicate instantly across continents, exchange information freely, participate in virtual learning and professional networks, access mentorship, and engage in economic activities regardless of physical distance. Aside from challenges such as poor network connectivity, information flow in the digital era faces few limitations. This letter aims to highlight the Public Health implications of infodemics in Sub-Saharan Africa and to contribute to ongoing policy discussions by advocating for the integration of infodemic management into epidemic preparedness and health system strengthening strategies

The rise of the internet and social media has fundamentally reshaped human interaction by increasing the speed, reach, and influence of information. McLuhan's concept of the "global village" captures this reality, describing a world where societies are increasingly interconnected through technologies that accelerate knowledge transfer within social and economic systems [1]. Digital platforms enable geographically distant individuals to access similar information simultaneously, share experiences, and express opinions that can influence others positively or negatively on a global scale.

This era is also defined by real-time communication and rapidly expanding social networks that transcend geographic boundaries. Information spreads faster than ever, shaping perceptions, attitudes, and behaviours. These dynamics were especially evident during the COVID-19 pandemic, when lockdowns and movement restrictions limited physical interaction. During this period, digital platforms became central to information sharing, commerce, entertainment, and social connection, accelerating the growth of new media platforms and expanding the influence of existing ones.

Sub-Saharan African countries experienced these transformations acutely. During the COVID-19 pandemic, their fragile health system faced a dual challenge: responding to the outbreak while managing an overwhelming influx of unfiltered health information. The World Health Organisation (WHO) describes this phenomenon as an infodemic–an overabundance of information, accurate or not, that accompanies an epidemic or outbreak [2].

An infodemic extends beyond misinformation and disinformation to include all forms of circulating information within the information ecosystem [3]. While misinformation refers to false information shared without intent to harm, disinformation involves deliberate deception; both contribute to the broader phenomenon of infodemics, which encompasses the entire information ecosystem during health emergencies. This ecosystem spans digital and physical spaces and interacts closely with social dynamics, health behaviours, and information-seeking practices. It is also shaped by people's experiences and interactions with the health system [3]. During the pandemic, the biological threat of COVID-19 was compounded by the rapid spread of infodemics, intensifying the burden on health systems and complicating the design of effective interventions.

During outbreaks, fear and uncertainty drive individuals to seek information aggressively from multiple sources, including peers, community leaders, and opinion shapers [4] As information production accelerates, accurate messages coexist with misinformation, disinformation, and outdated content across diverse channels. In such contexts, identifying trustworthy sources becomes difficult, conflicting messages are hard to process, and altered risk perception can significantly influence health-seeking behaviour and adherence to Public Health guidance [5-8].

Evidence from previous outbreaks illustrates the Public Health consequences of unmanaged infodemics. During the Ebola outbreak, widely circulated claims that consuming salt water could prevent infection resulted in avoidable morbidity and mortality. Similarly, vaccination programmes in Nigeria have been affected by persistent misinformation, including narratives questioning vaccine safety or intent [9]. Such narratives have fuelled vaccine hesitancy, including resistance

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to COVID-19 vaccination, even among educated and influential groups who cited exaggerated or fabricated side effects circulating on social media. Comparable impacts of infodemics have been documented during outbreaks of Zika, Ebola, polio, and measles [10].

Infodemics erode trust, weaken social cohesion, and undermine Public Health interventions by distorting knowledge, beliefs, and behaviours. In Africa, mistrust is compounded by perceptions of political elites' behaviour and widening socioeconomic inequalities, contributing to declining confidence in government and health institutions. During the COVID-19 pandemic, health workers promoting vaccination were sometimes met with hostility and violence, driven by conspiracy theories about government intentions.

Infodemics have also reshaped health-seeking behaviour, with some individuals favouring unproven traditional or spiritual remedies over evidence-based care for conditions such as mental illness and snakebite. Beyond direct health effects, infodemics have caused unreported deaths from unapproved treatments and contributed to stigma, discrimination, and artificial scarcity of essential commodities, as observed during the COVID-19 pandemic [11-13].

These patterns highlight a critical gap in epidemic preparedness: the limited integration of infodemic management into routine Public Health systems. Infodemiology, introduced by Eysenbach, provides a framework for analysing the distribution and determinants of health information to improve access to reliable knowledge [14]. Building on this, infodemic management encompasses coordinated strategies to monitor information flows, identify and address misinformation and disinformation, and promote timely, accurate communication. The WHO recommends approaches including community engagement, social listening, strengthening risk communication, and empowering individuals to make informed decisions [15]. Early intervention–particularly during the initial stages of an outbreak–is essential to prevent information gaps that can be filled by misleading narratives.

From a policy and systems perspective, integrating infodemic management into Public Health practice is increasingly necessary. This includes embedding infodemic surveillance within national health information systems, strengthening digital and health literacy, and incorporating risk communication into preparedness and response plans. Collaboration with media organisations, community leaders, and digital platform providers is also important to ensure consistent dissemination of credible information. In addition, building and maintaining public trust through transparent and culturally appropriate communication should be prioritised as a core function of health systems.

Infodemics pose a growing Public Health challenge in Sub-Saharan Africa, influencing trust, behaviour, and intervention effectiveness. Addressing this requires shifting from reactive communication to the systematic integration of infodemic management into preparedness and health system strengthening. With increasing public health emergencies and expanding digital information ecosystems, coordinated policy action is needed to equip health systems to manage both disease outbreaks and the complex information environments that accompany them.

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Authors' contributions

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HEALTH PROMOTION

Addressing HPV Vaccine Hesitancy: A Crucial Step Toward Cervical Cancer Prevention in Pakistan

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Keywords

HPV vaccine • Vaccine hesitancy • Cervical cancer prevention • Public health

Dear editor,
Cervical cancer remains a preventable tragic condition in Pakistan with hundreds of women being affected annually as a result of late presentation and persistent unawareness regarding prevention. Following the *Human Papilloma Virus* (HPV) Information Centre, cervical cancer is the second leading cancer among women between 15-44 years of age in Pakistan, where about 5,000 new cases are reported annually, and 3,000 deaths due to the frighteningly high death rate of 60-85% against the global average of 45% [1].
The HPV vaccine heralds an historic advancement in Pakistan's public health. Supported by the World Health Organization (WHO), United Nations Children's Fund (UNICEF), and Global Alliance for Vaccines and Immunisation (GAVI), the campaign aims to vaccinate 13 million girls ages 9-14 years in Punjab, Sindh, Islamabad, and AJK; the vaccination program starts in September 2025 [2]. Not only is this action in line with the World Health Organization's recommendation to immunize girls before they initiate sexual activity. The WHO 90-70-90 strategy aims to eliminate cervical cancer as a public health problem by 2030 through three key targets: vaccinating 90% of girls against HPV by age 15, screening 70% of women at least twice in their lifetime, and ensuring 90% of those diagnosed with cervical disease receive appropriate treatment [3], but this action also gives Pakistan a chance to minimize its burden of cervical cancer in the long run.
A general reluctance or resistance to vaccination fueled by disinformation and socio-cultural norms is diminishing the effectiveness of this lifesaving resource. Several parents wrongly assume the vaccine will lead to infertility or disturbed hormones, while others see the vaccine as a means of allowing sexual activity before marriage, which is sensitive in conservative Pakistan [4]. To address these barriers a multi-component strategy is required. First, trusted community leaders, including doctors, teachers, and religious scholars, need to be front-facing on awareness campaigns to address misinformation, and encourage the vaccine as a moral and collective public health responsibility Next, the routine HPV vaccination with other vaccine components in the childhood immunization schedule will not only help to normalize the vaccine like other vaccines for polio and measles, but also increase acceptance and familiarity of vaccination. Third, transparent messaging from the federal government and media about the vaccine's proven safety and efficacy will help to restore trust and confidence in the vaccine.
The prevention of cervical cancer is not only a medical issue, but a social obligation. Protecting young girls through HPV vaccination represents Pakistan's commitment to women's health, education, and empowerment. On the other hand, HPV is associated with genital warts, 90% of anal cancers as well as 60% of oropharyngeal cancers in men population [5]. However current vaccination campaign does not include the male population; including men in future efforts can help reduce transmission and related cancers. Clearly, Pakistan must take strong action against misinformation and ensure that no girl is left unprotected from a preventable disease.

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Infectious diseases

Fulminant Pertussis in infancy: The Critical Role of Clinical Acumen and Therapeutic Strategies - A case report

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Keywords

Bordetella • Whooping cough • Pertussis • Infant • Vaccination • Nigeria

Summary

Background. *Pertussis, also known as whooping cough, remains a significant cause of morbidity and mortality in early childhood, particularly in low- and middle-income countries (LMICs) with delayed vaccination schedules. Despite global immunization efforts, pertussis has re-emerged, presenting diagnostic and management challenges. Early recognition requires clinical acumen, as atypical presentations−especially fulminant cases−can mimic other respiratory conditions.*
Case Report. *This case report highlights a 9-week-old female infant with severe paroxysmal coughing and progressive respiratory distress, initially mismanaged due to delayed clinical suspicion and missed vaccination. Following appropriate antibiotic therapy and supportive measures, dramatic symptom resolution was observed. This case underscores the critical need for heightened awareness, rapid intervention, and strategic therapeutic approaches, particularly in vulnerable infant populations at risk for severe pertussis complications.*
Conclusion. *Persistent coughing, although a frequent clinical presentation in paediatric patients, requires an intuitive history and thorough evaluation to determine underlying etiologies. Accurate diagnosis of pertussis is essential for timely intervention, and prompt vaccination remains the most effective preventive measure.*

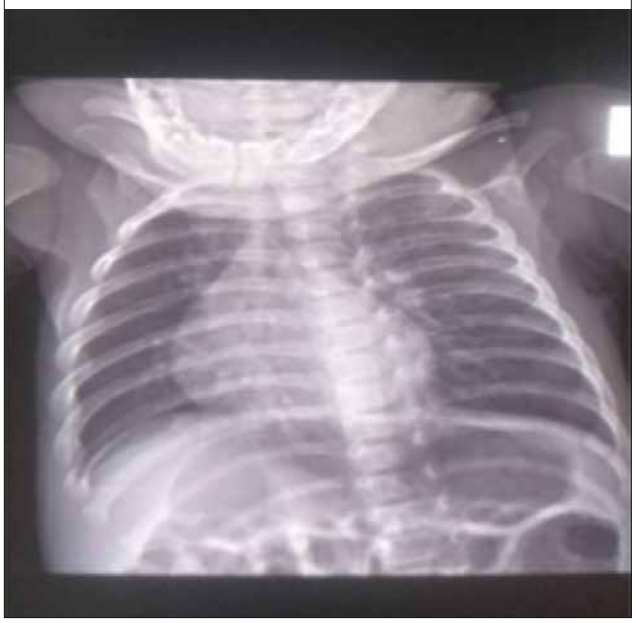
Introduction

Pertussis, commonly known as whooping cough, is a highly contagious respiratory infection caused by Bordetella pertussis [1]. It remains a major contributor to infant morbidity and mortality, particularly in low- and middle-income countries (LMICs), where diagnostic limitations and competing health priorities exacerbate the disease burden [2]. Infants under six months of age are disproportionately affected, accounting for approximately 10-15% of all reported pertussis cases, with over 90% of pertussis-related deaths occurring in this vulnerable group [3]. In Nigeria, routine pertussis vaccination does not commence until six weeks of age, leaving neonates and younger infants highly susceptible to severe infections [3]. This case highlights the critical need for earlier preventive strategies, improved diagnostic capacity, and timely therapeutic intervention in endemic regions. Additionally, it emphasizes the growing global resurgence of pertussis, even in high-income countries with strong vaccination programs, reinforcing the need for robust surveillance systems and enhanced vaccine strategies.

Case report

A 9-week-old female infant was brought to the hospital with progressive respiratory distress, paroxysmal coughing episodes, and cyanotic spells. The symptoms had evolved over several weeks with a prodrome of coryza that began six weeks prior to presentation, persistent machine-gun-like coughing that started five weeks earlier, and breathing difficulties that became apparent three weeks before admission. Fever was, however, not noted. The coughing episodes were paroxysmal, violent, and triggered by crying or feeding, occasional post-tussive vomiting, often culminating in cyanosis at their peak. A detailed immunization history revealed that the infant had missed a scheduled six-week vaccination for Pentavalent (DPT, Hep B, HiB), OPV1, Rota1, and PCV1 vaccines, as the child was ill and admitted at the time.
Initially, the mother administered home remedies for one week, including syrup Vitamin C, Paracetamol, and Probiotics. Later, at a private clinic, the child was admitted and nebulized with hypertonic saline and treated with Azithromycin, Cetirizine, Ketotifen, Prednisolone, and Montelukast. Relief of symptoms was transient with repeated episodes of fulminant paroxysmal cough, prompting referral to the teaching hospital.
Initial assessment at the Teaching Hospital showed an afebrile child with a body weight of 3,5 kg in a 9-week-old who was in obvious respiratory distress, with subcostal and substernal recessions and increased work of breathing. Her respiratory rate was 52 per minute, and oxygen saturation (SpO_2) was 97% in room air. Auscultation of

Fig. 1. AP view of patient Chest Radiography showing reticular shadows.



all lung zones had bronchovesicular breath sounds. The severity of the paroxysms was fulminant, with attendant central cyanosis, hypoxia, and apnea. Skin examination showed coalesced hypopigmented patches and papules on the scalp, neck, shoulders, and forearms. The remaining systemic examinations were unremarkable. The following diagnoses were considered: 1. Failure to thrive 2^0 Pertussis (R/o Bronchopneumonia and possibly cyanotic congenital heart disease) 2. Seborrheic dermatitis. Laboratory findings revealed an elevated peripheral white blood cell count of 13,480 cells/mm³ with lymphocytosis of 54.60% and thrombocytosis of 490,000 cells/mm³. The chest radiograph showed diffuse nodular reticular shadows with intact costophrenic angles. The test for HIV antibodies was negative, and echocardiography revealed a bicuspid aortic valve but no hemodynamic compromise, aortic stenosis, or coarctation.

Given the classical history of paroxysmal cough, the delayed immunization for up-to-date vaccination, and the relative lymphocytosis, Pertussis was strongly suspected. She was commenced on oral azithromycin while receiving intermittent intranasal oxygen support during paroxysmal episodes. A symptom-tracking chart was introduced for the mother to log paroxysms and cyanotic episodes. Within the week, the paroxysms reduced to a bare minimum, with resolution of cyanotic episodes. Before discharge, she was counseled on possible disease progression, vaccination importance, and home management strategies. All household contacts received Azithromycin prophylaxis to prevent further infections.

Discussion

Pertussis progresses through three clinical stages: the catarrhal stage, lasting one to two weeks and characterized by coryza, sneezing, mild cough, and low-grade fever; the paroxysmal stage, which lasts one to six weeks and involves rapid cough bursts, cyanosis, a high-pitched whoop, and possible vomiting; and the convalescent stage, which spans weeks to months and is marked by gradual recovery with persistent cough [4]. Our patient likely presented at the paroxysmal stage. Complications of pertussis can include pneumonia, subconjunctival haemorrhage, pulmonary hypertension and encephalopathy [5]. Other infections that present with similar complaints to pertussis are viral upper respiratory infection, bronchiolitis, pneumonia, and tuberculosis. The differentiating features however are the progression through the three stages and the persistent cough with mild or no fever [6].

Despite high vaccination coverage in many countries, pertussis continues to re-emerge worldwide [3]. In 2024, reported cases surged across the United States, with incidence six times higher than in 2023 [4]. In Nigeria, 11,281 cases were documented in 2009, ranking second globally [7].

Beyond clinical evaluation, various diagnostic approaches exist, including culture, which is the gold standard, polymerase chain reaction (PCR), which is a rapid method, and serology, which is particularly valuable in late-stage detection [8]. Unfortunately, in LMICs, limited accessibility and affordability make clinical evaluation with laboratory support the primary means of diagnosis, as seen in this case. The diagnostic challenges differ significantly between high-income countries and LMICs [9]. High-income countries benefit from advanced molecular techniques such as PCR and serology, which facilitate early and accurate diagnosis. LMICs, however, face limited access to PCR and culture, delayed clinical suspicion, and under-reporting, which often lead to missed or late diagnoses, contributing to higher mortality rates [9].

Approach considerations for treatment include supportive and pharmacological therapy [1]. Antibiotic options for management include Azithromycin, Clarithromycin, Erythromycin, and TMP-SMX (Septrin), alongside supportive care such as nutritional rehabilitation, oxygen therapy, and mechanical ventilation when indicated [1]. The goals of supportive therapy include limiting the number of paroxysms, observing the severity of cough, providing assistance when necessary, and maximizing nutrition, rest, and recovery and infants must be carefully observed for apnea, cyanosis, or hypoxia [1]. Antibiotics are of more value if administered early (1 or 2 weeks before the paroxysmal stage), but can still be used during the paroxysmal stage to hasten the eradication of *B. pertussis* and help prevent spread. They can also prevent or alleviate secondary bacterial infection [10].

The best way to prevent pertussis is through vaccination, using the three-dose primary series, diphtheria-tetanus-pertussis (DTP3). The world health organization (WHO) recommends the first dose be administered as early as 6 weeks of age; with subsequent doses given 4-8 weeks apart, at age 10-14 weeks and 14-18 weeks [11]. For the prognosis, most people infected with pertussis fully

recover, though this is usually after a prolonged illness that can span for months. Infants and older adults tend to have the highest mortality and morbidity, respectively. The infant death rate being about 2% of cases and accounting for 96% of pertussis-related deaths [6]. The index case however missed the timely immunization, which may have predisposed her to the infection.

Conclusion

Timely diagnosis and immunization are critical in pertussis management. Healthcare providers should maintain a high index of suspicion for pertussis in cases of persistent cough, even without typical fever. Early detection and intervention are vital to reducing mortality, particularly in neonates. Expanding diagnostic capabilities in LMICs, including accessible PCR testing, is strongly recommended. Vaccination policies should be advanced to start earlier in high-risk regions, and strengthening surveillance systems is essential to monitor and predict outbreaks.

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Conflict of interest statement

None.

Authors' contributions

OO: participated in patient management and data collection, drafted the initial manuscript and contributed to literature review; CFA: supervised clinical management and contributed to case analysis, and critically revised the manuscript for important intellectual content; ACA: provided senior clinical oversight and diagnostic guidance, reviewed and edited the final manuscript and approved the final version for submission.
All authors read and approved the final manuscript.

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Infectious diseases

Knowledge Level, Attitudes and Practice Towards Mpox, and Willingness to Receive the Mpox Vaccine Among Family Physicians Working in Family Health Centers in Ankara Province

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Keywords

Mpox • Knowledge • Attitude • Behavior • Family Physician • Vaccination

Summary

Introduction. *The increase in cases following the global mpox outbreak that began in May 2022 has highlighted the importance of early diagnosis, rapid response, and preventive measures in controlling the spread of the disease. The aim of our study was to determine the knowledge level, attitudes, and behaviors regarding mpox and the mpox vaccine among family physicians working at Family Health Centers in Ankara province.*
Materials and Methods. *This study is cross-sectional. The research was conducted between April 15, 2025, and July 15, 2025, using an online survey distributed via social media groups among primary care family physicians of the Ankara Provincial Health Directorate Public Health Services Department. The survey form consisted of a total of 49 questions: sociodemographic characteristics (14 questions), knowledge level regarding mpox (18 questions), attitude towards mpox (5 questions), willingness to use the mpox vaccine (5 questions), and Generalized Anxiety Disorder Scale (7 questions).*
Results. *A total 313 out of 1,741 family physicians participated in our study survey. The median age of family physicians was 36 (IQR: 30-47), 53.7% were female. Only 21.1% of family physicians had a good knowledge score about mpox. A statistically significant association was found between a good knowledge score about mpox and having previously heard of mpox and using research articles as a source of information about mpox ($p = 0.004$, $p = 0.036$).*
Conlusion. *Family physicians working at Family Health Centers in Ankara province had a low level of knowledge and low positive attitude towards mpox, and their rate of considering the smallpox vaccination for protection against mpox was a low. Therefore, it is recommended that awareness-raising and training programs be implemented for family physicians working in primary care regarding mpox.*

Introduction

Monkeypox (Mpox) is a viral zoonotic disease caused by the Monkeypox virus, an enveloped, double-stranded DNA virus belonging to the Orthopoxvirus genus of the Poxviridae family [1]. Monkeypox virus has two different types, clade I (clades Ia and Ib) and clade II (clades IIa and IIb) [1]. Currently, the increasing number of clade Ia and Ib cases in the Democratic Republic of Congo and other countries is a cause for concern [1].
Monkeypox virus was first identified in 1958 at the Copenhagen laboratory in Denmark [2]. The first human case was reported in a nine-month-old boy presenting with smallpox-like symptoms in the Democratic Republic of Congo in 1970 [3]. Following the eradication of smallpox and the end of smallpox vaccination worldwide in 1980, mpox cases have continued to occur regularly in Central and West African countries [1]. The first mpox cases outside of African countries were reported in the United States in 2003 [4]. In the Democratic Republic of Congo, thousands of mpox cases have been reported annually since 2005. In Nigeria, mpox re-emerged in 2017 and continued to spread among travelers within the country and internationally [1].
In 2022, mpox cases reported at least 116 countries worldwide. The World Health Organization (WHO) declared mpox a Public Health Emergency of International Concern (PHEIC) in July 2022. This designation was lifted in May 2023 following a decline in mpox cases from April 2023 onward [5]. The WHO declared a PHEIC for the second time in August 2024 due to a resurgence in mpox cases, and this declaration was subsequently ended on September 5, 2025, with the decline in case numbers [5]. Between January 1, 2022 and September 30, 2025, a total of 175,415 laboratory-confirmed of mpox cases and 467 deaths were reported from 142 countries [5]. A total of 71 laboratory-confirmed mpox cases were reported in Turkey between 2022 and 2025.
Mpox is transmitted from person to person through close contact with an infected individual [1]. Transmission from animals to humans also occurs through scratches and bites from infected animals or during activities such as hunting, skinning, trapping, and handling animal meat [1].

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The incubation period for mpox, defined as the time from exposure to symptoms onset, is generally 6-14 days but may range from 1 to 21 days (1). The most common symptoms of mpox are fever, rash, sore throat, headache, muscle pain, back pain, and lymphadenopathy. The rash progresses through stages of macules, papules, vesicles, pustules, and crusts that eventually dry and slough off [1].

Mpox is a self-limiting illness with symptoms typically lasting 2-4 weeks. Complications of Mpox include bronchopneumonia, sepsis, encephalitis, corneal infection resulting in vision loss, and secondary bacterial infections [1]. Children, pregnant women and immunocompromised individuals are reported to have a higher risk of severe illness and death due to mpox complications [1].

Currently, two FDA approved antiviral drugs are available for the treatment of mpox, Tecovirimat and Brincidofovir [3]. Isolation and vaccination are essential measures for preventing from person to person transmission. Three vaccines (ACAM2000, LC16m8 and MVA-BN) have been approved by the WHO for use against mpox [6].

The recent increase in mpox cases has highlighted the importance of early diagnosis, rapid response, and preventive management in controlling the spread of the disease. Healthcare professionals play a vital role in this process. WHO assessment reported that insufficient knowledge about the disease, especially among healthcare workers, posses a significant challenge in controlling spread of mpox [7]. Healthcare workers, who serve on the front lines in preventing the spread of infectious diseases need to possess the necessary knowledge and understanding to educate the public about mpox vaccine acceptance, positive attitudes, and trust. Furthermore, healthcare workers play an important role in significantly reducing vaccine hesitancy in settings where vaccines are available, which WHO has identified as one of the major challenges in mass vaccination efforts [8, 9].

In the systematic review and meta-analysis conducted by Jahromi et al., the level of knowledge of mpox among healthcare workers was reported to be 26%, and their positive attitudes towards mpox were 34.6% (10). In a study conducted by Sahin et al., the rate of good knowledge about mpox among physicians was 32.5%, and 31.4% of physicians planned to receive the mpox vaccine [11]. In a study conducted by Harapan et al. reported that only 36.5% of general practitioners had a good level of knowledge about mpox. Furthermore, the level of knowledge about mpox was found to be lower among those who graduated from universities in Sumatra or other islands, those over 30 years of age, and general practitioners working in private clinics [7]. In another study by Hasan et al., it was reported that 30.5% of general practitioners had a good level of knowledge about mpox, and 15.1% had a positive attitude. Furthermore, acquiring information about mpox through the medical curriculum and obtaining information about mpox within the last month were significantly associated with a good level of knowledge [11]. In this context, the aim of our study was to determine the knowledge level, attitudes, and behaviors regarding Mpox and the Mpox vaccine of family physicians working at Family Health Centers in Ankara province. it is anticipated that these findings will contribute to the planning of training programs on mpox and mpox vaccine, as well as the development of interventions to address the reasons for negative attitudes.

This study was presented at The National Vaccination and Immunization Congress 2025 (29 November-2 December 2025).

Materials and Methods

This study employed a cross-sectional desing. It was conducted using an online survey distributed to family physicians via social media groups (WhatsApp) between 15 April 2025 and 15 July 2025.

The study population consisted of 1741 family physicians working in Family Health Centers in Ankara province. The sample size was calculated as 281 family physicians using the OpenEpi 2013 Version 3.01 program, with a 95% confidence interval, a prevalence of 32.5% as reported by Sahin et al [11], and a deviation (d) of 0.05. After adding a 10% non-response rate, the required sample size was determined to be 309 family physicians. The study included family physicians working at Family Health Centers in Ankara province and those who voluntarily agreed to participate. Family physicians who refused to participate or did not approve the informed consent form were excluded from the study.

The data collection form was developed based on a review of the relevant literature [7, 10, 11]. The data collection form was distributed to family physicians via the Google Forms application through social media group (WhatsApp). Invitations to complete an anonymous online survey were distributed by social media (WhatsApp) and sent by e-mail to by the President of the Ankara Family Medicine Association (Ankara Family Medicine Association). Therefore, participants' phone numbers and email addresses were not collected. Before the data collection form was administered, family physicians were sent an 'Informed Consent Form' to obtain their consent for the study. The data collection form consisted of a total of 49 questions, including sociodemographic characteristics (14 questions), mpox knowledge level (18 questions), attitude toward mpox (5 questions), mpox vaccine willingness (5 questions), and Generalized Anxiety Disorder Scale (7 questions).

The first section of the data collection form consisted of 14 questions covering participants' sociodemographic and general information. The second section contained 18 questions assessing mpox knowledge level. The possible answers to each knowledge question were "yes," "no," and "I don't know." Mpox knowledge score are calculated by adding 1 to the total score for each correct answer, and adding 0 to the total score for each incorrect answer or "I don't know" answer. Accordingly, the total Mpox

knowledge level score was computed. Higher scores indicated a better level of knowledge. A cutoff of 70% (*i.e.* if a participant answered correctly 13 out of the total 18 questions) was used. The levels of knowledge were dichotomized into good and poor based on cutoff points (a 70% of the total score) [11]. Participants were asked about the likelihood of getting the smallpox vaccine to prevent monkeypox viral infection once made available. Responses were categorized as "willing" if the respondent selected agree and "unwilling" if they chose undecided or disagreed. The third section consisted of 5 questions regarding attitudes towards mpox, the fourth section consisted of 5 questions regarding willingness the mpox vaccine, and the fifth section consisted of 7 questions related to the Generalized Anxiety Disorder Scale.

Generalized Anxiety Disorder (GAD)-7 score is a validated, easy-to-administer, seven-item tool designed to measure generalized anxiety symptoms [12]. GAD-7 score assesses how frequently participants experienced each anxiety symptom in the past two weeks. GAD-7 score consists of seven-item, including inability to manage anxiety, restlessness, irritability, distress, worrying about many things, difficulty relaxing, and fear that something terrible might happen. Items are scored using a four-point scale ranging from "never=0" to "almost every day=3", indicating the frequency of symptoms. GAD-7 scores were categorized into four severity groups; 0-4 (minimal anxiety), 5-9 (mild anxiety), 10-14 (moderate anxiety), and 15-21 (severe anxiety). Anxiety cases were identified with 82% specificity and 89% sensitivity using a cutoff value of 10 for the GAD-7 score [12].

A pilot study of data collection form was conducted with 10 randomly selected family physicians, and any erroneous or unclear questions were removed. The participants were selected from family physicians who were not involved in the study.

SPSS 21.0 package program was used to analyze the data. The suitability of normal distribution of numerical variables was evaluated by using the Kolmogorov Smirnov Test. In descriptive analyses, if continuous variables are normally distributed, mean±standard deviation is given, if they are not normally distributed, median and interquartile range (IQR) are given, and categorical variables are given as numbers or percentages. Pearson chi-square and Fisher's exact test were used in the comparison of categorical variables in independent groups. Statistical significance level was taken as $p < 0.05$.

This study was approved by the Ankara Training and Research Hospital Scientific Research Ethics Committee (Date: 19.02.2025, Decision No: 425/2025). Permission was also obtained from the Ankara Provincial Health Directorate, Public Health Services Department, Primary Healthcare Services Research Requests Evaluation Committee (Date: 09.04.2025, No: 272812246). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) guidelines.

Results

Our study included 313 of 1,741 family physicians working at Family Health Centers in Ankara province. The mean age of the participating family physicians was 38.46 ± 10.97, 53.7% were female, 46.3% were male. It was found that 34.2% of participating family physicians had received information about mpox during their medical training, and 79.9% had heard of mpox before (Tab. I).

Among the 313 family physicians, the questions that received the highest rates of correct responses regarding mpox knowledge were as follows: 'Mpox is a viral infectious disease' (90.1%), 'Mpox affects both women and men' (84.3%), and 'Hand hygiene and mask use are important in preventing mpox' (80.2%). Conversely, the questions with the lowest rates of correct responses regarding mpox knowledge were: 'Mpox is more severe in adults than in children' (10.5%), 'Lymphadenopathy is the only clinical sign or finding used in the differential diagnosis of mpox and smallpox cases' (21.1%), and 'Mpox does not spread through droplets (coughing and sneezing) (22.0%) (Tab. II).

Of the 313 participating family physicians, 79.9% responded 'I agree' to the question, 'I want to learn more about mpox.' It was found that 69.6% respondent 'I disagreed' with the question, 'I think that mpox will not add a new burden to the health systems of affected countries (Tab. III).

Regarding willingness to receive the mpox vaccine, 16.3% of participants agreed with the statement, 'Mpox has decreased and I no longer need vaccination against mpox', 18.2% agreed with the statement, 'I am thinking of getting the smallpox vaccine to protect myself from mpox' and 36.4% agreed with the statement, 'I would be willing to get vaccinated against mpox if it were provided free of charge' (Tab. IV).

The total score of GAD scale of the participating family physicians was found to be 6.87 ± 5.11 (mean ± standard deviation). Based on the GAD scale score, 101 (32.3%) were classified as having minimal anxiety, 145 (46.3%) as having mild anxiety, 37 (11.8%) as having moderate anxiety, and 30 (9.6%) as having severe anxiety.

The mpox knowledge score of participating family physicians was calculated by adding 1 point to the total score for each correct answer to an 18-question, and 0 points for each incorrect answer or "I don't know" answer. Accordingly, the mean knowledge score of the participating family physicians was determined as 9.38 ± 4.08, and the median knowledge score was 10 (IQR:8-12). A 70% correct answer rate was defined for both good and poor information levels. Mpox knowledge score of 313 participating family physicians was found to be good in 21.1% (66) and poor in 78.9% (247) (Tab. V).

No statistically significant relationship was found between the mpox knowledge level of participating family physicians and the mpox attitude questions.

Of the 313 participating family physicians, 21.2% of those with a good mpox knowledge level score answered "I agree" to the question "I am considering

Tab. I. Sociodemographic characteristics, vaccination status, and responses to questions about mpox of participating family physicians in the study (N=313).

Median (Interquartile Range)	n (%)
Age, 36 (30-47)	
30 ≤ 31-39 40 ≥	55 (17,6) 48 (15,3) 210 (67,1)
Gender	
Female Male	168 (53,7) 145 (46,3)
Marital status	
Married Single Widowed/Divorced	223 (71,2) 79 (25,2) 11 (3,5)
Medical specialty	
General practitioner Family physician specialist	250 (79,9) 63 (20,1)
Medical practice experience	
Less than 1 year 1-5 years 5-10 years 10-20 years More than 20 years	40 (12,8) 54 (17,3) 69 (22,0) 74 (23,6) 76 (24,3)
Presence of a chronic illness	
Yes No	88 (28,1) 225 (71,9)
History of having COVID-19	
Yes No	185 (59,1) 128 (40,9)
COVID-19 vaccination status	
Yes No	300 (95,8) 13 (4,2)
COVID-19 vaccine dosage	
0 to 3 doses 4 or more doses	146 (46,6) 167 (53,4)
Influenza vaccine status	
Yes No	180 (57,5) 133 (42,5)
Receiving information about mpox during medical training	
Yes No	107 (34,2) 206 (65,8)
Have you heard of mpox before?	
Yes No	50 (79,9) 63 (20,1)
Presence of childhood smallpox vaccination	
Yes No	160 (51,1) 153 (48,9)
Sources used to obtain information about mpox	
Family or friends	
Yes No	61 (19,5) 252 (80,5)
Social media	
Yes No	109 (34,8) 204 (65,2)
TV and radio	40 (12,8) 273 (87,2)
Yes No	
Books	
Yes No	179 (57,2) 134 (42,8)
Research articles	
Yes No	240 (76,7) 73 (23,3)

getting vaccinated against smallpox to protect myself from mpox," while only 17.4% of those with a poor mpox knowledge level score answered "I agree". Those with a good mpox knowledge level score were more likely to agree with the question, "I am considering getting vaccinated against smallpox to protect myself from mpox," compared to those with a poor knowledge level score; however, the difference was not statistically significant (p=0.458). It was found that 33.3% of those with a good mpox knowledge score answered "I disagree" to the statement "Mpox has decreased and I no longer need vaccination against mpox," while 24.7% of those with a poor mpox knowledge score also answered "I disagree."(p=0.019). Of the 313 family physicians participating in the study, 77.3% of those with a good mpox knowledge score agreed with the statement, "The recommendation of the mpox vaccine by doctors, the community, and other professionals has a great impact on me," while only 57.1% of those with a poor mpox knowledge score agreed (p=0.004) (Tab. VI).

When participating family physicians were asked, ''I'm thinking of getting the smallpox vaccine to protect myself from mpox" Of those who had received the smallpox vaccine as a child, 50.9% responded "agree," 45.7% responded "undecided," and 62.7% responded "disagree," while of those who did not have received the smallpox vaccine as a child, 49.1% responded "agree," 54.3% responded "undecided," and 62.7% responded "disagree". Those who had received the smallpox vaccine as a child had a higher rate of agreeing responses to the question "I'm thinking of getting the smallpox vaccine to protect myself from mpox" compared to those who did not receive the smallpox vaccine, and the difference was statistically significant (p=0.039) (Tab. VII).

Discussion

Currently, mpox is not recognized as an international public health emergency. However, mpox cases continue to be reported in many countries [5]. Given that Turkey is a popular tourist destination, the level of knowledge and attitudes of physicians about mpox is crucial for developing a global strategy and combating mpox.

In our study, family physicians answered approximately half of knowledge the questions correctly (above 50%), whereas questions concerning the existence of a smallpox vaccine and whether the disease could be prevented through post-exposure vaccination had correct response rates below 40%. Additionally, only 21.1% of family physicians had a good level of knowledge about mpox. Family physicians with a good level of knowledge about mpox were more likely to have heard of mpox before and to use research articles as a source information. The rate of positive responses to family physicians' attitudes regarding mpox was below 40%, except of the question 'I want to learn more about mpox'. In a systematic review and meta-analysis conducted by Jahromi et al., which included six studies involving 14,388 healthcare professionals, it was reported that 26% of healthcare

Tab. II. The distribution of responses to questions about mpox knowledge level of participating family physicians in the study (N=313).

	n (%)
Mpox is a new infectious disease that emerged in 2022.	
True	99 (31,6)
I don't know	88 (28,1)
False	126 (40,3)
Mpox is a sexually transmitted disease.	
True	104 (33,2)
I don't know	88 (28,1)
False	121 (38,7)
Mpox is not transmitted to humans through bites or scratches from infected animals.	
True	41 (13,1)
I don't know	110 (35,1)
False	162 (51,8)
Mpox is transmitted from person to person through close contact.	
True	227 (72,5)
I don't know	66 (21,1)
False	20 (6,4)
Mpox is not spread through droplets (coughing and sneezing).	
True	150 (47,9)
I don't know	94 (30,0)
False	69 (22,0)
Mox is a disease that affects both women and men.	
True	264 (84,3)
I don't know	46 (14,7)
False	3 (1,0)
Hand hygiene and mask use are important in preventing mpox.	
True	251 (80,2)
I don't know	53 (16,9)
False	9 (2,9)
Mpox is a viral infectious disease.	
True	282 (90,1)
I don't know	28 (8,9)
False	3 (1,0)
Mpox is common in West and Central African countries.	
True	245 (78,3)
I don't know	63 (20,1)
False	5 (1,6)
Smallpox and mpox do not have similar symptoms and signs.	
True	42 (13,4)
I don't know	69 (22,0)
False	202 (64,5)
Skin papules and vesicles are not a symptom or sign of mpox.	
True	19 (6,1)
I don't know	57 (18,2)
False	237 (75,7)
Lymphadenopathy is the only clinical sign or finding used in the differential diagnosis of mpox and smallpox.	
True	66 (21,1)
I don't know	158 (50,5)
False	89 (28,4)
Mpox is more severe in adults than in children.	
True	103 (32,9)
I don't know	177 (56,5)
False	33 (10,5)
The fatality rate of mpox cases in the general population is 5-10%.	
True	87 (27,8)
I don't know	208 (66,5)
False	18 (5,8)
The chickenpox vaccine given in childhood provides protection against mpox	
True	110 (35,1)
I don't know	111 (35,5)
False	92 (29,4)
There is a specific treatment for mpox.	
True	26 (8,3)
I don't know	126 (40,3)
False	161 (51,4)
There is a smallpox vaccine that can be used for mpox.	
True	121 (38,7)
I don't know	155 (49,5)
False	37 (11,8)
Vaccination after exposure to the mpox virus can help prevent the disease.	
True	110(35,1)
I don't know	159(50,8)
False	44(14,1)

Tab. III. Distribution of responses to questions regarding the attitudes towards mpox of participating family physicians in the study (N=313).

	n (%)
I am confident that mpox can be controlled in global population	
Agree	128 (40,9)
Undecided	137 (43,8)
Disagree	48 (15,3)
I want to learn more about mpox.	
Agree	250 (79,9)
Undecided	46 (14,7)
Disagree	17 (5,4)
I don't think it's dangerous to travel to countries where the mpox outbreak has occurred.	
Agree	56(17,9)
Undecided	78(24,9)
Disagree	179(57,2)
I don't think mpox will affect social and economic life.	
Agree	48 (15,3)
Undecided	81 (25,9)
Disagree	184 (58,8)
I think mpox cannot add a new burden to the health systems of affected countries.	
Agree	35 (11,2)
Undecided	60 (19,2)
Disagree	218 (69,6)

during medical school or residency training, those who had previously been exposed to COVID-19 disease, and those who used research articles as a source of information were reported to be more likely to have knowledge of mpox [11]. In a study conducted by Alshahrani et al., it was found that the level of mpox knowledge in the general population was associated with age, marital status, place of residence, living in an urban area, education level, employment status,

Tab. IV. Distribution of responses questions about mpox vaccine willingness of participating family physicians (N=313).

	n (%)
I'm thinking of getting the smallpox vaccine to protect myself from mpox.	
Agree	57 (18,2)
Undecided	173 (55,3)
Disagree	83 (26,5)
Mpox has decreased and I no longer need vaccination against mpox	
Agree	51 (16,3)
Undecided	179 (57,2)
Disagree	83 (26,5)
I am concerned about the potential side effects of the mpox vaccine.	
Agree	86 (27,5)
Undecided	154 (49,2)
Disagree	73 (23,3)
The fact that the mpox vaccine is recommended by doctors, the community, and other professionals has a great impact on me.	
Agree	192 (61,3)
Undecided	100 (31,9)
Disagree	21 (6,7)
I am willing to get vaccinated if the mpox vaccine is provided free of charge.	
Agree	114 (36,4)
Undecided	164 (52,4)
Disagree	35 (11,2)

being a healthcare worker, income level and smoking status [14]. In contrast to these studies, our study found that the knowledge level of family physicians about mpox was associated only with whether they had heard of mpox before and whether they used research articles as a information source.

Vaccination currently represents the most effective means of preventing most vaccine-preventable diseases. In countries where mpox is endemic, challenges in prevention and treatment continue. Isolation and vaccination are the primary measures used to prevent from person to person transmissin. Three vaccines have been approved by the WHO for use against mpox [16]. WHO and Center for Disease Prevention and Control recommend the use of JYNNEOS, ACAM2000 and LC16m8 vaccines for pre- and post-exposure prophylaxis in specific risk groups [17, 18]. In a systematic review and meta-analysis conducted by Ulloque-Badaracco et al., the prevalence of mpox vaccine acceptance was reported as 56% [19]. In another systematic review and meta-analysis conducted by Leon-Figueroa et al., the prevalence of intention to vaccinate against mpox was found to be 61% [20]. Studies have suggested that differences in the prevalence of intention vaccination are attributable to doubts about the efficacy and safety of the mpox vaccine and fears about unknown side effects [20, 21]. In a systematic review of 14 studies involving 10 696 participants conducted by Tanashat et al., reported that the willingness to receive the mpox vaccine was 65% [22]. In a study conducted by Sahin et al., reported that 31.4% of physicians plan to get the mpox vaccine [11]. It was also found that those who learned about mpox during their medical training were more likely to receive the mpox vaccine when available. In contrast to these studies, The rate of considering getting the smallpox vaccine to protect themselves from mpox of family physicians was quite low (18.2%). Furthermore, those who did not consider getting the smallpox vaccine to protect against mpox had a higher rate of having received the smallpox vaccine as children. Nevertheless, the finding that 36.4% of family physicians expressed willingness to receive the mpox vaccine if it were provided free of charge and that 61.3% reported that recommendations from physicians, the community, and other professionals had a significant influence on their decision was encouraging with regard to future vaccination plans. Therefore, implementing training programs on the mpox vaccine for family physicians to enhance their knowledge level would contribute to increasing both knowledge and vaccination willingness in the broader community.

In a systematic review and meta-analysis by Mektebi et al., the acceptance rate of the Mpox vaccine among healthcare workers was reported as 58.5%, while the hesitancy rate was 41.5% [23]. Vaccine acceptance was 68% in countries in Asia and Africa, compared with 44.3% in countries in North America and Europe. The acceptance rate was 77.1% in studies conducted exclusively among physicians, compared with 49% in studies including all healthcare professionals [23]. Significant differences in mpox vaccine acceptance rates have been observed across different populations. Identifying the factors underlying these differences is crucial for developing interventions to increase vaccine acceptance. In our study, the rate of family physicians considering vaccination against smallpox to protect themselves from mpox was notably low. The reasons for this could not be investigated within the scope of our study; therefore, further multicenter studies are warranted.

In a meta-analysis conducted by Han et al., including 34 studies with 43,226 healthcare workers, they reported that 54% of healthcare workers were willing to be vaccinated against mpox and 40% had good knowledge about mpox [24]. The study also found that a history of smallpox vaccination did not significantly affect healthcare workers' willingness to receive another vaccine, whereas those who had been vaccinated against influenza or COVID-19 were more willing to receive the mpox vaccine. Studies have reported that willingness to be vaccinated against mpox is lower among low-income healthcare workers and higher among those with middle incomes. In our study, no correlation was found between family physicians' consideration of receiving the smallpox vaccine to protect against mpox and their influenza or COVID-19 vaccination status. Family physicians found no correlation between those considering getting the smallpox vaccine to protect against mpox and their vaccination status for influenza and COVID-19. However, it was found that those who received the smallpox vaccine as children were

Tab. V. Comparison of family physicians' knowledge level about mpox with sociodemographic characteristics, vaccination status, and questions about mpox.

	Poor Knowledge	Good Knowledge	*p*
	n (%)	n (%)	
Age			
30 ≤ 31-39 40 ≥	44 (17,8) 38 (15,4) 165 (66,8)	11 (16,7) 10 (15,2) 45 (68,2)	0,973
Gender			
Female Male	127 (51,4) 120 (48,6)	41 (62,1) 25 (37,9)	0,121
Marital status			
Married Single Widowed/Divorced	172 (69,6) 65 (26,3) 10 (4,0)	51 (77,3) 14 (21,2) 1 (1,5)	0,384
Medical specialty			
General practitioner Family physician	199 (80,6) 48 (19,4)	51 (77,3) 15 (22,7)	0,553
Medical practice experience			
Less than 1 year 1-5 years 5-10 years 10-20 years More than 20 years	34 (13,8) 45 (18,2) 49 (19,8) 64 (25,9) 55 (22,3)	6 (9,1) 9 (13,6) 20 (30,3) 10 (15,2) 21 (31,8)	0,071
Presence of a chronic illness			
Yes No	70 (28,3) 177 (71,7)	18 (27,3) 48 (72,7)	0,864
History of having COVID-19			
Yes No	147 (59,5) 100 (40,5)	38 (57,6) 28 (42,4)	0,776
COVID-19 vaccination status			
Yes No	236 (95,5) 11 (4,5)	64 (97,0) 2 (3,0)	1,000
COVID-19 vaccine dosage			
0 to 3 doses 4 or more doses	115 (46,6) 132 (53,4)	31 (47,0) 35 (53,0)	0,953
Influenza vaccine status			
Yes No	141 (57,1) 106 (42,9)	39 (59,1) 27 (40,9)	0,770
Receiving information about mpox during medical training			
Yes No	82 (33,2) 165 (66,8)	25 (37,9) 41 (62,1)	0,476
Have you heard of mpox before?			
Yes No	189 (76,5) 58 (23,5)	61 (92,4) 5 (7,6)	0,004
Presence of childhood smallpox vaccination			
Yes No	132 (53,4) 115 (46,6)	28 (42,4) 38 (57,6)	0,112
Sources used to obtain information about mpox			
Family or Friends			
Yes No	47 (19,0) 200 (81,0)	14 (21,2) 52 (78,8)	0,691
Social Media			
Yes No	92 (37,2) 155 (62,8)	17 (25,8) 49 (74,2)	0,082
TV and Radio			
Yes No	32 (13,0) 215 (87,0)	8 (12,1) 58 (87,9)	0,857
Books			
Yes No	138 (55,9) 109 (44,1)	41 (62,1) 25 (37,9)	0,362

▶

Tab. V. (*follows*).

	Poor Knowledge	Good Knowledge	*p*
	n (%)	n (%)	
Research Articles			
Yes	183 (74,1)	57 (86,4)	0,036
No	64 (25,9)	9 (13,6)	
GAD			
Minimal Anxiety	77 (31,2)	24 (36,4)	0,409
Mild Anxiety	113 (45,7)	32 (48,5)	
Moderate Anxiety	33 (13,4)	4 (6,1)	
Severe Anxiety	24 (9,7)	6 (9,1)	
GAD Score			
< 10	190 (76,9)	56 (84,8)	0,163
≥ 10	57 (23,1)	10 (15,2)	

Tab. VI. Comparison of responses to questions about mpox knowledge level and willingness to receive mpox vaccine among participating family physicians.

	Poor Knowledge	Good Knowledge	*p*
	n (%)	n (%)	
I'm thinking of getting the smallpox vaccine to protect myself from mpox			
Agree	43 (17,4)	14 (21,2)	0,458
Undecided	141 (57,1)	32 (48,5)	
Disagree	63 (25,5)	20 (30,3)	
Mpox has decreased and I no longer need vaccination against mpox			
Agree	35 (14,2)	16 (24,2)	0,019
Undecided	151 (61,1)	28 (42,4)	
Disagree	61 (24,7)	22 (33,3)	
I am concerned about the potential side effects of the mpox vaccine			
Agree	62 (25,1)	24 (36,4)	0,131
Undecided	128 (51,8)	26 (39,4)	
Disagree	57 (23,1)	16 (24,2)	
The fact that the mpox vaccine is recommended by doctors, the community, and other professionals has a great impact on me			
Agree	141 (57,1)	51 (77,3)	0,004
Undecided	90 (36,4)	10 (15,2)	
Disagree	16 (6,5)	5 (7,6)	
I am willing to get vaccinated if the mpox vaccine is provided free of charge			
Agree	92 (37,2)	22 (33,3)	0,127
Undecided	132 (53,4)	32 (48,5)	
Disagree	23 (9,3)	12 (18,2)	

professionals had good knowledge of mpox and 34.6% had positive attitudes towards mpox [10]. In another systematic review and meta-analysis conducted by Leon Figueroa et al., it was found that 33% of healthcare workers had good knowledge about mpox, 40% had a positive attitude towards mpox, and 58% intended to be vaccinated against mpox [11]. In a study by Alshahrani et al., the level of knowledge about mpox in the general population was reported as 48% [14]. Similarly, in study conducted by Youssef et al., it was found to be 33.04% of the level of knowledge about mpox [15]. Consistent with these findings, our study demostrated that family physicians had both a low level of knowledge about mpox and low positive attitudes towards mpox. These findings are concerning, as insufficient knowledge regarding mpox case management, early diagnosis, and treatment way contribute to the spread of the disease and inappropriate patient care. Therefore, there is a need to plan training programs for family physicians on mpox and mpox vaccine, to raise awareness, and to identify areas of deficiency.

Our study showed that 21.1% of family physicians had a good level of knowledge about mpox. Those with a good level of knowledge about mpox were more likely to have heard of mpox before and to use research articles as a source of information about mpox. In the systematic review and meta-analysis conducted by Jahromi et al., it was reported that 26% of healthcare workers had good knowledge of mpox, with the knowledge level of 34.8% among those with fewer than 5 years of professional experience and 41.6% among those with more than 5 years [10]. A study conducted by Sahin et al. found that only 32.5% of physicians had a good level of knowledge about mpox. In addition, women, participants over 30 years of age, participants from internal medicine departments, those who had knowledge of mpox

Tab. VII. Comparison of responses of participating family physician to the question, "I'm thinking of getting the smallpox vaccine to protect myself from mpox" with responses to questions about mpox, sociodemographic characteristics, and vaccination status.

	I'm thinking of getting the smallpox vaccine to protect myself from mpox			*p*
	Agree n (%)	Undecided n (%)	Disagree n (%)	
Age				
30 ≤ 31-39 40 ≥	9 (15,8) 6 (10,5) 42 (73,7)	31 (17,9) 28 (16,2) 114 (65,9)	15 (18,1) 14 (16,9) 54 (65,1)	0,799
Gender				
Female Male	28 (49,1) 29 (50,9)	90 (52,0) 83 (48,0)	50 (60,2) 33 (39,8)	0,349
Marital status				
Married Single Widowed/Divorced	39 (68,4) 14 (24,6) 4 (7,0)	119 (68,8) 49 (28,3) 5 (2,9)	65 (78,3) 16(19,3 2 (2,4)	0,278
Medical specialty				
General practitioner Family physician	47 (82,5) 10 (17,5)	138 (79,8) 35 (20,2)	65 (78,3) 8 (21,7)	0,834
Medical practice experience				
Less than 1 year 1-5 years 5-10 years 10-20 years More than 20 years	8 (14,0) 10 (17,5) 10 (17,5) 14 (24,6) 15 (26,3)	24 (13,9) 31 (17,9) 39 (22,5) 42 (24,3) 37 (21,4)	8 (9,6) 13 (15,7) 20 (24,1) 18 (21,7) 24 (28,9)	0,910
Presence of a chronic illness				
Yes No	22 (38,6) 35 (61,4)	44 (25,4) 129 (74,6)	22 (26,5) 61 (73,5)	0,148
History of having COVID-19				
Yes No	36 (63,2) 21 (36,8)	95 (54,9) 78 (45,1)	54 (65,1) 29 (34,9)	0,239
COVID-19 vaccination status				
Yes No	54 (94,7) 3 (5,3)	166 (96,0) 7 (4,0)	80 (96,4) 3 (3,6)	0,886
COVID-19 vaccine dosage 0,150				
0 to 3 doses 4 or more doses	23 (40,4) 34 (59,6)	77 (44,5) 96 (55,5)	46 (55,4) 37 (44,6)	0.150
Influenza vaccine status				
Yes No	35 (61,4) 22 (38,6)	97 (56,1) 76 (43,9)	48 (57,8) 35 (42,2)	0,777
Receiving information about mpox during medical training				
Yes No	23 (40,4) 34 (59,6)	56 (32,4) 117 (67,6)	28 (33,7) 55 (66,3)	0,542
Have you heard of mpox before?				
Yes No	48 (84,2) 9 (15,8)	130 (75,1) 43 (24,9)	72 (86,7) 11 (13,3)	0,064
Presence of childhood smallpox vaccination				
Yes No	29 (50,9) 28 (49,1)	79 (45,7) 94 (54,3)	52 (62,7) 31 (37,3)	0,039
Sources used to obtain information about mpox				
Family or Friends				
No Yes	42 (73,7) 15 (26,3)	138 (79,8) 35 (20,2)	72 (86,7) 11 (13,3)	0,149
Social Media				
No Yes	34 (59,6) 23 (40,4)	113 (65,3) 60 (34,7)	57 (68,7) 26 (31,3)	0,544
TV and Radio				
No Yes	48 (84,2) 9 (15,8)	150 (86,7) 23 (13,3	75 (90,4) 8 (9,6)	0,538
Books				
No Yes	22 (38,6) 35 (61,4)	77 (44,5) 96 (55,5)	35 (42,2) 48 (57,8)	0,729

▶

Tab. VII. (*follows*).

	I'm thinking of getting the smallpox vaccine to protect myself from mpox.			*p*
	Agree n (%)	Undecided n (%)	Disagree n (%)	
Research Articles				
No	9 (15,8)	49 (28,3)	15 (18,1)	0,064
Yes	48 (84,2)	124 (71,7)	68 (81,9)	
GAD Scale				
Minimal Anxiety	20 (35,1)	52 (30,1)	29 (34,9)	0,489
Mild Anxiety	20 (35,1)	85 (49,1)	40 (48,2)	
Moderate Anxiety	10 (17,5)	19 (11,0)	8(9,6)	
Severe Anxiety	7 (12,3)	17 (9,8)	6 (7,2)	
GAD Score				
10 <	40 (70,2)	137 (79,2)	69 (83,1)	0,178
10 ≥	17 (29,8)	36 (20,8)	14 (16,9)	

significantly less likely to consider getting another smallpox vaccine to protect themselves from mpox.
This study has several limitations. First, it is single-center, and cross-sectional study. Therefore, the findings cannot be generalized to a broader population. Second, the low number of mpox cases in Turkey, and family physicians' unfamiliarity with the disease may have influenced their knowledge, attitudes, and behaviors. Multicenter, prospective studies with large sample sizes are needed to further elucidate these issues.

Conclusion

In conclusion, our study found that family physicians working at Family Health Centers in Ankara province had a low level of knowledge and positive attitude towards mpox, and that their rate of considering getting the smallpox vaccine for protection against mpox was low. These results may hinder efforts to diagnose and treatment mpox cases in a timely manner. Furthermore, given the pivotal role of physicians in promoting vaccination, there is a need to enhance knowledge and awareness regarding mpox and mpox vaccine. Accordingly, it is recommended that awareness of mpox among primary care physicians be increased and that targeted training programs be implemented.

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Conflicts of Interest Statement

The authors declare no conflict of interest.

Author contributions

AM, EB, HG designed the study and contributed to the interpretation of the results. AM, EB processed the data and performed the analysis. All authors discussed the results and contributed to the final manuscript.

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HOSPITAL HYGIENE

Assessing Compliance with Hand Hygiene Practices in Healthcare Settings in Benin: a Cross-Sectional Study

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Keywords

Hand hygiene • Healthcare-associated infections • Compliance rate • Maternal and neonatal infection prevention

Summary

Introduction. *Hand hygiene is a cornerstone of preventing healthcare-associated infections, particularly in maternity and neonatology. This study evaluated the knowledge, attitudes, and practices of Benin healthcare professionals regarding hygiene deficiencies that contribute to maternal and neonatal infections via a data collection survey.*
Methods. *Hand hygiene knowledge was evaluated among healthcare professionals from six healthcare centers between August and September, 2023, using the WHO Hand Hygiene Self-Assessment Framework (HHSAF). Hand hygiene compliance was assessed by observing 30 trained IPC professionals across the hospitals during the five WHO moments.*
Results. *A total of 159 health care professionals were included in the study. Most healthcare workers demonstrated good awareness of the appropriate moments for hand hygiene, with a minimum knowledge rate of 65%. Hand hygiene compliance rates exceeded 50% across the surveyed facilities. Compliance rates varied notably by profession, with doctors showing the highest adherence, particularly in hand hygiene before patient contact (100%), followed by nurses (92.30%). Male professionals generally adhered to hand hygiene practices more than their female counterparts, with the highest male compliance at CHUD B/A (100%) and the lowest at HZ-Tanguieta (35%). However, no statistically significant differences in hand hygiene or glove-wearing compliance were observed across gender, department, or professional qualification ($p > 0.05$).*
Conclusions. *These findings provide valuable insights into current hygiene practices among healthcare professionals, highlighting areas requiring improvement to effectively reduce maternal and neonatal infections. The results will inform targeted training programs to enhance compliance and ultimately improve health outcomes for mothers and newborns.*

Introduction

Healthcare-associated infections (HAIs) are a significant public health concern globally, requiring serious attention [1, 2]. According to the World Health Organization (WHO), for every 100 hospital admissions, at least seven patients in high-income countries and ten in low- and middle-income countries acquire at least one HAI [3, 4] bacterial or fungal pathogens and the most common types of HAIs include: blood stream infections, pneumonias (e.g. ventilator-associated pneumonia. In developing countries, the prevalence of HAIs can reach 15.5% [5].
To mitigate HAIs, hand hygiene plays a crucial role, as hands are the primary vector for HAI transmission [6, 7]. Studies have shown that nine out of ten HAIs result from contamination by the hands of healthcare workers [8]. Previous research has further demonstrated that proper hand hygiene in healthcare environments significantly lowers HAI incidence [9, 10]. However, adherence to hand hygiene protocols remains insufficient in many healthcare settings, which contributes to the continued transmission of HAIs and antimicrobial resistance [11].

Maternal and neonatal infections are among the leading causes of maternal and neonatal mortality [12]. In 2017, WHO estimated that approximately 810 women died every day from preventable causes related to pregnancy and childbirth, totaling an annual 295,000 maternal deaths worldwide and the majority (94%) of these deaths occurred in low- and middle-income countries, and most were preventable [13]. In 2022, neonatal mortality rates varied across countries, ranging from 0.7 to 39.4 deaths per 1,000 live births, with newborns in the highest-mortality countries facing a 60-fold higher risk of death before the 28th day of life compared to those in the lowest-mortality countries [14].
In Benin, maternal and neonatal mortality remain pressing challenges. Each year, the country still records thousands of maternal and neonatal deaths, reflecting a heavy burden on the health system [15]. The maternal mortality ratio is estimated at about 400 deaths per 100,000 live births [16], a level comparable to neighboring countries such as Niger and Nigeria, and even to some more developed francophone countries in the region [17]. Neonatal mortality, although showing a modest decline over the past two decades, remains

high, with rates decreasing from nearly 40‰ in 2000 to about 30‰ in 2020 [18]. Our retrospective study in six reference hospitals during 2022 analyzed 123 neonates suspected of infection, examining birth weight, breastfeeding practices, delivery parameters, and laboratory-confirmed infection rates. Results showed that 32% of suspected cases were confirmed infections, with higher prevalence among premature newborns and in certain hospitals, highlighting critical gaps in diagnostic capacity, infection prevention practices, and awareness among healthcare workers and mothers [19. These findings underscore the urgent need to improve hand hygiene compliance, strengthen infection control measures in maternity and neonatology units, and implement targeted training programs to reduce maternal and neonatal infections. The main objective of this study was to assess healthcare professionals' knowledge, practices, and adherence to hand hygiene guidelines in maternity and neonatology.

Methods

Study framework

We conducted a cross sectional study following the WHO Hand Hygiene Self-Assessment Framework (HHSAF) among health care professionals in healthcare settings in Benin between august and september 2023. The study was conducted in six healthcare facilities across Benin, including the National University Hospital Center Hubert K. MAGA (CNHU-HKM), the Lagune Mother and Child University Hospital Center (CHU-MEL), the Departmental Hospital Center (CHD) Zou-Collines, the Departmental University Hospital Center (CHUD) Borgou-Alibori, the Zone Hospital (HZ) Tanguieta, and the Departmental Hospital Center (CHD) Oueme-Plateau (Fig. 1). These hospitals were selected for their high patient volumes and their role as reference centers for the 12 departments of Benin, covering regions across southern, central, and northern parts of the country. They conduct comprehensive bacteriological testing, including antibiotic susceptibility testing, and are equipped to carry out routine surveillance of healthcare-associated practices, such as hand hygiene.

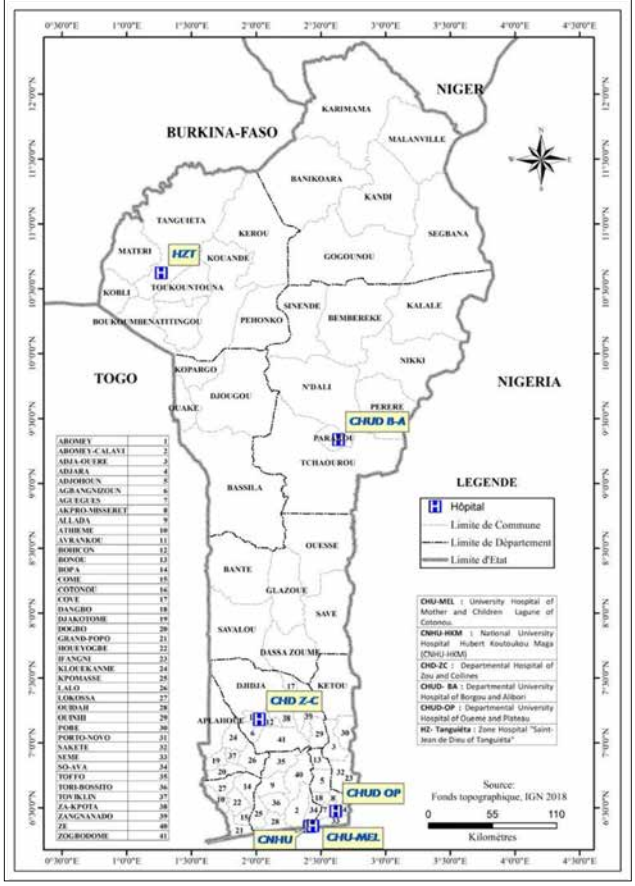
The map was designed with ArcGIS pro software version 10.8. https://enterprise.arcgis.com/fr/portal/10.8/use/what-s-new-in-portal-for-arcgis.htm.

Table S1 outlines key hospitals in Benin, categorizing them by location, healthcare level, bed capacity, and medical specialties. It highlights CNHU-HKM and CHU-MEL as national referral centers, while intermediary and peripheral hospitals serve regional healthcare needs, with some engaged in university research.

Data collection preparation and training process

The selection of data collectors (individuals with training in medical or paramedical fields) was based on their prior experience in data collection activities concerning the prevalence and determinants of neonatal

Fig. 1. Presentation of the study sites.



infections in Benin, which were part of a retrospective study conducted in the six hospitals. Kobo Collect was set up on tablets, and a training workshop, trained healthcare professionals and data collectors on study objectives, methodology, and digital questionnaire use, with participants also helping refine the instruments.

Sampling strategy

All healthcare professionals working in the Neonatal and Maternity Departments (including doctors, nurses, midwives, nursing assistants, and interns) who provided consent and were available during day and night shifts were included in the survey to assess their knowledge, attitudes, and hand hygiene practices. The questions were based on the WHO standard procedures. The collected data included demographic information (age and gender of participants), healthcare personnel qualifications, and their training on hygiene within the last three months. It also covered healthcare professionals' participation in hand hygiene promotion activities, their knowledge of cross-transmission, hand hygiene moments, efficacy of techniques, and best practices. Additionally, data were gathered on the use of hydroalcoholic products, hand hygiene frequency, constraints preventing compliance, reasons for non-compliance, and adherence rates to hand hygiene and glove-wearing practices by gender, department, and qualification. The data collection period

spanned from August to September, 2023. The interviews were conducted anonymously and the participants were not aware of any observation.

Hand hygiene compliance observation

Each hospital designated five Institutional IPC professionals, all previously trained and members of the IPC committee or team, resulting in a total of 30 professionals across the six hospitals. These individuals were observed during the five WHO moments for hand hygiene to assess compliance with hand hygiene protocols. Observers recorded whether the recommended timing was followed and the method of hand hygiene used (hydroalcoholic friction or handwashing). After data collection, the hand hygiene compliance rate was calculated.

Data processing and analysis

Upon completion of the data collection phase, data cleaning was performed to finalize the database, with a focus on forms validated by the quality control team. Hand hygiene knowledge was assessed using the WHO Hand Hygiene Self-Assessment Framework (HHSAF) and the Hand Hygiene Knowledge Questionnaire for Health-Care Workers, aligned with WHO-recommended strategies. The hand hygiene compliance rate (HHCR) was calculated using the following formula:

HHCR=(Number of observed hand hygiene actions performed/(Total number of hand hygiene opportunities))×100

Compliance rates were summarized as frequencies and percentages. Group comparisons by gender, department, and qualification were performed using Fisher's exact test. Odds ratios (ORs) with 95% confidence intervals were calculated to estimate the strength of associations. A significance level of $p < 0.05$ was applied. All analyses were conducted in Rstudio (R-3.0.1).

Results

Characteristics of healthcare professionals

The study on hand hygiene compliance and antimicrobial resistance in healthcare settings involved 159 participants across six healthcare centers. The majority were female (81.76%), with the highest age group representation being 20-35 years (45.28%), followed by 35-50 years (24.52%) and 50-65 years (14.46%) (Tab. S2).

Among the 159 professionals, male nurses were the most represented (42.76%), followed by midwives (36.47%), doctors (11.32%), and care assistants (15.72%), highlighting the key workforce involved in hand hygiene compliance (Tab. S3).

The study found that 65% of healthcare professionals received hygiene training within the last three months, while 35% did not. Training coverage varied across hospitals and departments, with neonatology units generally having higher participation rates (up to 91.67%) compared to maternity units, where some centers reported as low as 25% training coverage (Tab. I).

The study revealed that 52.20% of healthcare professionals did not participate in any hand hygiene promotion activities in the past year, while only 28.30% participated once. Participation rates decreased with frequency, with just 2.51% engaging in five or more activities (Tab. II).

Knowledge of healthcare personnel on hygiene

The study found that 57.23% of healthcare professionals had good knowledge of germ cross-transmission, while 42.79% had poor understanding. However, knowledge about microbial sources responsible for healthcare-associated infections (HAIs) was lower, with only 38.36% demonstrating good knowledge (Tab. III).

The study showed that healthcare professionals had strong knowledge of key moments for hand hygiene

Tab. I. Health care professional training on hygiene received within the last 3 months.

Centers	Number of participants	Taking training course within the last 3 months	
		YES	NO
CHU-MEL	Neonatology (n = 10)	80%	20%
	Maternity (n = 15)	53%	47%
CHUD-OP	Neonatology (n = 12)	91.67%	8.33%
	Maternity (n = 12)	58.33%	41.67%
CNHU-HKM	Neonatology (n = 15)	53.3%	46.7%
	Maternity (n = 14)	71.4%	28.6%
CHUD-BA	Neonatology (n = 5)	60%	40%
	Maternity (n = 28)	25%	75%
CHD-ZC	Neonatology (n = 2)	50%	50%
	Maternity (n = 16)	69%	31%
HZ-Tanguieta	Neonatology (n = 14)	86%	14%
	Maternity (n = 16)	81%	19%
Total	159	65%	35%

CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

Tab. II. Health care professional participation in hand hygiene promotion activities during the previous year.

	1	2	3	4	5 and more	None	Total
CHD Z/C	6	2	2	0	0	15	25
CHUD B/A	1	1	0	0	3	19	24
CHUD O/P	14	1	0	0	0	14	29
CHU-MEL	7	2	0	1	1	22	33
CNHU-HKM	9	1	0	0	0	8	18
HZ-Tanguieta	8	13	4	0	0	5	30
Total	45 (28.30%)	20 (12.57%)	6 (3.77%)	1 (0.63%)	4 (2.51%)	83 (52.20%)	159 (100%)

CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

Tab. III. Health care professionals' knowledge on the mode of cross-transmission of germs and the microbial source frequently responsible for HAIs.

Centers	Number of participants	Knowledge of transmission mode		Knowledge of the microbial sources responsible for HAIs	
		Good knowledge	Bad knowledge	Good knowledge	Bad knowledge
CHU-MEL	25	13	12	16	9
CHUD-OP	24	12	12	13	11
CNHU-HKM	29	17	12	10	19
CHUD-BA	33	21	12	4	29
CHD-ZC	18	6	12	3	15
HZ- Tanguieta	30	22	8	15	15
Total	159	91 (57.23%)	68 (42.79%)	61 (38.36%)	98 (61.64%)

CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

when interacting with patients, with 92.45% recognizing at least one critical moment. However, awareness varied across specific moments, with lower recognition rates for certain steps (*e.g.*, 54.08% for moment C). Among healthcare professionals themselves, knowledge was generally higher, with up to 85.53% identifying key moments, but gaps remained, particularly in less emphasized steps (Tab. IV). It was also noted that many professionals wore gloves before procedures, leading them to overlook this crucial moment of hand hygiene.

The study found that most healthcare professionals (89.93%) recognized that alcoholic hand rub is faster than washing with soap and water. However, most healthcare professionals (89.3%) recognized that hydroalcoholic friction causes greater skin dryness than hand washing. Overall, 79.87% demonstrated awareness of good hand hygiene practices (Tab. V).

Only CHU-MEL and CHUD-OP had more than 50% of staff aware of the minimum necessary duration of hydroalcoholic hand rub (Fig. 2).

Barriers to practicing hand hygiene

The study identified several reasons healthcare professionals cited for not performing hand hygiene, with the most common being "None" (62.89%). Other

Tab. IV. Health care professionals' knowledge on the moments of hand hygiene to prevent germs transmission between patient and caregiver.

Centers	Number of participants	Hand hygiene when interacting with patients				Health care professionals			
		A	B	C	D	A	B	C	D
CHU-MEL	25	22	24	21	23	25	22	19	23
CHUD-OP	24	23	14	8	15	21	22	12	18
CNHU–HKM	29	28	23	21	21	27	25	19	21
CHUD-BA	33	30	9	9	28	13	30	28	12
CHD-ZC	18	18	12	12	16	15	14	14	14
HZ-Tanguieta	30	26	20	15	19	24	23	11	19
Total	159	147 (92.45%)	102 (64.15%)	86 (54.08%)	122 (76.73%)	125 (78.61%)	136 (85.53%	103 (64.78%	107 (69.29%)

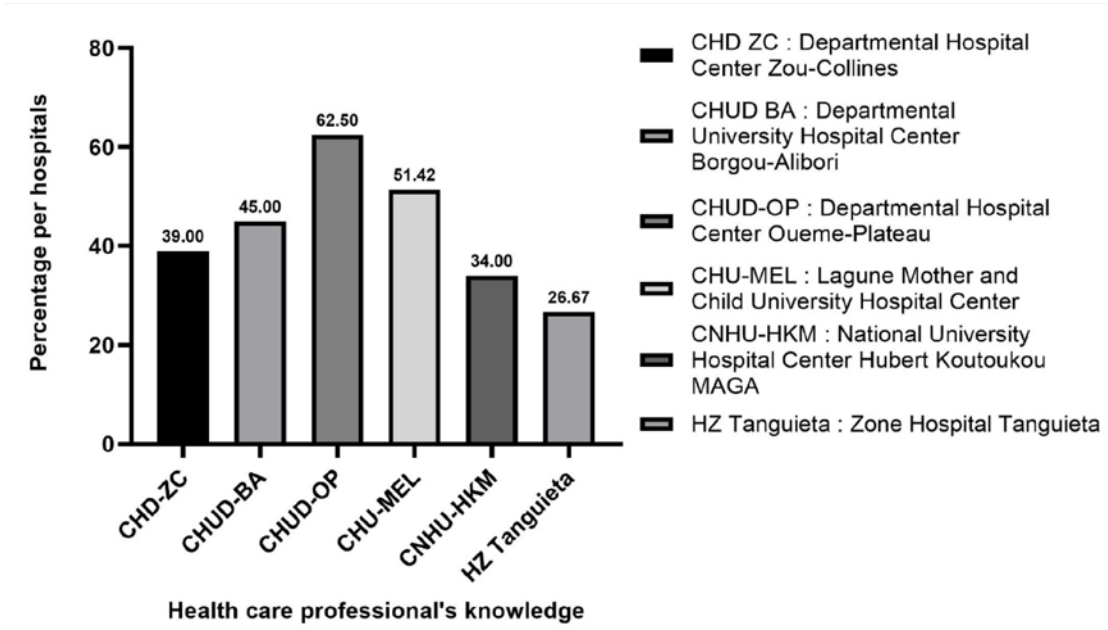
A: before contact with the patient; B: Immediately after a risk of exposure to a biological fluid; C: immediately before an aseptic procedure; D: after exposure to the patient's immediate environment; CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

Tab. V. Healthcare professionals' attitude on the efficacy of each hand hygiene technique and on good practices.

Center	Number of participants	Hand washing or hydroalcoholic friction			
		A	B	C	D
CHU-MEL	25	23	23	1	20
CHUD-OP	24	18	22	1	21
CNHU-HKM	29	27	27	3	23
CHUD-BA	33	33	32	8	26
CHD-ZC	18	17	15	1	15
HZ- Tanguieta	30	25	23	18	22
Total	159	143 (89.93%)	142 (89.3%)	32 (20.13%)	127 (79.87%)

A: alcoholic hand rub is faster than washing with soap and water; B: hydro-alcoholic friction causes greater skin dryness than hand washing; C: alcohol-based hand rub is more effective against germs than washing with soap and water; D: It is recommended to wash then use hydroalcoholic hand rubbing; CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

Fig. 2. Health care professionals' knowledge on the minimum duration necessary for hydroalcoholic hand rubbing.



reasons included lack of time (13.83%), work overload (11.94%), and limited facilities or equipment (4.40%). Fewer professionals mentioned issues like physical tiredness or lack of awareness (Fig. 3).

Hand hygiene compliance in hospitals

The study assessed healthcare workers' hand hygiene performance across six key areas. The results showed that 99.37% of healthcare workers (B) had the habit of washing their hands without supervision, while 98.74% (C) were comfortable reminding colleagues to wash their hands. However, only 44.02% (A) had undergone at least one assessment on compliance, and 64.77% (E) managed to wash their hands for the recommended 30 seconds. A notable 71.69% (D) followed the hand-washing technique as per WHO guidelines, while 88.05% (F) monitored the disinfection of surfaces and materials (Tab. VII).

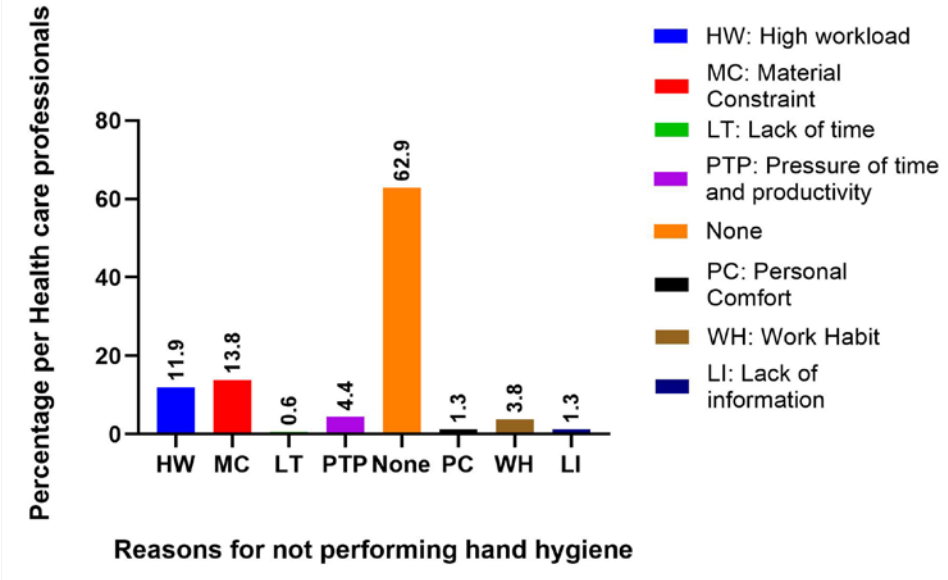
The data in the Figure 4 provides insights into healthcare workers' usual hand hygiene practices across various healthcare settings, showing that the most common practices are the use of hydroalcoholic solutions (UHS) at 57.86% and the use of gloves (UGF) at 23.27%, while only 1.25% follow ICLT (doing care as instructed) and 12.57% use CWE (going to another water point).

The Figure 5 shows the frequency of hand hygiene performance among healthcare workers, with 59.74% reporting that they "always" perform hand hygiene, 20.12% "often," and 17.61% "very often." Only 2.51% perform hand hygiene "sometimes," and no workers reported "never" performing it.

The Table VIII indicates that 74.21% of healthcare professionals across different departments use hydroalcoholic products (PHA) for hand hygiene, while 25.78% do not. Usage is generally high in neonatology and maternity units, though variability exists between healthcare centers, with CHUD-BA and HZ-Tanguieta showing lower adherence.

The Figure 6 shows that 45.28% of healthcare workers use hydroalcoholic gel "very often", 28.30% use it

Fig. 3. Health care professionals' probable reasons for not performing hand hygiene.



Tab. VI. Health care professionals' knowledge on situations to avoid for good hand hygiene practice.

Center	Number of participants	knowledge on matters to avoid for good hand hygiene practice			
		A	B	C	D
CHU-MEL	25	22	21	23	14
CHUD-OP	24	21	21	22	14
CNHU-HKM	29	25	26	29	9
CHUD-BA	33	31	30	33	25
CHD-ZC	18	17	15	18	11
HZ-Tanguieta	30	24	21	26	9
Total	159	140 (88.05%)	134 (84.27%)	151 (94.96%)	82 (51.57%)

A: wearing jewelry; B: presence of skin lesion; C: wearing artificial nails; D: regular use of a protective hand cream or lotion; CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

Tab. VII. Health workers hand hygiene performance.

	Number of Participants	A	B	C	D	E	F
CHU-MEL	25	15	25	24	21	16	19
CHUD-OP	24	7	24	24	19	13	23
CNHU–HKM	29	9	29	29	25	28	25
CHUD-BA	33	3	32	32	6	20	30
CHD-ZC	18	11	18	18	13	6	13
HZ-Tanguieta	30	25	30	30	30	20	30
Total	159	70 (44.02%)	158 (99.37%)	157 (98.74%)	114 (71.69%)	103 (64.77%)	140 (88.05%)

A: proportion of health workers having undergone at least one assessment on compliance with hand hygiene; B: proportion of health workers having the habit of washing their hands even in the absence of direct supervision or peer monitoring; C: proportion of health workers who find it comfortable to remind colleagues or other health professionals to wash their hands when necessary; D: proportion of health workers who follow the hand washing technique indicated by the WHO; E: proportion of health workers who manage to wash their hands for the recommended 30 seconds; F: proportion of health workers who have an eye on the disinfection of surfaces and materials; CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

"often", and 23.27% use it "sometimes", while only 3.14% never use it. This indicates that the majority of healthcare professionals integrate hydroalcoholic gel into their hand hygiene practices, though adherence levels vary across facilities.

The Table S4 indicates that the vast majority of healthcare workers (93.71%) use liquid soap for hand washing, while only 2.51% use bar soap and 3.77% use powdered soap. This suggests a strong preference for liquid soap across healthcare facilities.

Fig. 4. Health workers' usual ways to hand hygiene.

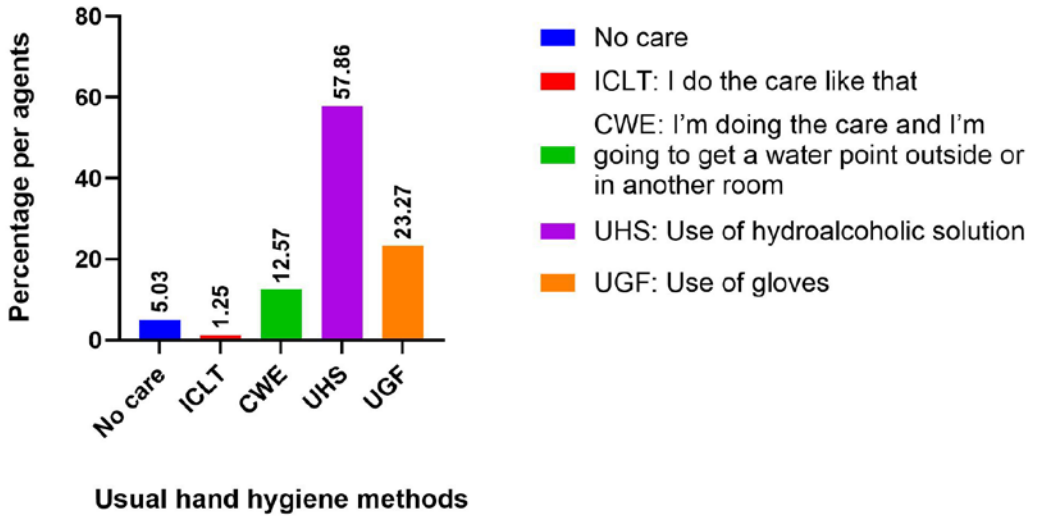


Fig. 5. Health workers' frequency of hand hygiene performance.

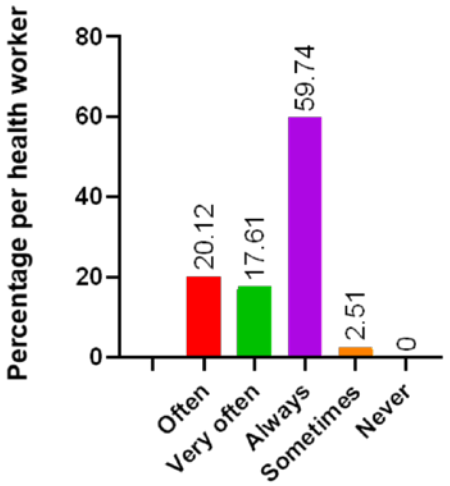


Fig. 6. Health workers' frequency of hydroalcoholic gel use.

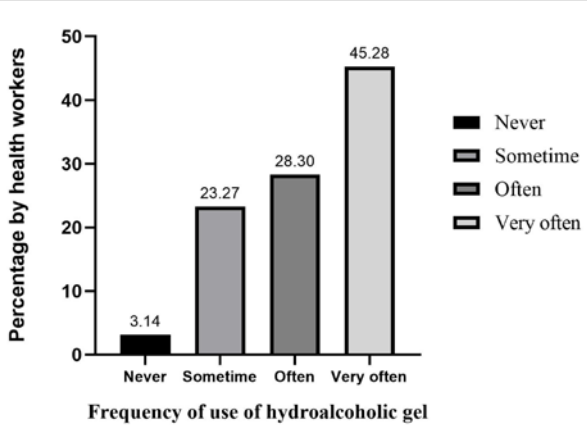


Figure 7 highlights gender-based compliance rates for hand hygiene and glove-wearing among healthcare professionals, showing that males have higher adherence in most categories, particularly in CR-AP (100%) and CR-HM (70%). Female professionals show lower overall compliance, except in CR-PG (45% vs. 40%). Notably, CR-APS compliance is very low for both genders (10% for females, 0% for males) (Fig. 7).

The Figure 8 shows that hand hygiene and glove-wearing compliance rates vary between neonatology and maternity departments, with neonatology workers having slightly higher adherence in most categories. CR-AP (hand hygiene before patient contact) is the highest in both departments (92.85% in neonatology and 81.25% in maternity), while CR-APS (post-exposure antisepsis) has the lowest compliance in both (7.14% and 6.25%, respectively).

Figure 9 highlights compliance rates for hand hygiene and glove-wearing based on healthcare workers' qualifications, showing that doctors generally have the highest adherence, particularly in CR-AP (100%) and CR-HM (85.71%). Nurses follow closely, with strong compliance in CR-AP (92.30%) but lower in other areas. Midwives show moderate adherence, while care assistants exhibit the lowest compliance overall. CR-APS (post-exposure antisepsis) remains the weakest point across all qualifications, with minimal adherence.

Across gender, department, and qualification, Fisher's exact tests showed no statistically significant differences in compliance with hand hygiene and glove wearing

Fig. 7. Health professionals' rate of hand hygiene and glove wearing compliance by gender.

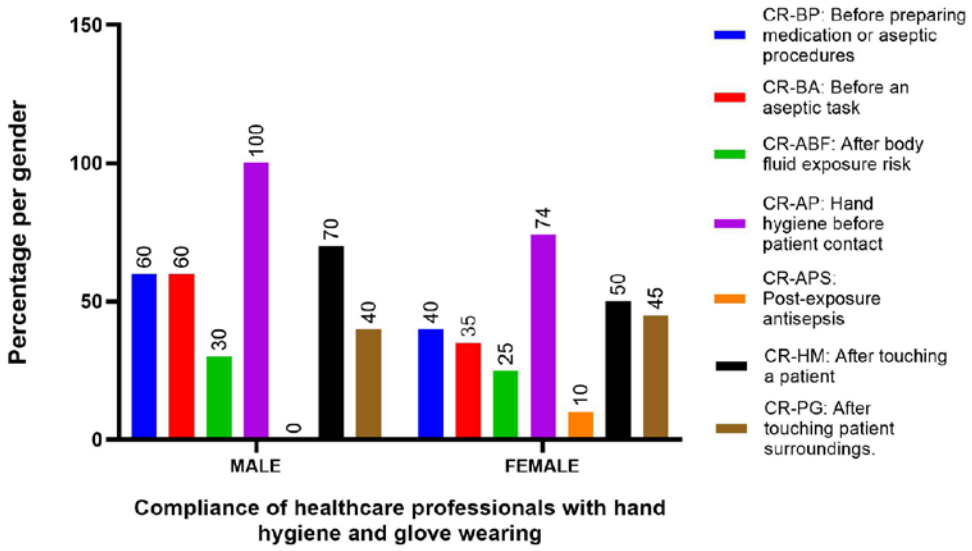
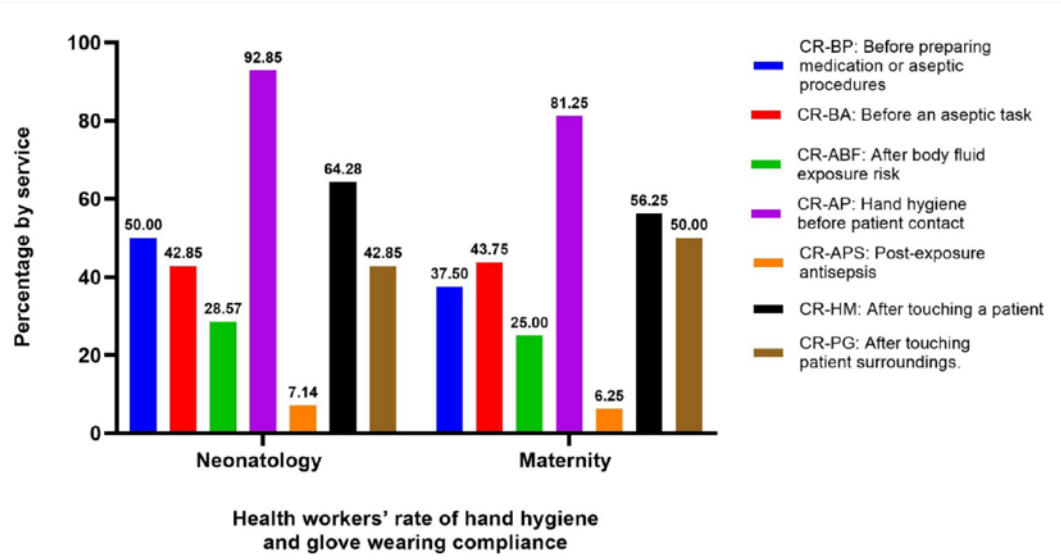


Fig. 8. Health workers' rate of hand hygiene and glove wearing compliance by department.



indicators (all $p > 0.05$). Odds ratios suggested some trends: male professionals had slightly higher odds of compliance for hand hygiene before patient contact (OR = 3.0, 95% CI: 0.52-17.2) and after touching a patient (OR = 1.4, 95% CI: 0.29-6.7), while female professionals showed marginally higher odds after patient surroundings contact (OR = 0.8, 95% CI: 0.18-3.5). Similarly, health workers in neonatology tended to report higher odds of compliance compared to those in maternity, particularly for hand hygiene before preparing medication (OR = 1.67, 95% CI: 0.39-7.1). Regarding qualification, no significant differences were observed across midwives, nurses, doctors, and assistants, although doctors often presented numerically higher compliance rates. Overall, the lack of statistical significance reflects the limited sample size, but the observed trends may suggest differences worth exploring in larger studies (Tab. IX).

Discussion

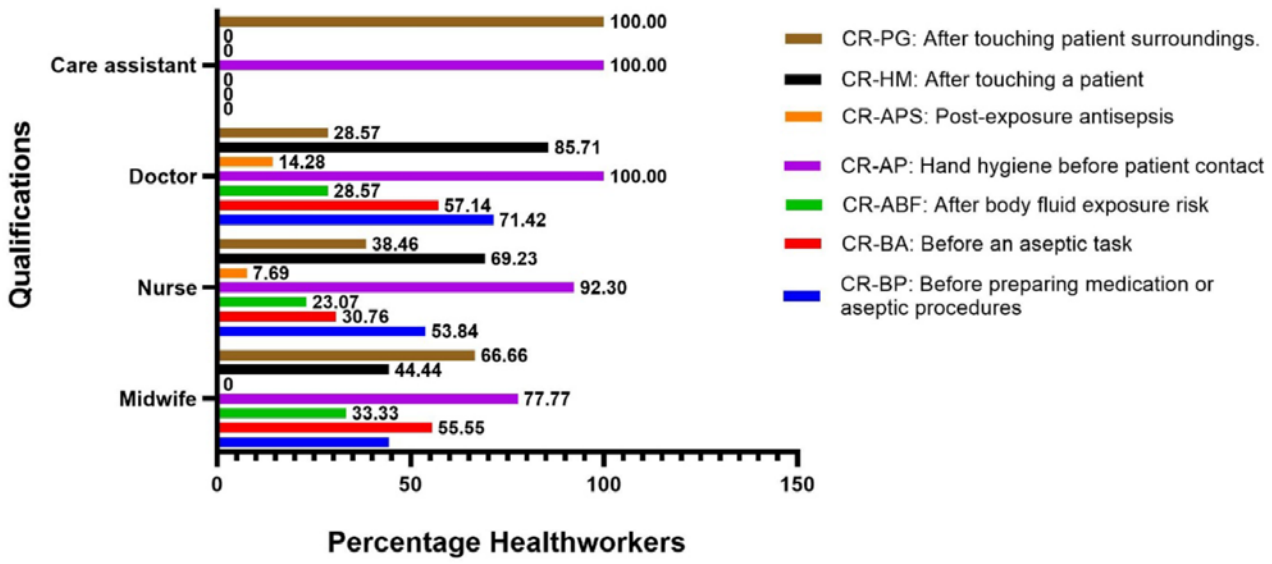
On 159 healthcare professionals participated in this study, women constituted the majority of the study population (80.36%), irrespective of the health center. This highlights the predominance of women in the healthcare sector, particularly in maternity and neonatology departments, a trend consistent with findings from similar studies [1, 2]. A critical observation concerns training in hand

Tab. VIII. Health care professionals use of hydroalcoholic product by department.

Centers	Number of participants	Use of PHA	
		YES	NO
CHU-MEL	Neonatology (n = 10)	9	1
	Maternity (n = 15)	14	1
CHUD-OP	Neonatology (n = 12)	11	1
	Maternity (n = 12)	10	2
CNHU-HKM	Neonatology (n = 15)	14	1
	Maternity (n = 14)	13	1
CHUD-BA	Neonatology (n = 5)	3	2
	Maternity (n = 28)	13	15
CHD-ZC	Neonatology (n = 2)	2	0
	Maternity (n = 16)	14	2
HZ-Tanguieta	Neonatology (n = 14)	6	8
	Maternity (n = 16)	9	7
Total	159 (100%)	118 (74.21%)	41 (25.78%)

CNHU-HKM: National University Hospital Center Hubert K. MAGA; CHU-MEL: the Lagune Mother and Child University Hospital Center; CHD: the Departmental Hospital Center Zou-Collines; CHUD: the Departmental University Hospital Center Borgou-Alibori; HZ: the Zone Hospital Tanguieta; CHD: and the Departmental Hospital Center Oueme-Plateau.

Fig. 9. Health workers' rate of hand hygiene and glove wearing compliance by department.



hygiene. A significant proportion (78%) of healthcare staff had received hospital hygiene training in the last three months, while 22% had not received any during this period. This suggests a substantial commitment to infection prevention, as also noted in previous studies [3, 4]. This could be attributed to limited promotional activities and the prioritization of participation by hospital authorities over healthcare staff.

Significant disparities were observed in the knowledge of healthcare-associated infections (HAIs) and germ transmission among the six hospitals. A study [5] demonstrated that under-trained staff significantly increase the risk of nosocomial infections, emphasizing the need for continuous education [6, 7]. This study reported that at least 80% of hospital staff must master infection prevention principles for effective HAI control [8]. The findings highlight the necessity of targeted training programs, regular awareness campaigns, and internal audits in underperforming hospitals to enhance infection control measures.

The study also identified gaps in knowledge of hand hygiene during aseptic procedures. Only 65.47% of staff knew the correct practice before an aseptic procedure, a critical moment for preventing infections. A study [8] stressed the importance of enhancing hand hygiene knowledge before critical procedures to minimize germ transmission. Encouragingly, 100% of staff recognized the need to wash hands after touching a patient, aligning

Tab. IX. Fisher's Exact Test p-values and odds ratios for compliance rates of hand hygiene and glove wearing, by gender, department, and qualification.

Compliance indicator	Gender *(p-value)*	Department *(p-value)*	Qualification *(p-value)*
CR-BP	*p-value:* 0.71	*p-value:* 0.71	*p-value:* 0.55
	OR (95% CI): 1.50 (0.33-6.80)	OR (95% CI): 1.67 (0.39-7.10)	OR (95% CI): -
CR-BA	*p-value:* 1.00	*p-value:* 1.00	*p-value:* 0.55
	OR (95% CI): 1.00 (0.21-4.64)	OR (95% CI): 0.96 (0.23-4.00)	OR (95% CI): -
CR-ABF	*p-value:* 0.66	*p-value:* 1.00	*p-value:* 1.00
	OR (95% CI): 1.33 (0.25-7.08)	OR (95% CI): 1.20 (0.22-6.40)	OR (95% CI): -
CR-AP	*p-value:* 0.27	*p-value:* 0.60	*p-value:* 0.55
	OR (95% CI): 3.00 (0.52-17.2)	OR (95% CI): 2.11 (0.40-11.1)	OR (95% CI): -
CR-APS	*p-value:* 0.50	*p-value:* 1.00	*p-value:* 0.78
	OR (95% CI): -	OR (95% CI): 1.14 (0.07-18.3)	OR (95% CI): -
CR-HM	*p-value:* 0.66	*p-value:* 1.00	*p-value:* 0.55
	OR (95% CI): 1.40 (0.29-6.74)	OR (95% CI): 1.38 (0.29-6.58)	OR (95% CI): -
CR-PG	*p-value:* 0.71	*p-value:* 0.71	p-value: 0.33
	OR (95% CI): 0.80 (0.18-3.52)	OR (95% CI): 0.75 (0.17-3.29)	OR (95% CI): -

($p > 0.05$): no statistically significant differences in compliance.
OR > 1: the first group (Male, Neonatology) has higher odds of compliance.
OR < 1: the first group (Male, Neonatology) has lower odds of compliance.
OR ≈ 1: no difference.
CR-BP: Before preparing medication or aseptic procedures; **CR-BA:** Before an aseptic task; **CR-ABF:** After body fluid exposure risk; **CR-AP:** Hand hygiene before patient contact; **CR-APS:** Post-exposure antisepsis; **CR-HM:** After touching a patient; **CR-PG:** After touching patient surroundings.

with WHO guidelines [9]. However, misconceptions about the effectiveness of alcohol-based hand rubs (ABHR) persist, with some believing them to be less effective than conventional hand-washing, contrary to findings by a study [5], which demonstrated their superior efficacy in hospital settings.

Furthermore, only two hospitals had over 50% compliance with the recommended ABHR application time (20-30 seconds), as per WHO standards [9]. Ignorance of this requirement could contribute to persistent HAIs. Additionally, less than 50% of staff regularly used protective hand creams, which help prevent skin irritation and encourage adherence to hygiene protocols, as highlighted by certain authors [10]. These findings reinforce the need for ongoing staff training, awareness campaigns, and regular compliance audits. Differences in adherence to hand hygiene highlight the role of material resources, institutional policies, and workload in influencing hygiene practices. One study noted that in low-income settings, inadequate access to health infrastructure and training hinders hand hygiene implementation despite adequate theoretical knowledge [7].

A study found that high workloads in poorly structured environments often lead to hygiene lapses, increasing HAI risks [8]. The high workload reported by 43.35% of staff at HZ Tanguieta underscores the need for better human resource management to ensure compliance with hygiene practices. Addressing these issues requires harmonized working conditions and improved resource management in healthcare institutions. The reported absence of constraints at CHD Zou-Collines suggests adequate institutional support, while constraints at CHD Ouémé-Plateau and HZ Tanguieta call for further investigation into underlying factors. Implementing a multimodal strategy based on WHO recommendations can significantly improve adherence to hand hygiene [11, 20].

The study found that over 50% of healthcare workers followed proper hand hygiene practices, an encouraging figure. However, only 48.65% had undergone compliance assessments, highlighting the need for improved monitoring and evaluation systems to enhance patient safety. A preference for alcohol-based hand sanitizers was observed in some hospitals, in line with WHO recommendations favoring ABHR for its efficacy and ease of use [9].

Hospitals with high ABHR use showed lower glove consumption, potentially indicating over-reliance on ABHR at the expense of gloves, which are essential for certain medical procedures. Additionally, hand hygiene was better adhered to in Neonatology than in Maternity, despite higher glove use in the latter. These findings suggest the need for department-specific adaptations in hygiene protocols. Strategies such as using emoticons as reminders and implementing motivation-boosting initiatives have been suggested to enhance healthcare workers' compliance [12, 13].

The relatively small sample size (159 participants) may not fully capture variations in hand hygiene practices across all healthcare facilities in Benin. Additionally, self-reported data on hand hygiene compliance may be subject to social desirability bias, leading to potential overestimation of adherence rates. The study also lacks an assessment of environmental and institutional factors, such as hospital infrastructure and availability of hygiene resources, which could influence compliance. Furthermore, the limited inclusion of care assistants in the study reduces the generalizability of findings across all healthcare worker categories.

Conclusion

The study highlights significant gaps in healthcare workers' knowledge, attitudes, and practices regarding hand hygiene in Benin's referral hospitals. While awareness and training exist, disparities in adherence and knowledge levels persist, reflecting systemic weaknesses in the healthcare system. Addressing these issues requires a systemic and transversal approach, with clear responsibilities assigned to healthcare institutions and policymakers. Future efforts should integrate hand hygiene into national policies, ensure sustained training and infrastructure, and strengthen monitoring and accountability to reduce HAIs and improve patient safety in Benin.

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Ethical approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study received ethical approval from the Research Ethics Committee of the Institute of Applied Biomedical Sciences in Cotonou on 22/12/2022 (Approval No. 155). Prior to data collection, informed written consent was obtained from all participants after clearly explaining the objectives of the study. As all participants were adults, representative consent was not required. No minors were involved in the study. The consent process was conducted in accordance with the approved ethical guidelines, and no waiver of consent was requested or granted by the ethics committee.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

AK, BL, KF, KS, HK, AY, LBM, VD: contributed to the conception and design of the study, to drafting the article and/or revising it critically for important intellectual content. All authors gave final approval of the version to be submitted. AK, BL, KF, KS, HK: contributed to the acquisition and analysis of data.

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Supplementary Material

Tab. S1. Main characteristics of the six hospitals.

Hospital name	Location	Urban/rural	Level	Number of beds	Specialities	University/ research
CNHU-HKM (National University Hospital Center Hubert K. MAGA)	Cotonou	Urban	Central/National	679	Medicine, Pediatrics, Surgery, Gynecology-Obstetrics, Radiology, Laboratory, Otorhinolaryngology, Ophthalmology, Cardiology, Dermatology, Urology, Blood Bank, Psychiatry, Other specialties.	Yes
CHU-MEL (Lagune Mother and Child University Hospital Center)	Cotonou	Urban	Central/National	258	Medicine, Pediatrics, Surgery, Gynecology-Obstetrics, Radiology, Laboratory, Otorhinolaryngology, Ophthalmology, Cardiology, Dermatology, Urology, Blood Bank, Psychiatry, Other specialties.	Yes
CHD Ouémé-Plateau (Departmental Hospital Center Ouémé-Plateau)	Porto-Novo	Urban	Intermediary/Departmental	327	Medicine, Pediatrics, Surgery, Gynecology-Obstetrics, Otorhinolaryngology, Ophthalmology, Radiology, Laboratory, Other specialties, Blood Bank	No
CHD Zou-Collines (Departmental Hospital Center Zou-Collines)	Abomey	Rural	Intermediary/Departmental	512	Medicine, Pediatrics, Surgery, Gynecology-Obstetrics, Otorhinolaryngology, Ophthalmology, Radiology, Laboratory, Other specialties, Blood Bank	No
CHUD B/A (Departmental University Hospital Center Borgou-Alibori)	Parakou	Rural	Intermediary/Departmental	272	Medicine, Pediatrics, Surgery, Gynecology-Obstetrics, Otorhinolaryngology, Ophthalmology, Radiology, Laboratory, Other specialties, Blood Bank	Yes
HZ Tanguieta (Zone Hospital of Tanguieta)	Atacora region	Rural	Peripheral	424	General Medicine, Emergency Surgery, Gynecology-Obstetrics, Curative Care, Childbirth, Radiology, Laboratory, Vaccination, Pharmacy	No

Tab. S2. Age and gender of the study participants.

Centers	Number of participants	Gender		Age		
		F	M	[20-35]	[35-50]	[50-65]
CHU-MEL	25	21	4	14	7	4
CHUD-OP	24	22	2	9	10	5
CNHU-HKM	29	26	3	10	15	4
CHUD-BA	33	29	4	9	21	3
CHD-ZC	18	10	8	7	7	4
HZ-Tanguieta	30	22	8	23	4	3
Total	159	81.76% (130)	18.23% (29)	45.28% (72)	24.52% (64)	14.46% (23)

Tab. S3. Distribution of Caregivers by category involved in hand hygiene compliance.

Hospital	Services	Caregivers				Total
		Male nurse	Midwife	Doctor	Care assistant	
CHU-MEL	Neonatology	8	0	2	0	10
	Maternity	3	22	0	0	15
CHUD-OP	Neonatology	11	0	1	0	12
	Maternity	3	8	1	0	12
CNHU-HKM	Neonatology	11	0	2	2	15
	Maternity	1	11	2	0	14
CHUD-BA	Neonatology	2	0	2	1	5
	Maternity	9	9	2	8	28
CHD-ZC	Neonatology	2	0	0	0	2
	Maternity	7	4	3	2	16
HZ-Tanguieta	Neonatology	6	0	1	7	14
	Maternity	5	4	2	5	16
Total		68 (42.76%)	58 (36.47%)	18 (11.32%)	25 (15.72%)	159

Tab. S4. Type of soap used by health workers for hand washing.

	Liquid soap	Bar soap	Powdered soap	Total
CHD Z/C	19	0	6	25
CHUD B/A	24	0	0	24
CHUD O/P	26	3	0	29
CHU-MEL	33	0	0	33
CNHU-HKM	17	1	0	18
HZ-Tanguieta	30	0	0	30
Total	149 (93.71%)	4 (2.51%)	6 (3.77%)	159 (100%)

HOSPITAL HYGIENE

Persistence of Biofilm-Forming and Multidrug-Resistant *Staphylococcus aureus* on High-Touch Hospital Surfaces Despite Routine Cleaning and Disinfection

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Keywords

Hospital surface contamination • *Staphylococcus aureus* • Antimicrobial resistance • Biofilm

Summary

Background. *Contaminated hospital surfaces play a key role in the transmission of healthcare-associated infections (HAIs), particularly those caused by antimicrobial-resistant pathogens. Despite routine cleaning and disinfection, high-touch surfaces may remain reservoirs for multidrug-resistant organisms, including biofilm-forming Staphylococcus aureus.*
Methods. *An environmental surveillance study was conducted in a single-bed room of an Internal Medicine ward in a hospital in Northern Italy. High-touch surfaces in the near-patient area and room furniture were sampled twice daily over one week, before and after routine cleaning/disinfection with chlorine-based agents (0.1-0.5% Cl). Cleaning effectiveness was evaluated using aerobic colony count (ACC) and detection of S. aureus as indicators of environmental hygiene, applying accepted microbiological benchmarks (ACC < 5 CFU/cm²; S. aureus < 1 CFU/cm²). S. aureus isolates were characterized by PFGE, spa typing, antimicrobial susceptibility testing, and biofilm production assays.*
Results. *Mean ACC decreased significantly after cleaning/disinfection (10.06 ± 15.67 vs 2.89 ± 5.52 CFU/cm²; p < 0.001), with a substantial reduction in non-compliant samples. However, residual contamination persisted on high-touch surfaces. S. aureus was detected in 12/238 samples, including post-cleaning samples from the near-patient area. Molecular analysis identified four distinct strains; notably, a spa type t032 (MLST ST22) isolate−methicillin-resistant, multidrug-resistant, and a strong biofilm producer−persisted on the bedside table handle both before and after cleaning.*
Conclusion. *Routine cleaning and disinfection significantly reduce environmental bioburden but may not reliably eliminate biofilm-forming multidrug-resistant S. aureus from critical hand-contact surfaces. These findings highlight the need for continuous microbiological surveillance and targeted IPC interventions to address environmental reservoirs of antimicrobial resistance in healthcare settings.*

Introduction

Healthcare-associated infections (HAIs) represent one of the major challenges in healthcare settings.
In the most recent report on hospital-acquired healthcare-associated infections (HAIs), referring to the period 2022-2023, the European Centre for Disease Prevention and Control (ECDC) estimated that approximately 4.3 million cases of HAIs occurred across the European Union and European Economic Area (EU/EEA), corresponding to a prevalence rate of 7.1% [1].
These infections cause significant patient morbidity and can prolong hospital stays, leading to substantial additional costs beyond those associated with the patient's primary condition [2, 3].
Furthermore, bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae*, and *Clostridioides difficile* are increasingly resistant to antibiotics, making infection prevention even more crucial today [4-6].

The hospital environment has been shown to serve as a reservoir for microorganisms responsible for infections [7-10]. It is also well-documented how easily pathogens can be transferred from colonized and/or infected patients to surfaces within the patient's room and from these surfaces to the hands of healthcare workers [11]. Nosocomial pathogens can persist on surfaces in hospital environments – such as patient rooms – for days, months, or even years, increasing the risk of transmission to susceptible individuals [12]. MRSA strains have been detected on 1-27% of sampled surfaces in patient rooms, with this figure rising to 64% in burn units and in the presence of MRSA-positive patients.
MRSA strains can remain viable for over 14 days on furniture surfaces and over 6-9 weeks on cotton fabrics. Additionally, it has been shown that pathogens, including some *S. aureus* strains, are able to form biofilms on surfaces. This enables them to proliferate, exchange antibiotic resistance genes with other bacteria, and persist for extended periods within the protective biofilm matrix.

In addition to hand hygiene, surface cleaning/disinfection are critical to reducing the transmission of pathogenic microorganisms and the risk of nosocomial infections [13, 14].

CDC guidelines for routine and terminal cleaning of hospital rooms emphasize the importance of disinfecting so-called "high-touch surfaces", those more likely to harbor and transmit microbial pathogens [15]. While conventional hospital environments such as restrooms, shared surfaces, and sinks are subject to frequent cleaning, high-touch surfaces are often inadequately cleaned despite their well-recognized role in cross-contamination [16-20]. The CDC recommends disinfecting high-touch surfaces in patient rooms at least once a day, while the cleaning of low-touch surfaces should follow hospital schedules and depend on the visibility of dirt [15]. Available studies suggest that daily disinfection of high-touch surfaces with detergents and/or disinfectants significantly reduces environmental contamination and the incidence of healthcare-associated infections [21]. This risk-based approach is essential to determine the frequency and method of cleaning across all patient care areas, thereby reducing the risk of infection transmission [22, 23].

Today, there are alternatives to traditional microbiology, such as ATP bioluminescence testing, which, although not a substitute for microbiological culture methods, is a useful tool for assessing cleaning effectiveness [24].

With regard to microbiological techniques for evaluating cleaning/disinfection efficacy, the scientific literature has proposed two complementary indicators: "the identification of an indicator organism of potential high-risk to patients in any amount, and second, the quantitative assessment of organisms found within a specified area, regardless of identity" [25]. So, in this study, *S. aureus* (<1 CFU/cm²) was selected as a marker of potential high risk to patients and second, the quantitative assessment of microbial load on hand-contact sites, regardless of the identity of the isolates, using the aerobic colony count (ACC). In this case, ACC <5 CFU/cm² is considered acceptable, whereas the finding of ≥5 CFU/cm² may indicate an increased risk of infection in that environment [25, 26].

As part of a surveillance activity assessing the implementation of Infection Prevention and Control (IPC) measures in a hospital in Northern Italy, a study was conducted to evaluate the effectiveness of cleaning/disinfection procedures targeting high-touch surfaces in an internal medicine ward. The evaluation was based on both the ACC and the detection of *S. aureus*.

A further objective, in case of *S. aureus* detection, was to assess the presence of clinically and epidemiologically relevant strains and to characterize them through biomolecular analyses.

Methods

Setting

The study was conducted in a single-bed inpatient room in the Internal Medicine department of a hospital in Northern Italy. During the study period, the room consecutively hosted alert, oriented, and ambulatory patients.

Sampling was carried out in a single-bed inpatient room; the patients were not found to be colonized by *S. aureus* in order to avoid confounding variables in the assessment of surface colonization.

During the sampling period, both healthcare personnel and cleaning staff were informed of the assessment being conducted.

Environmental disinfection

In the examined facility, after cleaning, daily environmental disinfection was performed on all room surfaces using chlorine-based disinfectants (0.1-0.5% Cl) and color-coded microfiber cloths, according to contamination levels and surface type.

Outsourced personnel were responsible for performing cleaning and disinfection activities. Daily disinfection was performed twice a day. Extraordinary cleaning was carried out immediately in the event of accidental contamination with biological fluids or other hazardous materials. Terminal cleaning was performed upon patient discharge or transfer. Each cloth was replaced after the disinfection of each patient unit and was not reused across different patient units.

The disinfectant was left on the surface for the recommended contact time of 5 minutes before drying or reuse.

Surface Sampling and Microbiological Analysis

High-touch surfaces were identified within the patient area, including furniture in the room, selected from those listed in the CDC checklist [27].

For the patient area, surfaces sampled in the vicinity of the patient included the bedside table, call button, headboard, footboard, and bed rails. Furniture surfaces sampled in the room included the table and chair. The surface of the bedside table was covered with non-porous plastic material, while the various components of the bed (footboard, headboard, and side rails) were made of metal and partially covered with non-porous plastic material, the same applied to the furniture. All surfaces were undamaged.

Sampling was performed twice a day, before and after sanitization, over the course of one week.

Where surface type permitted, a 10×10 cm area was sampled using a delimiting template; for irregular surfaces, the available area was sampled, preferably approximating 100 cm², and the sampled dimensions were recorded accordingly. Microbial concentration was expressed as CFU/cm².

Sampling was performed using swabs with internal shafts, rayon tips, and 10 mL of isotonic saline solution containing neutralizing agents to inactivate disinfectants and sanitizing agents.

Microbiological Analysis

Samples were immediately transported to the laboratory and processed to determine the ACC at 37°C and the

presence of *S. aureus* as an indicator of human-derived contamination.
Prior to inoculation, swabs were vortexed for approximately 1 minute to facilitate the detachment of microorganisms from the swab surface.

Determination of ACC at 37°C

To determine the aerobic colony count at 37°C, 1 mL of the solution contained in the swab vial was inoculated onto Nutrient Agar plates (ISO 6579, Liofilchem, Italy). The inoculum was spread over the plate using a sterile L-shaped rod to allow uniform distribution and facilitate colony counting after incubation.
Plates were incubated at 37°C for 48 hours. The final concentration in CFU/cm² was calculated considering both the inoculated volume and the sampled surface area.

Determination of *Staphylococcus aureus*

To detect *S. aureus*, duplicate 1 mL aliquots of the swab solution were plated onto blood agar and incubated at 37°C for 48 hours.
Suspected colonies grown on blood agar were subcultured onto selective Mannitol Salt Agar and subsequently identified using MALDI-TOF (Biomerieux, Marcy-l'Étoile, France).
The final concentration in CFU/cm² was calculated by considering the inoculated volume and the sampled surface area.
Two standard microbiological thresholds were used to assess cleaning effectiveness, as proposed by Dancer: <5 CFU/cm² regardless of species, and < 1 CFU/cm² for *S. aureus* [26].

Molecular Analysis via PFGE – *Staphylococcus aureus*

PFGE analysis of *S. aureus* was performed following the protocol described in "Pulsed-Field Gel Electrophoresis of *Staphylococcus aureus*" by Golding et al. [28].
Images were captured using a Gel Doc XR and analyzed using Image Lab Software and GelJ 2.2 software.

Molecular Analysis via spa Typing – *Staphylococcus aureus*

The procedure involved the preparation of pure *S. aureus* cultures on TSA (Trypticase Soy Agar II with 5% sheep blood), incubated for 16-18 h at 37°C.
Bacterial DNA was extracted by lysing cells with lysostaphin using the QIAGEN QIAamp DNA Mini Kit. DNA amplification was performed following the protocol described by Shopsin et al [29] and by Harmsen et al [30].
After purification of the amplified using the High Pure Product Purification Kit (ROCHE), the next step involved sequencing (Sanger – GATC Eurofins Genomics).
The analysis of the DNA sequence electropherograms, conducted using the FincTV Software, and the comparison with sequence repeats available in the RIDOM Spa server database (http://spaserver.ridom.de/) allowed the identification of the SPA Typing corresponding to each profile previously determined by PFGE technique.
Using the RIDOM Spa server database, it was also possible to assign a correspondence between the identified SPA Typing profiles and an MLST profile.

Evaluation of antibiotic resistance of *Staphylococcus aureus*

The identified colonies were tested for antibiotic resistance using the VITEK 2 Compact system (Biomerieux), with a library updated according to the most recent EUCAST breakpoint criteria.

Evaluation of biofilm formation

S. aureus isolates (PFGE profiles A, B, C, D) were cultured using a protocol designed to induce biofilm production in biofilm-forming strains, following the method described by Cramton [31].
Briefly, the isolates were first grown on blood agar plates for 24 hours. Subsequently, 1-2 colonies from each strain were inoculated into 2 mL of Tryptic Soy Broth (TSB) and incubated overnight at 37°C.
After incubation, the bacterial suspension was adjusted to a 1.0 McFarland standard, and after diluted 1:100 in TSB supplemented with 0.5% glucose.
The diluted bacterial suspension was then inoculated into sterile 96-well microtiter plates and incubated at 37°C for 24 hours, together with the negative control, in this case the control wells contained sterile broth.
Following incubation, the contents of each well were removed, and the plates were washed with Phosphate-Buffered Saline (PBS, pH 7.3). The wells were stained with 1% crystal violet, rinsed with water, air-dried, and the stained biofilm was then solubilized with 20% ethanol to detect the biofilm adhered to the bottom of the wells.
Each experiment was performed in independent replicates for each isolate to ensure the reliability and representativeness of the experimental data.
Biofilm density was classified according to the scheme of Stepanovic et al [32]. The cut-off value (ODc) for each microtiter plate was defined as three standard deviations above the mean OD of the negative control. Isolates were then classified into four categories based on ODc and average OD of the strain: strong biofilm producer (4ODc ≤OD); moderate biofilm producer (2ODc ≤OD ≤4ODc); weak biofilm producer (ODc ≤OD ≤2ODc); and non-biofilm producer (OD ≤ODc). For the biofilm formation assay, four wells per strain were used, and each test was repeated three times.
Biofilm growth was evaluated by measuring the optical density (OD) at 570 nm (EPOH, EPOCH Agilent BioTek, Santa Clara CA, USA)

Statistical analysis

Statistical analysis was carried out using STATA SE 19™ (StataCorp, College Station, TX, USA). Results were analysed in terms of descriptive statistics, expressed as means ± standard deviations for continuous variables, and as frequencies (percentages) for categorical variables.
To evaluate the effect of the intervention on contamination

rates, a 2×2 contingency table was constructed, and Fisher's exact test was used due to the small sample size, while comparisons between pre- and post-intervention groups were performed using the Wilcoxon signed-rank test for paired samples. A p-value < 0.05 was considered statistically significant.

Results

Aerobic colony count (ACC)

The mean values of ACC detected on all sampled surfaces before (phase 1) and after the cleaning/disinfection procedure (phase 2) were 10.06 ± 15.67 CFU/cm² and 2.89 ± 5.52 CFU/cm², respectively, showing a statistically significant reduction ($p < 0.001$).
An analysis of the ACC was then carried out based on the different areas in the two phases (1 and 2).
It was found that the ACC in the near patient area and furniture decreased from 10.41 ± 13.53 CFU/cm² and 10.86 ± 21.04 CFU/cm² (phase 1) to 2.88 ± 6.50 CFU/cm² and 1.96 ± 4.22 CFU/cm² (phase 2), respectively.
The difference in the mean ACC values across areas (near patient, furniture) between phases 1 and 2 was always statistically significant ($p < 0.001$).
However, considering the wide range of ACC values observed for each area, the percentage of non-compliant samples results (≥ 5 CFU/cm²) before and after cleaning/disinfection was also evaluated.
The results showed how the cleaning/disinfection procedure reduced the percentage of non-compliant results samples (CFU ≥ 5 CFU/cm²), dropping from 51.65% to 12.09%, 39.29% to 3.57%, for the near patient area and furniture respectively.
The reduction in non-compliance results was statistically significant both for all sampled surfaces and when grouped by area ($p < 0.01$).
Nevertheless, results showed that cleaning/disinfection never completely eliminated non-compliance results.

Staphylococcus aureus

A total of 12/238 samples tested positive for *S. aureus* (>1 CFU/cm²), of which 9 were detected in phase 1 (corresponding to 7.56% of the samples) and 3 in phase 2 (corresponding to 2.52% of the samples).
Cleaning/disinfection eliminated the microorganism from all surfaces except those in the patient area.

Biomolecular Analysis Results of *Staphylococcus aureus* Strains

A. Molecular Typing by PFGE

PFGE analysis identified a total of four different banding patterns. Figure 1 shows the PFGE similarity analysis for the samples examined.
Based on the profiles highlighted by the PFGE analysis, the samples were classified as follows:

- Samples 1, 2, 3, 5, 6, 7 and sample 11 were assigned to profile A;
- Samples 8, 9, and 10 were assigned to profile B;
- Sample 4 was assigned to profile C;
- Sample 12 was assigned to profile D.

B. Molecular genotyping by SPA typing

For the four *S. aureus* profiles (A, B, C, and D) identified by PFGE, a further molecular genotyping analysis was performed using the SPA typing technique [29, 30].
The analysis of the DNA sequence electropherograms, conducted using FinchTV Software and comparison with the repeat sequences available in the RIDOM Spa server database (http://spaserver.ridom.de/), allowed determination of the SPA type for each profile previously identified by PFGE.
Using the RIDOM Spa server database, it was also possible to assign three of the identified SPA typing profiles to corresponding MLST profiles.
Table I reports, for each PFGE profile, the corresponding ST profile (Spa Typing with the DNA repeat code sequence) and, when available, the corresponding MLST profile.

Antibiotic Resistance Assessment

Table II reports the antibiograms of the *S. aureus* isolates,

Fig. 1. PFGE similarity analysis for the samples analyzed.

Tab. I. PFGE profile, ST profile (Spa Typing with DNA repeat code sequence), and MLST profile (when available) of Staphylococcus aureus isolates.

PFGE Profile	SPA Typing Repeat Sequence	SPA-Typing ST	MLST
A	26-23-17-34-17-20-17-12-17-16	t002	ST5; ST231
B	26-23-23-13-23-31-29-17-31-29-17-25-17-25-16-28	t032	ST22
C	04-20-12-17-17	t1312	-
D	26-23-17-34-17-20-17-12-17-16	t002	ST5; ST231

Tab. II. Evaluation of the antibiotic susceptibility profile of *Staphylococcus aureus* strains.

Antibiotics	A	b	c	D
Linezolid	S	S	S	S
Daptomycin	S	S	S	S
Teicoplanin	S	S	S	S
Vancomycin	S	S	S	S
Levofloxacin	I	**R**	I	I
Polymyxin	S	S	S	S
Tetracycline	S	S	S	S
Tigecycline	S	S	S	S
Gentamicin	S	S	S	S
Fusidic acid	S	S	S	S
Rifampicin	S	S	S	S
Trimethoprim / sulfamethoxazole	S	S	S	S
Erythromycin	S	**R**	S	S
Clindamycin	S	**R**	**R**	S
Cefoxitin	S	**R**	S	S
Benzylpenicillin	**R**	**R**	R	S
Oxacillin	S	**R**	S	S
Methicillin	S	**R**	S	S

S: Sensitive; I: Intermediate; R: Resistant.

indicating the susceptibility levels (sensitive, resistant, or intermediate) to the different antibiotics tested.

The analyses showed that strain D is sensitive to all tested antibiotics and intermediate to Levofloxacin; strain A is resistant to Benzylpenicillin and intermediate to Levofloxacin; strain C exhibits resistance to Benzylpenicillin and Clindamycin and is intermediate to Levofloxacin.

Strain B, on the other hand, shows resistance to seven antibiotics, including methicillin.

Biofilm production

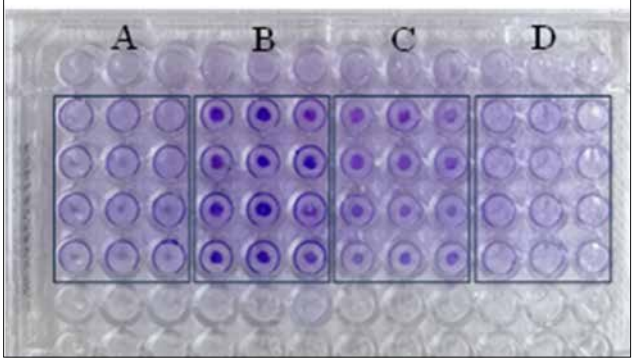
Biofilm growth assays revealed different mean absorbance values for each isolate, indicative of varying biofilm-forming capacities (Fig. 2).

Based on the tests performed, it emerged that the *S. aureus* isolates belonging to strains A, B, and C are strong biofilm producers; notably, strain B exhibited a biofilm production capacity more than twice that of strains A and C. Conversely, strain D was classified as a moderate biofilm producer.

Isolates belonging to strain B were identified in the near patient area, specifically on the bedside table handle, both before and after cleaning/disinfection.

Colonies of strains A, C and D were isolated only on furniture surfaces prior to cleaning/disinfection.

Fig. 2. Strains A, B, C, D and biofilms.



Discussion

Many studies have demonstrated the ease with which pathogens can be transferred from colonized and/or infected patients to surfaces within the patient's room and/or from surfaces to healthcare workers' hands.

Continuous evaluation and monitoring of cleaning/disinfection interventions to reduce the risk of transmission of environmental pathogens through defined procedures have been key elements of infection prevention and control practices in acute care hospitals for years [33].

The results of the present study showed that although

cleaning/disinfection procedures are effective in reducing microbial contamination, they do not always fully restore acceptable conditions, both regarding ACC and *S. aureus*, only partially reducing the risk of pathogen cross-transmission. In this study, microbiological identification was limited to *S. aureus*, as it is considered by the scientific literature to be a valid indicator of infection risk [25, 26]. Secondly, the study was conducted when there were no active infectious outbreaks or evidence of an increase in the prevalence of HAI that would require the research to be extended to other microorganisms. Moreover, this last assessment would have required the expenditure of economic resources, time, and personnel.

Regarding *S. aureus*, the results highlighted the persistence of a strain characterized as SPA Typing t032 MLST ST22, resistant to five classes of antibiotics, including methicillin. This strain, found in the near patient area (bedside table handle), proved to be a strong biofilm producer, more so than the other three strains, a characteristic that likely allowed it to survive the action of sanitizing agents.

Since no swabs were performed on the patients who occupied the beds, it was not possible to verify their colonization status or hypothesize the source of the strains found on the surfaces.

Spa Type t032 is widely distributed in Europe and is considered prevalent alongside two other spa types, t002 (also identified in this study) and t008. The scientific literature describes it as exclusively associated with MRSA and tightly linked to ST22. ST22, also known as the EMRSA-15 strain, is a widely spread, highly virulent clone in Europe and is significantly associated with hospital-acquired infections. It is also known for its rapid dissemination in healthcare environments [34]. In a study conducted in Portugal, ST22 accounted for 72% of nosocomial isolates and was able to replace previously circulating STs such as ST239 and ST247 [35].

According to Soliman et al. [36], ST22 possesses factors such as cna, sdrE, hlg, and ica, which confer colonization and virulence capabilities in hospital settings.

The spa type t002 ST5, belonging to clonal complex CC5, is historically associated with multidrug-resistant nosocomial strains, particularly in Asian countries and North America, although in our case the isolates were sensitive to several antibiotics (except for resistance to benzylpenicillin and intermediate sensitivity to levofloxacin).

It frequently harbors adhesion factors such as fnbA, cna, sdrE, hlg, and ica, which are associated with adhesive capacity, biofilm formation, and nosocomial virulence.

The ST5 allelic profile is very similar to that of ST231, also belonging to CC5. Both share a common evolutionary ancestry: ST231 is likely derived from ST5 via mutation or recombination in the yqiL gene [37]. They also display phenotypic similarities, as ST231 strains tend to resemble ST5 strains, particularly in their antibiotic resistance profiles, as evidenced by the findings of our study.

The persistence of MRSA (ST22) and the nonconformities in ACC detected in phase 2 underline the importance of microbiological monitoring of surfaces to promptly identify any risk conditions.

In hospitals, the presence of pathogenic microorganisms on surfaces is in itself a significant non-compliance, since even minimal quantities can pose a risk in conditions favorable to transmission.

For this reason, the results called into question the execution modalities of the cleaning/disinfection procedures. Therefore, after communicating microbiological results both to the ward and the hospital Infection Control Committee, a comprehensive improvement process was initiated through audits with cleaning staff, emphasizing the need to increase adherence to cleaning/disinfection techniques and, for all healthcare personnel, hand hygiene.

One aspect that must be taken into account with regard to hospital sanitation is that many hospitals (such as the one where the study was conducted) rely on outsourced companies, which often represent a significant operational constraint in terms of the possibility of changing the frequency, methods, and protocols of disinfection.

At the end of the improvement process, subsequent checks showed no nonconformities.

According to Dancer [26] the monitoring of microbial bioburdens on surfaces, compared to less expensive and faster methods such as ATP testing and other screening tools, should, be implemented as an integral part of environmental control protocols. While these conventional techniques may offer useful support for general assessments, they cannot replace more accurate quantitative and specific methods for the detection and identification of pathogenic microorganisms. For this reason, direct microbiological monitoring remains essential, particularly as a downstream component of a standardized control system that should consistently be in place.

Beyond confirming the efficacy of cleaning/disinfection, the collection of environmental surveillance data over time would allow predictive modeling in relation to healthcare-associated infection (HAI) rates and even enable forecasting of cross-infection episodes and epidemic outbreaks [26].

Conclusion

Improving the effectiveness of environmental disinfection in healthcare facilities must rely on a comprehensive strategy involving training and education of cleaning/disinfection and healthcare personnel, as well as implementation of verification systems to ensure the adequacy of disinfection.

A further development of this research could be the evaluation of timing and dynamics of surface contamination in patient wards to better define protocols for more effective cleaning/disinfection in reducing cross-infection.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: MLC and MS; management of microbiological samples: SC and AMS; data collection: CD and SC; biomolecular analysis: GO, ES and CP; formal analysis: AC and MS; data interpretation: CD, MS, SB, ES and EP; writing–original draft preparation: MLC and GO; writing–review and editing: MLC, MS and CP; supervision: MLC.
All authors have read and agreed to the published version of the manuscript.

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Nosocomial infections

Prevalence and antimicrobial resistance of *Escherichia coli* in a Tertiary-level hospital

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Keywords

E. coli • Multiresistant • ESBL

Summary

This study was designed to achieve more effective treatment for patients and to encourage the development of new antibiotics, specifically targeting multidrug-resistant Escherichia coli. This bacterium is one of the primary causative agents of hospital-acquired infections (HAI). It is classified as a critical priority pathogen for the development of new antibiotics according to the World Health Organization (2024). In this study, 76 isolates from four bacterial genera were analyzed. E. coli was identified as the most prevalent infectious agent with 52% of the isolates, followed by Klebsiella pneumoniae (20%), Pseudomonas aeruginosa (12%), and Acinetobacter baumannii (16%). Internal Medicine was the hospital department with the highest frequency of E. coli infections. Sixty-five percent of the samples were derived from urine. This bacterium was more prevalent in females (57.5%) than in males (42.5%). The highest resistance rates were observed for Ampicillin and Ciprofloxacin, with 90% and 77.5% respectively, while the lowest resistance was found for the Carbapenems Ertapenem, Meropenem, and Aminoglycoside Amikacin, with 22.5%. Twenty-two point five percent of the E. coli isolates were classified as resistant, and 77.5% as multidrug-resistant. Sixty-two point five percent were extended-spectrum beta-lactamase (ESBL) producers. All of these isolates resisted Ampicillin, while 4% were resistant to Ertapenem, Meropenem, and Amikacin. E. coli was identified as the primary causative pathogen of HAI in the Hospital under study and demonstrated resistance to most currently prescribed antibiotics.

Introduction

Antibiotic resistance is an escalating public health issue, necessitating the establishment of global surveillance networks. The increase in microbial resistance to antibiotics has led to higher morbidity and mortality from infections, prolonged hospital stays, increased antibiotic use, and excessive hospitalization costs [1]. Given this situation, there is a pressing need to understand the prevalence of hospital-acquired infections caused specifically by *Escherichia coli*, which would provide information on resistance profiles in each healthcare institution to enable effective patient treatment and to underscore the importance of developing new antibiotics for multidrug-resistant microorganisms.

A review of the antimicrobial resistance (AMR) commissioned by the UK government posited that antimicrobial resistance could result in 10 million deaths annually by 2050 [2]. It has been estimated that in 2019, 1. 27 million deaths were directly attributable to resistance, contributing to 4.95 million deaths associated with bacterial AMR globally. *E. coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* accounted for 929,000 deaths out of the 1.27 million fatalities attributable to resistance, with *E. coli* responsible for the highest number of deaths that year [3].

E. coli is one of the most well-adapted bacterial organisms and versatile pathogens. It causes a variety of human infections, including gastrointestinal diseases and extraintestinal infections [4]. Infections caused by extraintestinal pathogenic *E. coli* (ExPEC) constitute a serious public health issue globally. The most concerning include urinary tract infections, severe neonatal meningitis, serious intra-abdominal infections, and, more rarely, pneumonia, infections of intravascular devices, osteomyelitis, soft tissue infections, or sometimes bacteriemia [5]. This bacterium is one of the leading causative agents of hospital-acquired infections, and due to the acquisition of antibiotic resistance mechanisms, it has been classified as a pathogen of public health significance. It is included in the ESKAPE group, which comprises pathogens exhibiting multidrug resistance [6]. *E. coli* is designated

as a critical priority on the list published and updated by the World Health Organization (WHO) in 2024, which categorized priority bacterial pathogens for the development of new antibiotics, emphasizing resistance to third-generation cephalosporins and Carbapenems in this enterobacterium [7].

Materials and methods

Study Design

A retrospective descriptive study was conducted on strains isolates between March and December 2019. The distribution of the patients in the database contains a representative demographic coverage of the state. The database used includes patients from multiple regions across the state of Sinaloa and contains key demographic variables, such as age and sex. This statewide geographic distribution, together with the inclusión of basic demographic characteristics, provides demographic coverage of the state population and allows for a representation of patients of Sinaloa.

Data identified for patients and isolates included: age, sex, sample type, tested antibiotic agents, susceptibility testing methods, resistance profiles, and institution type. Individual laboratory techniques performed antimicrobial susceptibility testing using Clinical and Laboratory Standards Institute (CLSI)-approved methods and interpreted results using Food and Drug Administration (FDA)/CLSI breakpoints and interpretive criteria [8].

Selections of strains

Hospital-acquired infections were reported over a one-year period at the Culiacan General Hospital "Bernardo J. Gastelum," and isolates were selected based on the following criteria. First, these isolates corresponded to Gram-negative bacteria associated with more severe complications in hospitalized patients, namely *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii.* Second, these genera are included in the World Health Organization (WHO) list of priority pathogens for the development of new antibiotics. Third, they were the bacterial genera with the most complete susceptibility data available.

The isolates were obtained from urine, sputum, wound, and blood samples from various departments within the aforementioned hospital. We selected isolates belonging to the bacterial genus *E. coli* for our analysis, as this species represents the leading cause of hospital-acquired infections. Inclusion criteria comprised: (i) clinical isolates identified as *E. coli* using automated systems; (ii) isolates associated with hospital-acquired infections, defined as infections occurring ≥48–72 h after hospital admission; and (iii) isolates obtained from hospitalized patients during the study period. Only the first isolate per patient per infectious episode was included. Exclusion criteria included: (i) isolates not identified as *E. coli*; (ii) isolates from infections acquired before hospital admission; (iii) isolates with incomplete susceptibility data or obtained outside the study period.

E. coli isolates were considered as 100% of the samples because, following their selection, the study specifically focuses on the analysis of isolates of this bacterium.

Identification, antimicrobial susceptibility, and ESBL production

For identification, ESBL production, and susceptibility profiling, automated systems Microscan® and Vitek® were utilized. The susceptibility profile of the *E. col*i isolates was determined against 13 antibiotics from four different families: beta-lactams (Ampicillin, AMP; Cefuroxime, CFX: Ceftriaxone, CRO; Ceftazidima, CAZ; Cefotaxima, CTX; Cefepime, FEP, Ertapenem, ETP; and Meropenem, MEM), aminoglycosides (Amikacin, AMK; Gentamicin, GEN), Fluoroquinolones (Ciprofloxacin, CIP), and Sulfonamides (Trimethoprim and Sulfamethoxazole, SXT). Additionally, the isolates were classified as susceptible (S), Intermediate (I), or resistant (R) according to the CLSI 2021 criteria [8].

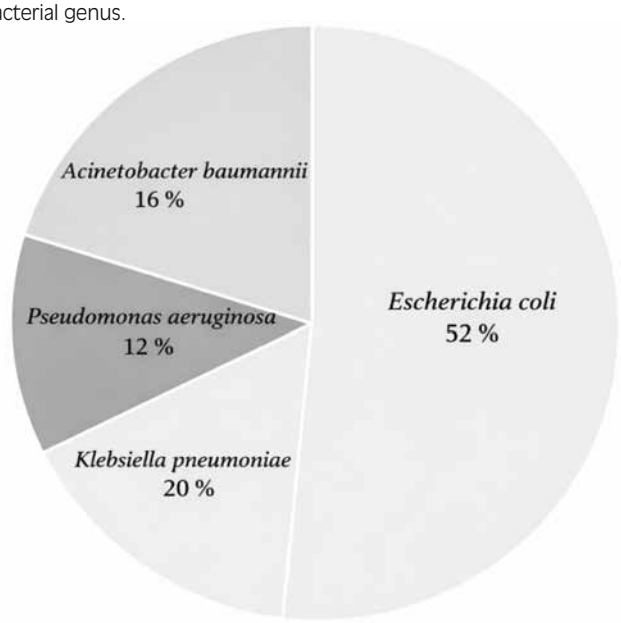
Statistical analysis

A microbiological and epidemiological analysis was conducted through a descriptive statistical study of qualitative variables. Following the determination of the susceptibility pattern, all data were consolidated in Microsoft Excel®, including resistance by antibiotic and by class, as well as variables such as age, sex, and the hospital department from which the samples were obtained.

Results

A total of 1,860 hospital-acquired infections caused by bacteria were reported in the state of Sinaloa over one year, of which 303 were at the Culiacan General Hospital, "after Gastelum ("Bernardo J Gastelum") and 76 were analyzed. Bacteria were obtained from the genera: *E. coli* 52% (40 isolates), *Klebsiella pneumoniae* 20% (15 isolates), *Pseudomonas aeruginosa* 12% (9 isolates), *and Acinetobacter baumannii 16%* (12 isolates) as shown in Figure 1. All the isolates were obtained from patients at a third-level Hospital of Culiacan, Sinaloa, "Bernardo J Gastelum", from samples of urine, sputum, blood, and wounds collected from the services of hemodialysis, internal medicine, pediatric emergencies, traumatology, neurosurgery, outpatient consultations, and emergency care. Of the 76 isolates analyzed, 55.3% (42 isolates) were from male patients and 44.7% (34 isolates) from female patients. According to the patient's age, 26.3% (20) were between 40 and 59 years old, 23.7% (18) were 60 years or older or had no age record, 22.3% (17) were between 19 and 39 years old, while only 3.95% (3) were patients aged between 0 and 18 years. Regarding the type of sample, 42.1% (32 samples) came from urine cultures, 32.9% (25 samples) from sputum, 13.1% (10 samples) from the wound, 9.2% (7 samples) from blood, and 1.32% (1 sample) from pleural fluid and catheter samples.

Fig. 1. Percentage of Isolates by bacterial genus.



PRESENCE OF *E. COLI* ACCORDING TO AGE, SEX, AND SAMPLE TYPE

Regarding age, infections caused by *E. coli* were most prevalent in patients aged 40-59 years (32.5%). Meanwhile, 25% of patients with *E. coli* infections were between 19 and 39 years old, 22.5% were over 60 years old, and only 5% of patients were between 0 and 18 years old. 15% of patients did not have an age record. The presence of infections caused by *E. coli*, 57.5% of the patients were females, while 42.5% were males. Of all the isolates obtained, 65% were from urine samples, 20% were from sputum, and 7.50% were obtained from blood and wound sources.

E. COLI PRESENCE BY MEDICAL SERVICE AND SAMPLE TYPE

Of the 40 *E. coli* isolates, 40% were obtained from the internal medicine service, 27.5% from external sources, and 10% from neurosurgery and outpatient clinics. Five percent of the isolates originated from the hemodialysis unit, while 2.5% were obtained from the pediatric emergency and traumatology, and general emergency services.

Of the isolates from internal medicine, 56.25% were from urine cultures, 25% from sputum cultures, 12.5% from blood cultures, and 6.25% from wound cultures. Regarding the isolates of neurosurgery, 50% were obtained from sputum cultures, while 25% were from blood and urine cultures. Of external consultation, 75% were from urine cultures and 25% from secretion cultures. Of the hemodialysis area, 100% were from urine cultures. 2.5% of isolates was collected from pediatric emergencies, traumatology, and general emergencies. In pediatric emergencies and traumatology, 100% of the samples were obtained from urine cultures, while in general emergencies, 100% were from wound cultures (Tab. I).

It is noteworthy that 72.5% of all *E. coli* isolates analyzed came from hospitalized patients in the mentioned medical services, while 27.5% were of external origin. Of the external isolates, 81.81% were from urine cultures, and 9.09% each were from sputum and wound cultures.

ANTIBIOTIC SUSCEPTIBILITY PROFILE OF *E. COLI* ISOLATES

The susceptibility profile of 40 isolates was determined against 13 antibiotics from four different families; the isolates are classified as susceptible (S), intermediate (I), or resistant (R) concerning the aforementioned antibiotics.

A total of 40 isolates (100%) are resistant to antibiotics. In beta-lactams, 90% (36 isolates) exhibited resistance to Ampicillin. Resistance rates were 67.5% for Cefuroxime (27 isolates), and 62.5% for Ceftriaxone, Ceftazidime, Cefotaxime, and Cefepime, with 25 isolates. In aminoglycosides, 45% of isolates were resistant to Gentamicin (18 isolates). For fluoroquinolones, 77.5% presented resistance to Ciprofloxacin (31 isolates), while in sulfonamides, 55% showed resistance to Trimethoprim/Sulfamethoxazole (22 isolates) (Fig. 2).

The 2.5% of isolates (one isolate) were resistant to carbapenems, Ertapenem, Meropenem, and the aminoglycoside Amikacin. It is important to note that in third and fourth-generation cephalosporins, over 50% of the isolates exhibited resistance. These data may reflect inappropriate use of this type of antibiotic, although this was not directly evaluated.

ANTIBIOTIC RESISTANCE OF *E. COLI* BASED ON SAMPLE TYPE (40 ISOLATES)

Considering the sample type and the antibiotic resistance of *E. coli,* the following results were determined (Tab. II). Sixty-five percent of samples (26 isolates)

Tab. I. Percentage (%) of ***E. coli*** presence by medical service and sample type.

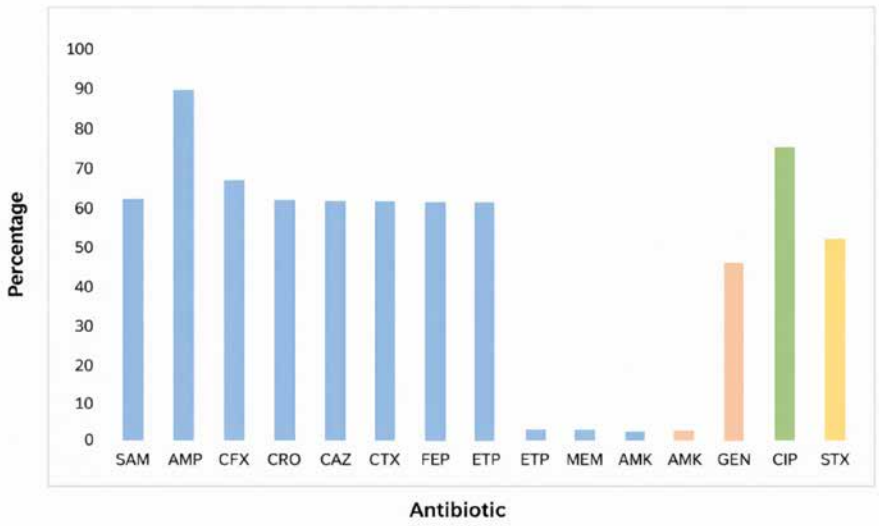
	Medical service	% (n)	Sample	% (n)
E. coli (52 %)	Hemodialysis	5% (2)	Urine culture	100% (2)
				100% (2)
	Internal medicine	40% (16)	Urine culture	56.25% (9)
			Expectoration culture	25% (4)
			Wound culture	6.25% (1)
			Blood culture	12.5% (2)
				100% (16)
	Pediatric emergencies	2.5% (1)	Urine culture	100% (1)
				100% (1)
	Traumatology	2.5% (1)	Urine culture	100% (1)
				100% (1)
	Neurosurgery	10% (4)	Expectoration culture	50% (2)
			Blood culture	25% (1)
			Urine culture	25% (1)
				100% (4)
	External consultation	10% (4)	Urine culture	75% (3)
			Secreción culture	25% (1)
				100% (4)
	Emergencies	2.5% (1)	Wound culture	100% (1)
				100% (1)
	External origin	27.5% (11)	Urine culture	81.81% (9)
			Expectoration culture	9.09% (1)
			Wound culture	9.09% (1)
				100% (11)
	Total	100% (40)		100% (40)

Number of isolates (n). (n=40). 100 % (40).

were collected from urine. The isolates from these samples exhibited 88% resistance to Ampicillin (23 isolates), 62% resistance to Cefuroxime (16 isolates), and 54% resistance to Ceftriaxone, Ceftazidime, and Cefepime (14 isolates). Regarding aminoglycosides, eight isolates exhibited resistance to Amikacin (31%), and 42% to Gentamicin. While 77% was reported for Ciprofloxacin and Trimethoprim/Sulfamethoxazole (20 isolates). This type of sample did not present resistance to the carbapenems evaluated.

Twenty percent of the samples were collected from sputum, of which 100% exhibited resistance to

Fig. 2. Percentage of antibiotic resistance in *E. coli* (40 isolates).

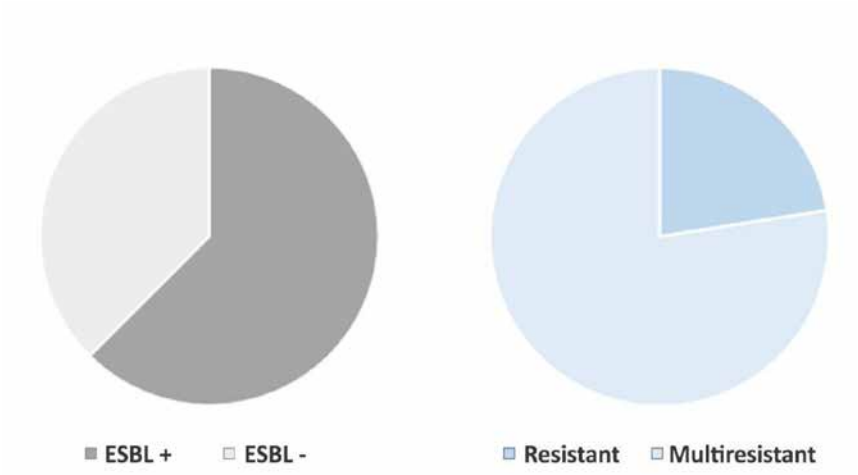


Beta-lactams are shown in blue, Aminoglycosides in pink, Fluoroquinolones in green, and Sulfonamides in yellow. Ampicillin/Sulbactam, SAM; Ampicillin, AMP; Cefuroxime, CFX; Cefriaxone, CRO; Ceftazidima, CAZ; Cefotaxima, CTX; Cefepime, FEP; Ertapenem, ETP; Meropenem, MEM; Amikacin, AMK; Gentamicin, GEN; Ciprofloxacin, CIP; Trimethoprim and Sulfamethoxazole, SXT.

Tab. II. Antibiotic resistance of *E. coli* based on sample type (40 isolates).

	Sample type			
Antibiotic	Urine 65% (26)	Sputum 20% (8)	Blood 7.5% (3)	Wound 7.5% (3)
Ampicilina/Sulbactam	65% (17)	50% (4)	67% (2)	100% (3)
Ampicilina	88% (23)	100% (8)	67% (2)	100% (3)
Cefuroxima	62% (16)	88% (7)	33% (1)	100% (3)
Ceftriaxona	54% (14)	88% (7)	33% (1)	100% (3)
Ceftazidima	54% (14)	88% (7)	33% (1)	100% (3)
Cefepime	54% (14)	88% (7)	33% (1)	100% (3)
Ertapenem	0% (0)	13% (1)	0% (0)	0% (0)
Meropenem	0% (0)	13% (1)	0% (0)	0% (0)
Amikacina	31% (8)	38% (3)	33% (1)	100% (3)
Gentamicina	42% (11)	38% (3)	33% (1)	100% (3)
Ciprofloxacino	77% (20)	63% (5)	67% 2)	100% (3)
Trimetoprima/Sulfametoxazol	77% (20)	50% (4)	33% (1)	33% (1)

Fig. 3. Percentage of isolates ESBL producer and multiresistant.



Gray graph, ESBL production. Blue graph, resistance classification.
Extended spectrum betalactamases, ESBL. ESBL producer, ESBL +. ESBL no producer, ESBL -.

Ampicillin (eight isolates), while 88% (seven isolates) were resistant to cephalosporins evaluated (Cefuroxime, Ceftriaxone, Ceftazidime, and Cefepime). For the aminoglycosides, Amikacin and Gentamicin, resistance rates of 38% were observed (three isolates), while 63% were resistant to Ciprofloxacin (five isolates) and 50% to Trimethoprim and Sulfamethoxazole. Thirteen percent of isolates were resistant to Ertapenem and Meropenem (one isolate).

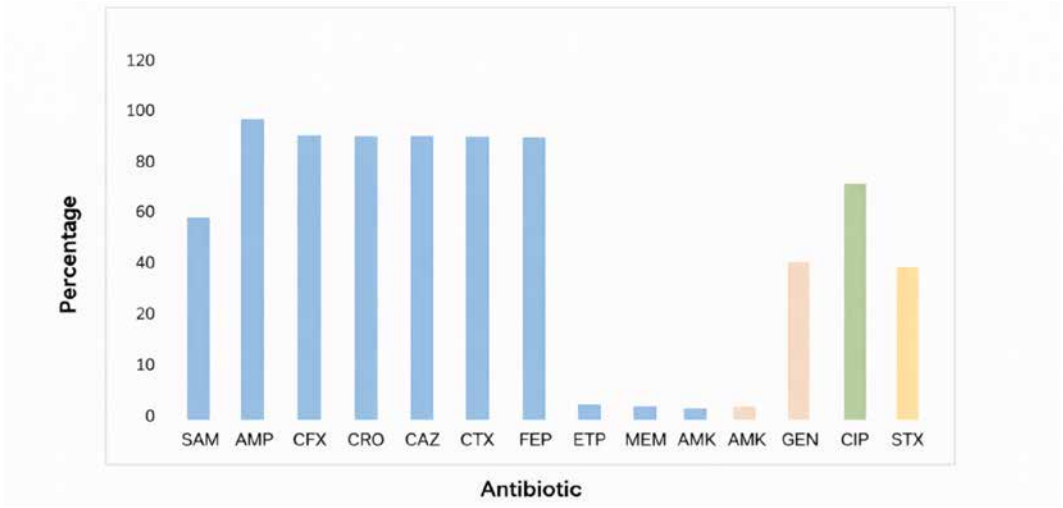
Seven point five percent of the isolates were derived from blood and wound samples. Among the blood samples, 67% of the isolates (two) presented resistance to Ampicillin and Ampicillin/Sulbactam. Thirty-three percent of the isolates from this sample type were resistant to Cefuroxime, Ceftriaxone, Ceftazidime, Cefepime, Amikacin, Gentamicin, and Trimethoprim/Sulfamethoxazole, while 67% were resistant to Ciprofloxacin. No resistance was observed to the evaluated carbapenems.

The isolates derived from wound samples; one hundred percent demonstrated resistance to Ampicillin, Ampicillin/Sulbactam, Cefuroxime, Ceftriaxone, Ceftazidime, Cefepime, Amikacin, Gentamicin, and Ciprofloxacin. Thirty-three percent of the isolates showed resistance to Trimethoprim/Sulfamethoxazole, while no resistance was observed to Eratapenem and Meropenem.

Percentage of resistance, multi-resistance in isolated ESBL producers

Of the 40 isolates previously mentioned, 25 are ESBL producers, which represent one of the principal mechanisms of resistance associated with *E. coli*. This means that 62.5% of the isolates (25) are ESBL producers, while 37.5% (15) are nonproducers (Fig. 3). Twenty-two point five percent (9 isolates) out of the total evaluated were resistant to at least one of the evaluated antibiotics, while 31 isolates (77.5%) were categorized as multidrug-resistant (Fig. 3) according to the criteria

Fig. 4. Percentage of antibiotic resistance in *E. coli* ESBL producer (25 isolates).



Beta-lactams are shown in blue, Aminoglycosides in pink, Fluoroquinolones in green, and Sulfonamides in yellow. Ampicillin/Sulbactam, SAM; Ampicillin, AMP; Cefuroxime, CFX; Cefriaxone, CRO; Cefrazima, CO; Ceftazidima, CAZ, Cefotaxima, CTX; Cefepime, FEP; Ertapenem, ETP; Meropenem, MEM; Amikacin, AMK; Gentamicin, GEN; Ciprofloxacin, CIP; Trimethoprim and Sulfamethoxazole, SXT.

established by Magiorakos et al. [9], indicating resistance to one antibiotic in three or more families of these antimicrobials.

According to the prevalence of resistance among ESBL-producing isolates (Fig. 4), 100% (25 isolates) exhibited resistance to Ampicillin, while over 90% of the isolates were resistant to third and fourth-generation cephalosporins; 96% were resistant to Cefuroxime, Ceftriaxone, Ceftazidime, Cefotaxime, and Cefepime (24 isolates). Sixty-four percent showed resistance to Gentamicin (16 isolates), 84% to Ciprofloxacin (21 isolates), and 56% to Trimethoprim/Sulfamethoxazole (14 isolates). The lowest percentage of resistance was observed against the evaluated carbapenems (Ertapenem and Meropenem) and the aminoglycoside Amikacin, with a resistance rate of 4% (one isolate).

Discussion

Hospital-acquired infections represent a global health issue that escalates healthcare costs and promotes the selective emergence of multidrug-resistant microorganisms. Certain pathogenic species exhibit resistance and are frequently found in hospital settings. *E. coli* is one of the primary causative agents of HAI. Previous studies reported positive culture results for nosocomial infections by the Hospital Epidemiological Surveillance System of the Mexican Social Security Institute, identifying *E. coli* as the most frequently isolated microorganism and of greatest epidemiological relevance, accounting for 16.9% of the total of infections, followed by coagulase-negative *Staphylococcus* and *Pseudomonas aeruginosa* [10]. In this study, it was found that *E. coli* was the main causative agent of infections, responsible for 52% of total infections, followed by *Klebsiella pneumoniae*, *Acinetobacter baumannii,* and *Pseudomonas aeruginosa*. Our results are comparable to those reported by the Epidemiological Bulletin of Healthcare-Associated Infections in Mexico [11], from July to August 2023, *E. coli* was categorized as the principal causative agent of HAI. In the state of Sinaloa [12], in January 2025, this bacterium was the second most prevalent microorganism responsible for hospital infections, accounting for 11.24% of total infections, following *Acinetobacter baumannii* with 13.48%.

Of a total of 40 *E. coli* isolates studied, 40% (16 isolates) originated in the internal medicine department. Notably, this department yielded the majority of the sample types analyzed in this study, including urine, sputum, wound, and blood (Tab. II). Our results are comparable to a related study at the Bajio National Medical Center [13], where the largest number of samples originated in the Internal Medicine department, primarily urine cultures, followed by secretions and blood cultures. These data could reflect a correlation between the hospital area and the types of samples analyzed. Urine samples have been reported as the most frequent, consistent with Chuquisapon et al. [14], with 53.7% of a total of 67 samples, followed by blood samples and bronchial secretions, also belonging to internal medicine.

According to the origin of the samples by sex, 57.50% were obtained from females (23 isolates), whereas 42.5% (17 isolates) were obtained from males. Recent data have reported a higher frequency of *E. coli* in females, specifically among hospitalized patients. Our findings are consistent with those reported by Lopez-Maman [15], who reported the presence of *E. coli* in patients at the Northern Hospital in Bolivia, highlighting

a greater frequency of this bacterium in female patients compared to *Klebsiella pneumoniae.* Notably, the frequency of *E. coli* is higher in females than in males; these results may reflect a correlation between the most frequent sample type (urine) and the presence of *E. coli* in women, as this genus is more commonly associated with urinary tract infection. The higher prevalence of urinary tract infections in women is primarily explained by anatomic conditions: first, the urethra and perianal area are closer together; second, the urethra is shorter in females, reducing the distance that bacteria must travel to reach the bladder; and third, women experience hormonal fluctuations that can disrupt natural defense mechanisms, such as changes in vaginal acidity [16]. Regarding the age groups most affected by *E. coli* infections, similar data to this work have reported a higher prevalence of this bacterium in individuals over 50 years old, likely due to anatomical, physiological, or pathological changes [17]. In this study, it was determined that 32.50% of patients infected with this bacterium were in the age range of 40 to 59 years, and 22. 5% were 60 years or older.

Regarding the resistant percentages to the 13 antibiotics belonging to four families of these medications, the results of 40 isolates studied are comparable to those reported by the University Plan against Antimicrobial Resistance (PUCRA) [18], in conjunction with data reported by Garza et al. [19] from the Thematic Network for Collaboration and Surveillance of Antimicrobial Resistance (INFIVAR) in 2019. Where 86% of isolates were resistant to Ampicillin, and 62.5% resistant to Ceftriaxone and Cefepim. The lowest resistance percentages reported by PUCRA were for Meropenem (0.7%), which coincides with our isolates, as we also observed the lowest resistance for this antimicrobial at 2.5%. The low percentages of resistance to carbapenems may be attributed to their classification as a last-resort treatment. However, in some countries, they are no longer effective in more than half of patients with *K. pneumoniae* infections due to resistance. Factors contributing to resistance include the excessive and indiscriminate use of antibiotics, lack of access to clean water, and inadequate disease prevention and control measures [19].

Considering the type of sample and the resistance of *E. coli,* resistance percentages varied. The 65% of the samples were collected from urine (65%). It is important to note that when a urinary tract infection occurs due to *E. coli*, some antibiotics, such as Trimethoprim, are commonly used. According to the results, more than 70% of isolates from this type of sample are resistant to this antibiotic. The high rates of resistance could be attributed to the fact effective drugs are becoming scarce. The resistance rate to Ciprofloxacin, also used to treat urinary infections, ranged from 8.4% to 92.9% for *E. coli* and from 4.1% to 79.4% for *K. pneumoniae* in countries that reported data to the Global Antimicrobial Resistance Surveillance System (GLASS) [20]. Twenty percent of the samples were collected from sputum. In cases of bacterial infections such as pneumonia caused by *E. coli*, third and fourth-generation cephalosporins are typically prescribed. According to the World Health Organization´s updated list of priority pathogens resistant to antibiotics in 2024 [7], *E. coli* is classified as a critical priority due to its resistance to Carbapenems and the aforementioned cephalosporins. Twenty-five countries, territories, and regions reported data to the GLASS on sepsis due to methicillin-resistant *Staphylococcus aureus* (MRSA), and 49 countries provided data on sepsis caused by *E. coli*. The median resistance rate observed for MRSA was 12.11%, while for third-generation cephalosporin-resistant *E. coli*, it was 46% [21].

Sixty-two point five percent of our studied isolates were ESBL producers, comparable to a related study in southern Mexico, where 50% of the isolates were producers of these enzymes [13]. This increases the risk of infections resistant to cephalosporins, which leads to a high number of complications for hospitalized patients [22-24].

Our data show a 90% of resistance rate to Ampicillin and 56% to Trimethoprim/Sulfamethoxazole, whereas resistance rates of 40% to Ampicillin and 35.1% to Trimethoprim/Sulfamethoxazole have been reported in an outpatient study conducted in the central region of the state of Sinaloa [25]. Based on these findings, we suggest that resistance rates may vary depending on the origin of the isolates; however, a consistent pattern is often observed in which isolates are resistant to at least one antibiotic among those evaluated.

Jaqueti et al. [26] reported 66.7% and 4% of resistance to Gentamicin and Amikacin, respectively, in ESBL-producing *E. coli* strains; while our isolates exhibited a resistance of 64% to Gentamicin and 4% to Amikacin, indicating a notable difference in resistance to this aminoglycoside. This discrepancy may be due to variations in antibiotic prescribing practices across different región of the world. For instance, the mentioned study was conducted in Madrid, Spain, where the Madrid Medical Association has recently called for awareness regarding the rational use of antibiotics to address multidrug-resistant bacteria, which are responsible for approximately 4,000 deaths annually in Spain and over 35,000 in Europe [27].

We observed that in isolates that are ESBL producers, there is a higher percentage of resistance to beta-lactams compared to the isolates in general. The presence of ESBL may be associated with an increased resistance rate to other antibiotic classes, although this was not directly evaluated. This is related to the fact that ESBLs have traditionally been described as being encoded on extrachromosomal elements. These genes, along with those that encode resistance to other antimicrobials, may reside on the same conjugative plasmid and, therefore, are transmitted together from one microorganism to another, conferring a multidrug resistance profile [28].

Hospital-acquired infections are a global public health problem that is increasing with the acquisition of antibiotic resistance. *E. coli* is one of the main causative agents of these infections, exhibiting resistance primarily to third and fourth-generation cephalosporins, affecting the entire population, prolonging patient hospitalization, and bringing about economic impact. Monitoring the

presence of this bacterium and its resistance profiles in hospitals is of utmost importance to provide each patient with the appropriate treatment and also to provide information highlighting the importance of developing new antibiotics to treat infections caused by such microorganisms.

Conclusion

E. coli was identified as the most prevalent infectious agent with 52% of the isolates, followed by *Klebsiella pneumoniae* (20%), *Pseudomonas aeruginosa* (12%), and *Acinetobacter baumannii* (16%).

Internal medicine was the hospital department with the highest frequency of *E. coli* infections, predominantly in urine samples. Of the patients affected, 57.5% were female, and 42.5% were male.

The highest resistance rates were observed for Ampicillin and Ciprofloxacin, with 90% and 77.5% respectively, while the lowest resistance was found for the Carbapenems Ertapenem, Meropenem, and Aminoglycoside Amikacin, with 2.5%.

Twenty-two point five percent out of the total evaluated were resistant to at least one of the evaluated antibiotics, while 31 isolates were categorized as multidrug-resistant. Sixty-two point five percent of the isolates are ESBL producers, while 37.5% (15) are nonproducers. An increase in resistance was observed in ESBL-producing isolates, 100% (25 isolates) exhibited resistance to Ampicillin, while over 90% of the isolates were resistant to third and fourth-generation cephalosporins, and 84% to Ciprofloxacin.

Due to the emerging problem of antibiotic resistance, our work presents data that emphasize the importance of understanding the prevalence of infections, in this specific case of *E. coli*, to prescribe the appropriate treatment and underline the need for the development of new antibiotics.

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Conflicts of interest statement

The authors declare that there are no conflicts of interest that may have influenced the work presented in this article.

Authors' contributions

GGVR designed the research, performed the microbiological analysis, and wrote the article. YPAS created the tables and conducted the literature review. MEBF collected data. SBF collected and provided data. SPDC performed the literature review. EHG reviewed the data analysis. DMM created figures. DCG performed the final manuscript editing. JRPU coordinated the research. All authors reviewed, read, and approved the manuscript, and provided feedback and contributions to the final work.

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HEALTH PROMOTION

Barriers to Preventive Healthcare Among College Students: A Mini-Review of the Literature

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Keywords

Preventive healthcare • College students • Barriers • Health literacy

Summary

Preventive healthcare is vital for promoting the long-term health of individuals. College students often underutilize such services associated with preventive healthcare in spite of increased autonomy and health risks that can emerge during early adulthood. This demographic of students represents a transitional population with increasing independence and unique health needs. Despite this, they exhibit persistently low engagement in preventive health services. This literature review synthesizes evidence on barriers to preventive care access and utilization among college students in the United States and similar high-income settings. Common barriers include lack of knowledge, perceived invulnerability, healthcare avoidance behaviors, cost and insurance gaps, confidentiality concerns, and systemic access issues. Understanding these multi-faceted barriers is essential to designing targeted interventions at individual, institutional, and policy levels that improve preventive care engagement and long-term health outcomes among these emerging adults.

Introduction

Preventive healthcare is foundational to long-term health outcomes. Among key aspects of preventive healthcare, immunizations, screenings, counseling, and health risk assessments, are recommended for young adults to reduce disease incidence and promote lifelong health [1]. However, college students exhibit suboptimal engagement with preventive services, posing challenges to both individual and public health. Unlike pediatric or older adult populations, young adults face unique transitional barriers during their college years that influence care utilization. Despite this, many young adults, particularly college students, underutilize preventive services even when accessible through campus clinics. Transitional independence, health behaviors, and evolving risk profiles position college students as a critical target for preventive care initiatives. Evidence shows that college students disproportionately seek care for acute symptoms while largely ignoring preventive services [1]. This review synthesizes recent PubMed-indexed studies to elucidate barriers affecting preventive healthcare access and uptake among college students.

Methods

This review synthesizes evidence from peer-reviewed PubMed-indexed studies on barriers to preventive healthcare utilization among college students and young adults. Key search terms included *"college students," "healthcare-seeking behavior," "preventive services,"* and *"barriers to care."* Several peer-reviewed journals were analyzed. However, the themes included in the comprehensive review [1] which examined 28 quantitative and qualitative studies describing healthcare-seeking behaviors and barriers among college populations, remains a primary anchoring focus on this review, but it does not encompass the totality of the comprehensiveness of it.

Results

This review identifies several recurring themes related to barriers to preventive healthcare utilization among college students across included studies. These barriers can be categorized into structural/logistical, psychosocial/perceptual, informational, and institutional factors. Across studies, preventive healthcare utilization among college students was consistently low. Structural barriers were frequently reported, including cost, insurance limitations, and time constraints. Even among insured students, out-of-pocket costs and lack of understanding regarding coverage reduced utilization [2]. Time limitations due to academic and work obligations were also cited as key barriers to services such as vaccinations and routine screenings [3]. Psychosocial barriers were also prominent. Many students demonstrated perceived invulnerability to health risks, reducing motivation to seek preventive care [1]. Fear of procedures, potential diagnoses, and stigma, particularly related to mental

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health, further discouraged engagement [3, 6]. Health literacy and awareness gaps were consistently identified across studies. Students with limited knowledge of available services or preventive guidelines were significantly less likely to engage in care [4, 5, 8]. Male students and non-health majors were particularly affected by these gaps. Institutional and provider-level factors also influenced utilization. Lack of provider recommendation was associated with reduced uptake of services such as HPV vaccination [5]. Additionally, variability in screening practices across campus health centers contributed to inconsistent access to preventive care [9]. Overall, these results highlight the primary barriers identified across studies and set the stage for a more detailed exploration of how they influence healthcare utilization among college students.

Conceptual Framework: Healthcare-Seeking Behavior

Preventive health behaviors among college students are conceptualized within broader healthcare-seeking models, including individual, system, and environmental determinants. Key themes influencing healthcare-seeking behaviors, including barriers to accessing care and health information utilization among college students and young adults (18–39 years) were identified [1]. While these models are not exclusive to preventive services, they provide a foundation for understanding barriers that impede preventive care utilization. A review found that although most students experience significant health risks (e.g., stress, sexual activity, poor diet, substance use), only a minority utilize preventive services [1]. Of enrolled students, only approximately 32% accessed campus health services annually, and only about 15.6% of those visits were for preventive care [1]. Lack of access and awareness, cost, and fear were all aspects that contributed to reduced preventive healthcare engagement. There were several barriers that were identified as precluding this population from taking advantage of preventive healthcare.

Structural and Logistical Barriers

Cost and Insurance Coverage

Insurance status is closely tied to preventive care uptake among young adults. A national survey found that young adults with health insurance were significantly more likely to receive basic preventive services than uninsured peers, yet even insured students underuse services as recommended [2]. Cost remains a barrier even for insured students due to copayments, out-of-pocket expenses, and confusion about coverage scope.

Time Constraints and Convenience

Time constraints are a significant barrier to preventive healthcare. College students often have full schedules that include academics, extracurricular activities, and work. Research on influenza vaccination uptake found that students cited limited time and convenience as reasons for not obtaining vaccines, reflecting challenges in integrating preventive care into busy academic schedules [3]. Clinic hours or appointment requirements can often conflict with academic or work responsibilities. Constraints such as these can also impact other preventive services, compounding barriers.

Access and Awareness of Services

Poor awareness of available preventive services is another barrier. In reproductive health studies, knowledge of available services was critical. Students lacking such knowledge were less likely to engage in care, particularly male students [4]. Similarly, research on HPV vaccination shows that not knowing where to obtain the vaccine and the absence of proactive provider recommendation impede uptake among college students [5]. Preventive services are not readily available and accessible to this demographic.

Psychosocial and Perceptual Barriers

Perceived Vulnerability and Risk

College students have been exposed to environments that shape their healthcare experiences. Avoidance of healthcare settings due to negative past experiences or underlying cognitive patterns can hinder preventive care seeking. Additionally, they often believe they are invulnerable to health risks, which reduces perceived need for preventive services. This perceived invulnerability is documented in healthcare-seeking literature, where students delay care because health concerns are not viewed as serious [1]. An inaccurate perception of vulnerability and risk can also influence the engagement in preventive health services.

Fear and Stigma

Fear related to preventive procedures and health outcomes can deter students. Influenza vaccine studies reported fear of side effects and negative attitudes toward vaccination as obstacles to uptake [3]. Additionally, stigma, particularly around mental health services, limits engagement with prevention-oriented counseling or screening, with students identifying stigma and discomfort as significant barriers [6]. Research suggests that early maladaptive schemas and fears of institutional betrayal contribute to avoidance behaviors that deter students from routine check-ups and preventive screening [7]. Stigmas associated with preventive care, as well as fear of engaging in associated services, can lead to reduced prevention services engagement.

Social Influences and Norms

In addition to stigmas, negative social influence

from peers or lack of support structures also affects preventive health behavior. In vaccine adoption contexts, negative peer influence contributed to reduced uptake, demonstrating how social norms can discourage preventive actions [3]. Social influence as well as socially constructed norms of that demographic do not necessarily facilitate preventive healthcare actions.

Health Literacy and Knowledge Gaps

Knowledge gaps regarding available services and the importance of preventive care contribute to low utilization. Health literacy, including knowledge of disease prevention and screening guidelines, plays a critical role in preventive care engagement. Many students are unaware that routine screenings and checkups can be accessed through campus health centers or covered by insurance, reinforcing reliance on acute care only [1]. This lack of awareness extends to cancer screenings. A study on colorectal cancer screening among university students found knowledge gaps about cancer risk factors and screening methods, particularly outside medical education tracks, contributing to low screening uptake [8]. Similarly, reproductive health research identified that limited knowledge of available services correlates with lower preventive care engagement, especially among male students [4]. The informational access that knowledge and health literacy afford could be potential means to an end for engaging college age students in preventive health services.

Institutional and Provider-Level Barriers

Lack of Provider Recommendation

Provider engagement is a known facilitator of preventive care. Yet, the absence of active recommendation from a provider can undermine uptake. College-aged students reported that lack of clinician recommendation significantly reduced HPV vaccination engagement, highlighting missed opportunities for preventive counseling in campus health settings [5]. Providers, especially those who operate at the university and campus health settings, are uniquely positioned to help drive an increase in preventive healthcare.

Variability in Screening Practices

Practice variation in college health centers also affects preventive care delivery. Some screenings, such as for intimate partner violence, obesity, and eating disorders, occur less consistently than others, reflecting institutional differences that may create uneven access to comprehensive preventive services [9]. Industry standards and guidelines can influence practice variation, leading to an impact of the utilization of preventive services. There is an opportunity to standardize such practices in an effort to increase preventive healthcare.

Discussion

Barriers to preventive healthcare among college students manifest at multiple levels: individual (time, perceptions, knowledge), interpersonal (social influence, stigma), and systemic (service awareness, provider engagement). These barriers intersect and amplify one another. For example, low health literacy may exacerbate perceptions of invulnerability, while structural service constraints compound knowledge gaps. Psychological factors such as perceived invulnerability and healthcare avoidance intersect with systemic barriers such as insurance gaps and cost. Knowledge deficits amplify these barriers, as students often lack awareness of available preventive services or underestimate their importance. The literature highlights a multifaceted set of limitations to preventive healthcare among college students.

Interventions tailored to student populations should address these multi-level barriers. Such interventions must be holistic, addressing behavioral, practical, and systemic challenges. Educational campaigns integrated into orientation and campus life can correct misconceptions about care access and confidentiality. Policy interventions (*e.g.*, expanded student coverage under parental insurance, subsidy programs) may mitigate financial barriers. Embedding preventive services into routine campus activities, such as wellness fairs or academic coursework, can normalize and facilitate engagement. Additional strategies may include extended clinic hours, targeted health education to improve literacy and risk perception, proactive provider recommendations, and stigma reduction campaigns to normalize preventive care. Technology, such as mobile scheduling platforms and digital reminders, could also mitigate logistical barriers. Such interventions and tools could serve to help reduce deterrents.

Conclusion

College students underutilize preventive healthcare services due to a complex interplay of personal, economic, and systemic barriers. Improving preventive healthcare engagement among college students requires understanding the diverse barriers that deter service utilization. Structural constraints, psychosocial perceptions, knowledge gaps, and variability in provider practices collectively hinder preventive care uptake. Increased health education, improved insurance accessibility, and targeted intervention to combat stigma and avoidance are critical to improving preventive care usage. Recognizing these barriers in young adult populations will not only improve individual health outcomes but also strengthen long-term health engagement as students transition into full adulthood. Addressing these deterrents through coordinated institutional policies, student-centered health promotion, and evidence-based interventions is essential to optimize preventive health outcomes during this pivotal stage.

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This article does not contain any studies with human or animal participants. There are no human participants in this article and informed consent is not required.

Data availability statement

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Authors' contributions

CH solely conceived and designed the manuscript, conducted the research, analyzed and interpreted data, and wrote the manuscript.

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HEALTH PROMOTION

Cost-Benefit Analysis of Increasing the Exclusive Breastfeeding Rate in Italy

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Keywords

Cost • Breast feeding • Otitis media • Gastroenteritis • Respiratory disease

Summary

Introduction. *Exclusive breastfeeding (EBF) is widely regarded as the optimal method for feeding newborns. While existing literature primarily emphasizes the medical benefits, such as enhanced disease resistance and improved health indicators, this paper proposes a conservative cost-saving exercise of exclusive breastfeeding during the first five months of an infant's life.*
Methods. *Based on the EBF rates in Italy for 2019, the last year with data unaffected by the COVID-19 pandemic, we carried-out a conservative cost-saving exercise considering otitis media, gastroenteritis, and respiratory diseases, applying the methodology proposed by Weimer et al. (2001) and Coco (2007). Cost of hospitalization in case of complications or infant death were not included in the analysis.*
Results. *The total savings considering all three simulations combined under different EBF rate scenarios range from a minimum of € 10,5 million (EBF rate of 40%) to a maximum of € 33.7 million (EBF rate of 71%). Moreover, these estimated savings increase when the cost of formula milk is included.*
Conclusion. *Estimates provided in this work are very conservative. Nonetheless, they pointed out important savings due to increasing EBF rates. Policies such as the Baby-Friendly Hospital and the Baby-Friendly Community Initiatives promoted by United Nations International Children's' Emergency Fund and the World Health Organization are valuable tools to improve EBF and we highly recommend their adoption more widely in Italy.*

Introduction

Since the mid-20th century [1], the popularity of formula milk has surged, reaching significant shares in infant feeding. In the most industrialized countries, the percentage of exclusive breastfeeding (EBF) at six months was less than 30%. However, this trend has gradually reversed, and EBF has become more prevalent. This shift is attributable to various factors, including international organizations like United Nations International Children's' Emergency Fund (UNICEF), which disseminated guidelines to increase EBF rates, governments that adopted these recommendations, and individual healthcare providers who implemented national guidelines.
The rationale for promoting EBF is well-founded. Research has demonstrated that EBF is associated with better health outcomes for newborns, even in critical situations such as extremely premature infants [2, 3]. In the short term, EBF is linked to lower rates of diarrhea, respiratory infections, ear infections, bacterial meningitis, urinary tract infections, necrotizing enterocolitis, sudden infant death syndrome, diabetes, ulcerative colitis, lymphomas, allergies, digestive diseases, and otitis media. Additionally, EBF has been shown to enhance cognitive abilities [1].
EBF also benefits maternal health [4]. Studies have observed that EBF is associated with lower rates of ovarian cancer, premenopausal breast cancer, and type 2 diabetes. Furthermore, EBF has been linked to improved cardiovascular health and a reduced incidence of postpartum depression. Notably, mothers who practiced EBF weighed eight kilograms less than other mothers six years postpartum [5].
Given these numerous benefits, it is recommended to practice EBF for the first six months of an infant's life and to continue breastfeeding [6] though not exclusively, for the next eighteen months. In fewer than 5% of cases, breastfeeding is not recommended due to specific maternal conditions such as drug use, chemotherapy, HIV positivity, or other illnesses [7].
Despite the strong recommendations for EBF, many mothers choose not to practice it even when they are able to. The primary reasons for the decline in EBF rates include aggressive marketing by formula milk producers, lack of support from family members, insufficient medical knowledge, and inadequate hospital policies. Additionally, cultural factors, work environments, religious beliefs, and general societal attitudes also play a role.
It is worth noting that the reduction in EBF rates has predominantly affected developed countries. Studies have shown a negative correlation between EBF and development [8]. Additionally, macroeconomic factors such as investments in public health services, the presence of women in parliament, the availability of dairy products, investments in family support, maternity

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leave policies, and opportunities for part-time work for women all influence EBF rates.
In the past, several studies have illustrated the advantages of increasing EBF rates. Some of these studies performed cost-benefit analyses to investigate the potential impact of higher EBF rates on communities. This approach is essential because focusing solely on the medical aspects does not provide a complete understanding of the phenomenon.
Several international studies have quantified the costs associated with low EBF rates, including works by Weimer (2001) [9], Coco (2007) [10], and Quesada (2020) [8]. In Italy, such studies are limited, and there is a lack of recent field research (Bonati, 1998) [11].
The purpose of this paper is to address this gap. It aims to present EBF rates for 2019, the last year with data unaffected by the COVID-19 pandemic, and to propose a conservative cost-saving exercise, considering otitis media, gastroenteritis, and respiratory diseases.

Methods

The base year for this study is 2019, the last year with available data unaffected by the COVID-19 pandemic. Simulations are based on data concerning newborns in 2019. For other statistics, including medical data (such as morbidity rates) and economic data, 2019 records were used when available. If 2019 data were not available, the closest available data were chosen, with each source, year, and selection rationale specified in detail.
For the simulation, this study applied the methodology proposed by Weimer (2001) [9] and attempted to replicate the study conducted by Coco (2007) [10].
Complications, hospitalizations (except for respiratory diseases) and infant mortality were excluded leading to deliberately conservative estimates.

Otitis Media

Otitis media is an infection that predominantly affects newborns and infants. It is estimated [12] that more than 60% of children under three years old have had this infection at least once, and 25% have had it more than once. Existing databases do not report the exact number of affected infants in Italy or the proportion of those exclusively breastfed (EBF) versus the rest of the population. However, literature indicates that this infection affects fewer infants who are EBF up to six months, approximately 26% [8].
Combining these proportions with the 2019 newborn data in Italy (420,000) and the EBF rate at 4-6 months (23,6%) and considering that 25% [13] of these infants develop the disease compared to 53% among non-EBF infants, an increase in EBF rates would lead to a decrease in the occurrence of otitis media. To analyze the impact of increased EBF rates, we replicate the methodology used by Coco (2007) [10].
This paper first analyzes the direct and indirect costs, estimates them for each case, and finally proposes the overall result.

Direct costs:
- Medical check-up: between € 50 and € 100, with an average value of € 75 assumed for each case, considering only one visit without complications.
- Drug cost: estimated at € 3,27 per treatment.

Indirect costs:
On average, 5,6 working hours are lost per case, with each hour valued at € 17,12, totaling € 95,86.
Additional costs: € 13,95 for babysitting, daycare, trips to the doctor, parking fees, and other related expenses (in this case the values included in Coco, 2007 [10] are implemented; the cost has been actualized to 2019 ($ 15,87) and this value has been converted in euro).
This research includes various costs, both direct and indirect. The cost of therapy is standardized worldwide, allowing us to refer to medical treatments in Italy, considering the cost of the antibiotic amoxicillin and referring to the Italian Society of Paediatric Infectious Diseases tables [12, 14].
The cost of each working hour is calculated based on the gross annual income of € 29,601 [15] and 1,710 working hours per year [16].
It is worth noting that this simulation adopts a conservative approach, assuming each episode of otitis media is successfully treated without further complications requiring additional medical checks, hospitalizations, or stronger drug prescriptions. The total cost of each episode is calculated to be € 189,16.

Gastroenteritis

Gastroenteritis refers to inflammatory episodes of the gastrointestinal tract, causing diarrhea, vomiting, or abdominal cramps. These episodes can have various causes; however, modern literature indicates that Rotavirus is the primary cause in newborns. In this analysis, the authors follow the approach outlined by Weimer (1999) [17]. This simulation focuses on episodes characterized by three or more instances of diarrhea occurring within 24 hours. Additionally, the analysis considers only infants in their first six months, during which scientific literature has found a 29% probability of gastroenteritis in EBF infants compared to a 71% probability in non-EBF infants.

Respiratory Diseases

Respiratory diseases are a significant class of illnesses affecting newborns. Due to their prevalence, scientists have focused on investigating whether different breastfeeding practices impact the incidence of these diseases. A study by the University of Padua found that respiratory diseases were the third most common reason for emergency room visits, accounting for 10% of all visits, and this percentage rose to 25% for more severe cases [18, 19]. According to Quesada et al. (2020) [8], in Spain in 2014, non-EBF newborns had a 37% higher chance of experiencing respiratory diseases compared to 25% for EBF infants. Subsequent studies, including those by Frank et al. (2019) [20] and Pandolfi et al. (2019) [21], also reported higher percentages of respiratory diseases among non-EBF infants.

Given the specific nature of these diseases, the methodology used in previous sections was adapted to include the cost of hospital recovery. Using the number of newborns in Italy, the percentages reported by Quesada [8], and data from the hospital services price list, the authors estimate the direct cost to be € 459 (for ordinary recovery of less than one day) and indirect costs as in the previous simulations.

Direct cost of formula milk

Compared with EBF, formula milk needs the purchase of a product. Considering that at two and a half months a newborn needs at least 150 ml of milk five times a day, in five months (151 days in the shortest scenario, January-May) it will be 113,25 lt. consumed. The preparation of 1 lt of milk requires 132 gr of formula milk.
The closest year it was possible to estimate the price was the 2022 with an average of the price of formula milk equal to 21,76 €/kg [23]. Considering all these data it emerges that the direct cost in formula milk is € 298,43 per newborn in the first 5 months.

Sensitivity analysis

The total robustness of the analysis can be tested via a one-way sensitivity analysis on the most optimistic simulation where EBF is at its maximum of 71%. To do so, it is possible to recreate two opposite scenarios where the incidence of diseases increases or is reduced of 20%. The same applies to the price of formula milk.

Results

In the first row of Tables I, II, and III, the expected number of cases for each disease under study is estimated based on the actual EBF rates at five months of age. These numbers are then multiplied by the estimated cost for each disease, allowing for the calculation of the total costs associated with these diseases during the first months of life for infants in Italy.

Next, different scenarios were hypothesized, characterized by increasing EBF rates up to 71%. This percentage reflects the rate of EBF infants at hospital discharge following delivery [23]. The authors used this upper limit as it represents the maximum percentage observed at any point; typically, this percentage decreases to 65% by the first pediatric screening, usually after the first month.
As illustrated in Table I, if the EBF rate at hospital discharge following delivery were maintained in the subsequent months, the total savings for otitis media alone would amount to € 10.012.349.
Similarly, the gastroenteritis simulation (Tab. II) shows significant cost savings, up to € 15.018.524, if the EBF rate increases to the level observed at hospital discharge.
For respiratory diseases (Tab. III), an increase in the EBF rate would result in substantial cost savings compared to the initial scenario.
The total savings considering all three simulations combined under different EBF rate scenarios range from a minimum of € 10.5 million (EBF rate of 40%) to a maximum of € 33.7 million (EBF rate of 71%).
Finally, Table IV shows that an increase of EBF to the maximum level of 71% would lead to a saving increase of € 56.414.877, if costs of formula milk were considered.
Tables V and VI illustrate the results of the sensitivity analysis. All savings are compared to the initial costs where the EBF has the value of 26%. Scenario A refers to the worst simulation where diseases have an increase of the 20%, as well as the price of formula milk. Whilst scenario B refers to the best simulation where diseases have a decrease of the 20% as well as the price of formula milk.
The results of the sensitivity analysis for the three diseases combined range from € 10,4 million in the worst scenario to € 57 million in the best one.
Similarly, doing the same analysis, the savings from the purchase of the formula milk range from € 49.14 million to € 63,69 million.
Based on our sensitivity forecasts, combined results bring a total amount of savings of 59,51 million in the

Tab. I. Otitis Media Simulation.

% EBF	N. EBF	N. Not EBF	Total cases	Costs	Savings
26%	109.222	310.862	192.062	€ 36.330.524	€ 0
40%	168.034	252.050	175.595	€ 33.215.571	€ 3.114.953
50%	210.042	210.042	163.833	€ 30.990.605	€ 5.339.920
65%	273.055	147.029	146.189	€ 27.653.155	€ 8.677.369
71%	298.260	121.824	139.132	€ 26.318.175	€ 10.012.349

Tab. II. Gastroenteritis Simulation.

% EBF	N. EBF	N. Not EBF	Total cases	Costs	Savings
26%	109.222	310.862	252.386	€ 47.741.424	€ 0
40%	168.034	252.050	227.686	€ 43.068.994	€ 4.672.430
50%	210.042	210.042	210.042	€ 39.731.545	€ 8.009.879
65%	273.055	147.029	183.577	€ 34.725.370	€ 13.016.054
71%	298.260	121.824	172.991	€ 32.722.900	€ 15.018.524

Tab. III. Respiratory Diseases Simulation.

% EBF	N. EBF	N. Not EBF	Total cases	Costs	Savings
26%	109.222	310.862	144.509	€ 66.352.553	€ 0
40%	168.034	252.050	138.628	€ 63.652.158	€ 2.700.395
50%	210.042	210.042	134.427	€ 61.723.305	€ 4.629.248
65%	273.055	147.029	128.126	€ 58.830.025	€ 7.522.528
71%	298.260	121.824	125.605	€ 57.672.713	€ 8.679.840

Tab. IV. Formula milk Simulation.

% EBF	N. EBF	N. Not EBF	Costs	Savings
26%	109.222	310.862	€ 92.770.986	€ 0
40%	168.034	252.050	€ 75.219.638	€ 17.551.348
50%	210.042	210.042	€ 62.683.131	€ 30.087.855
65%	273.055	147.029	€ 43.878.072	€ 48.892.914
71%	298.260	121.824	€ 36.356.108	€ 56.414.877

Tab. V. All diseases sensitivity forecast, when the incidence of diseases is reduced or increases of 20% (scenario A versus scenario B).

Scenarios	N. EBF	N. Not EBF	Costs	Savings
Base	298.260	121.824	€ 116.713.788	€ 33.710.713
A	298.260	121.824	€ 140.056.546	€ 10.367.955
B	298.260	121.824	€ 93.371.030	€ 57.053.471

Tab. VI. Formula milk sensitivity forecast, when the milk formula price is reduced or increases of 20%.

Scenarios	N. EBF	N. Not EBF	Costs	Savings
Base	298.260	121.824	€ 36.356.108	€ 56.414.877
A	298.260	121.824	€ 43.627.330	€ 49.143.656
B	298.260	121.824	€ 29.084.887	€ 63.686.099

worst scenario (A) and € 120,74 million in the best one (scenario B) showing that the economic impact of the increase of EBF to 71% is positive and the only difference is in the magnitude of the positive effect. The robustness analysis shows that the conclusions remained unchanged across all tested scenarios

Discussion

This study conducted a conservative cost-saving exercise, of exclusive breastfeeding (EBF) following methodologies from current scientific literature. Three diseases were included: otitis media, gastroenteritis, and respiratory diseases, considering all babies born in Italy in 2019. The authors estimate that at least € 33.710.713 could be saved if the EBF rate remained constant at 71% (the rate observed when mothers leave the hospital) in the first five months of newborns' lives [23]. In addition, avoided cost of exclusive formula milk would be € 56.414.877.

Studies following the methodology of Weimer (2001) [9] have shown that increasing the EBF rate can significantly reduce costs, sometimes within a short period, even less than a year. In this study, three simulations were conducted for otitis media, gastroenteritis, and respiratory diseases. The simulations began with an EBF rate of 29% and increased to a maximum of 71%. Four different scenarios were estimated for each EBF rate, calculating the presumptive number of cases and the expected incidence rate of each disease, multiplied by the total number of cases in 2019. The total number of expected cases was then multiplied by the costs associated with each disease to estimate the total cost for each scenario. Finally, the estimated savings were calculated by comparing the different scenarios for each EBF rate. For the first two simulations, otitis media and gastroenteritis, a six-month interval was used, the period with the highest morbidity and mortality rates.

These simulations allowed for a conservative cost-saving exercise, estimating the economic savings of increasing the EBF rate in different scenarios. Similar studies conducted in the US in 1998 estimated an expected total savings of $ 3,6 billion [9] Other authors, like Coco (2007) [10], proposed a broader cost-benefit analysis discussing different treatments for otitis media in the US context during 2000 and 2001, directly estimating the costs associated with this disease.

In these studies, data sources varied widely. In Weimer (2001) [9], costs were published by the Agency for Health Care Policy and Research (AHCPR).

The approach proposed by Weimer (2001) [9], is the

first of many studies where the same methodology is adapted to different contexts and data sources. Among these, Quesada et al. (2000) [8], developed four different scenarios: otitis media, gastroenteritis, necrotizing enterocolitis, and respiratory diseases. The context was 2014, and costs were provided by the "Ministerio de Sanidad, Consumo y Bienestar Social," Madrid. Following their analysis, the best scenario estimated savings of € 479.790.646.

Some studies focus on a single disease but analyze the effect of EBF on a sample directly observed by the authors. For instance, Pandolfi et al. (2019) [21], conducted a study based on a pool of 496 patients, all newborns screened at the "Ospedale Bambino Gesù" Children's Hospital in Rome. Analyzing the factors that cause respiratory diseases, they found that the most influential variable in their statistical model (using multivariable logistic regression analysis) was the absence of EBF by the mother.

Two main reasons guided the authors in choosing the methodology for this work. First, in many studies like the work of Weimer (2001) [9], cost estimations in a specific context were already provided by other trusted and well-known institutions. While using such data allows for sophisticated analysis, it also limits the ability to replicate or adapt the research to different contexts. For example, insurance data provided by institutions cannot be modified and must be accepted as they are. Secondly, these studies may raise concerns about the compatibility of various methodologies implemented. As some of the previously cited studies use data from other institutions, comparing them can be challenging or impossible.

In contrast, Coco (2007) [10], proposes a bottom-up approach that considers all parameters in detail, allowing for replication and adaptation of the methodology. Using data from a specific year, it is possible to estimate different values for each simulation, which can then be analyzed in detail.

Due to lack of available data in Italy, morbidity, hospitalization, direct and indirect cost estimations from other countries were used. Despite cost actualization, confounding factors (epidemiologic, services utilization, organizational as well as health policy and national educational and cultural pattern) might influence results and this might be a limitation of this study. Spain and Italy have high cultural affinity and a public healthcare system. The U.S. healthcare system is private insurance-based, with a lot of variability of quality and high costs. All three countries have first level pediatricians, which might influence newborn hospitalization rates while mothers' attitude towards work opportunities after birth delivery might influence costs. Thus, although transferability of EBF cost saving estimation is interesting, it should be cautiously interpreted.

We deliberately excluded complications, hospitalizations (except for respiratory diseases), and infant mortality and assumed that EBF cost is "zero" carrying out a conservative cost estimation, rather than a cost-benefit analysis. The simulation of the savings due to avoidance of exclusive formula milk consumption and the sensitivity forecasts (scenarios A e B) we provide strengthen the validity of our study.

The assumption that EBF cost is "zero" is partially true. In the developed world, breastfeeding is accompanied of several "must-have" products such as like pads, shields, ointment, nursing bras and shirts, pillows, pumps, pump accessories, *etc*. [24] Besides, it is argued that mothers who are breast feeding would need up to 500 extra calories per day [25]. In this framework, the UNICEF and WHO policies to promote EBF like the Baby-Friendly Hospital and the Baby-Friendly Community Initiatives (BFHI and BFCI) are valuable investments. Implementation costs include staff training, policy review and external assessment to achieve UNICEF certification, and depend on the hospital size and technological capacity. Arslanian et al. (2022) estimated BFHI staff training costs in the first year ranging between US$ 7,3-125,4 per birth in the US and between PPP (purchasing power parity) 2,7-6,1 per birth in Mexico [26]. For 1 US$ invested in BFHI implementation, a return on investment of US$49 and AUS$55 were calculated in Indonesia and in Australia respectively [27, 28]. In Italy, the Agency for Health Protection of Bergamo, accredited by UNICEF (in 2017 and renewed in 2023) and active in the BFCI program, successfully increased the EBF rate in 3-month-old babies from 36,6% in 2014 to 64,5% in 2020 [29]. Despite wide consensus on the positive return of the investments in BFHI abroad, no data are available on the implementation cost and the break-even point in Italy, according to our knowledge.

Conclusion

The simulations indicate that increasing the rate of exclusive breastfeeding (EBF) in newborns can lead to significant cost savings. To achieve these savings, the UNICEF and WHO policies BFHI and BFCI should be more widely adopted.

It is important to note that the estimates provided in this work are very conservative and do not include some parameters due to a lack of data. For instance, none of the simulations include the cost of hospitalization in case of complications or infant death. Including such values would make the simulations more accurate; however, the provided results would likely increase in magnitude without altering the final conclusions.

Future research should include these values to provide more precise estimates. Additionally, as more recent data become available from public institutions, updated estimates will be possible. Finally, including more diseases not covered in this study, such as necrotizing enterocolitis, would offer a better representation of the benefits of increasing EBF rates [30, 31].

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Conflicts of interest statement

Non declared.

Authors' contributions

EU and CT collaborated to the Introduction and Discussion sections. EU set the methodology and carried out the statistical analysis.

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HEALTH PROMOTION

Assessing Knowledge, Attitudes, and Practices of Adults Aged 21-62 Regarding Antibiotic Use for Treatment of Upper Respiratory Tract Infections in Children: A multi-country Cross-Sectional Study

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Keywords

Upper respiratory tract infections • Parental knowledge • Antibiotic misuse • Antimicrobial resistance • Self-medication

Summary

Objectives. *Antibiotic resistance is a growing global concern, often driven by inappropriate antibiotic use for viral upper respiratory tract infections (URTIs) in children. This study assessed parental knowledge, attitudes, and practices (KAP) toward antibiotic use and identified influencing factors.*

Study Design. *Multi-country, cross-sectional, web-based study.*

Methods. *From July 2023 to June 2024, adults aged 21-62 years from 9 Arab countries completed a validated online questionnaire. Data were analyzed using descriptive statistics and logistic regression.*

Results. *Of 2,172 participants from 9 Arab-speaking countries, most were highly educated with healthcare backgrounds. While physicians were the main information source, misconceptions persisted-especially regarding antibiotic use for fever and earaches. Higher income and medical training were protective factors. Self-medication was common despite good knowledge.*

Conclusion. *Parental misconceptions regarding antibiotics in pediatric URTIs remain prevalent. Educational interve.*

Introduction

Upper respiratory tract infections (URTIs) are prevalent in children and a major cause of pediatric clinic visits [1, 2]. Children in Germany, for instance, experience an average of 3.4 episodes of the common cold annually during infancy, 2.3 in preschoolers, and 1.1 in school-aged children [3]. URTIs are primarily viral [4-6], making antibiotic treatment ineffective [4, 7]. Antibiotics do not reduce URTI complications significantly [8]. Despite this, unnecessary antibiotic use remains high due to both overprescription and self-medication by parents [9-12].

Antimicrobial resistance (AMR) occurs when microorganisms evolve to resist antibiotics, reducing their efficacy [13, 14]. Antibiotics have been vital in treating bacterial infections since the 20th century, but bacterial resistance emerged in the late 20th century, particularly in intensive care units, where it contributes to numerous deaths annually [15]. Misuse and overuse of antibiotics are significant contributors to the rise of AMR [16-18]. AMR is now one of the top ten global health threats [19]. In 2019, AMR-related deaths totaled 4.95 million, with 1.27 million directly attributed to bacterial resistance [20, 21]. It also imposes a substantial economic burden, raising healthcare costs, affecting international trade, and reducing productivity. Without intervention, AMR could cost the global economy 100 trillion USD by 2050 [21]. The WHO has urged researchers to prioritize AMR in their work [22]. Although new antibiotics offer hope, their effectiveness will be limited without curbing antibiotic misuse [23]. Strict guidelines are essential to prevent misuse and the spread of resistance in healthcare and community settings [14].

Parents often misunderstand the indications for and proper use of antibiotics [24-26]. These misconceptions contribute to the spread of antibiotic resistance [16-18]. Parental knowledge and attitudes significantly impact antibiotic prescribing, as physician decisions are often influenced by the desire for parental satisfaction [27]. If parents expect antibiotics to improve their child's condition, they may pressure doctors for prescriptions, leading to overuse [28]. While numerous studies have assessed the knowledge, attitudes, and practices (KAP) regarding antibiotic use in treating URTIs in children, there remains a gap in qualitative research,

particularly in some countries [29]. High-quality studies are needed to identify the issues parents face in managing URTIs.

This study aims to assess the KAP of adults aged 21-62 years regarding antibiotic use for URTIs in children and identify factors contributing to antibiotic overuse. It also explores the common misconceptions and beliefs surrounding antibiotic use and examines how socioeconomic and cultural factors influence overuse.

Methods

Study Design and Setting

This multi-country cross-sectional study was conducted across all 22 Arab-speaking countries (including Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, the United Arab Emirates, and Yemen) between 23 July 2023 and 05 June 2024. The questionnaire was distributed electronically across the Middle East and North Africa (MENA) region to ensure a broad representation of the Arab population.

The aim was to estimate public knowledge, attitudes, and practices (KAP) regarding the use of antibiotics in children with upper respiratory tract infections (URTIs). Given the online nature of the study, participants were recruited using a convenience and snowball sampling strategy. The questionnaire was developed using Google Forms and distributed via social media platforms (such as WhatsApp, Facebook, and LinkedIn) and professional networks. The invitation included a brief cover letter explaining the study's objectives, the voluntary nature of participation, and a statement ensuring anonymity and data confidentiality. To ensure a wider reach across most of Arab countries, collaborators in different regions helped disseminate the link within their respective local communities and networks.

Clinical Trial Registration

As this was a non-interventional, observational study, clinical trial registration was not applicable.

Study Population

The study population consisted of adults in Arab speaking countries aged 21 to 62 years who were admitted on a random basis. Estimating the target population of adults aged 21 to 62 years across Arabic-speaking countries is a complex endeavor, necessitating a rigorous approach to derive a reliable estimate. According to recent demographic estimates, the total population of the Arab-speaking countries in 2022 is approximately 464 million individuals [30]. Based on the age distribution data, it is projected that adults within the 21 to 62-year age range constitute roughly 45% of this total population [46]. This leads to an estimated population of approximately 208 million adults within this specific age group.

Eligibility Criteria

Inclusion criteria:

- Adults aged 21 to 62 years residing in Arabic-speaking countries.
- Able to read and understand Arabic.
- Provided e-informed consent by agreeing to a mandatory consent statement at the beginning of the online questionnaire.
- From either medical or non-medical educational/professional backgrounds.

Exclusion criteria:

- Individuals younger than 21 or older than 62 years (to ensure a working-age adult sample and minimize age-related bias).
- Participants residing outside the targeted Arab countries.
- Individuals who did not provide informed consent.
- Incomplete survey submissions.

Participant Selection and Screening

To maintain scientific rigor in a virtual environment, the online questionnaire employed an automated screening mechanism using survey skip logic. This "digital gatekeeping" ensured that the inclusion and exclusion criteria were strictly enforced from the outset; participants were required to complete mandatory fields regarding their age, country of residence, and informed consent. Any individual falling outside the specified age range of 21-62 years, residing outside the Arab countries, or declining to provide informed consent was immediately redirected, and their session was terminated. This systematic filtering process, which also automatically excluded incomplete submissions, ensured that all analyzed responses met the predefined study protocol without the need for person-to-person selection.

Sample Size Calculation

Hypothesis 1: Sample Size for a Defined Population

To determine the appropriate sample size for a known target population of approximately 208 million individuals, we used Cochran's formula with a finite population correction (FPC) [50]. A confidence level of 95% was selected, corresponding to a Z-score of 1.96, with a margin of error of ± 5% and an estimated response proportion (P) of 0.5, which maximizes variability. After applying the finite population correction to adjust for the large but finite population size, the resulting minimum required sample size was approximately 384 individuals.

Hypothesis 2: Sample Size for an Indeterminate (Infinite) Population

In scenarios where the population size is unknown or considered infinite, Cochran's standard sample size formula without the finite population correction is applied [50]. Using the same confidence level (95%), margin of error (± 5%), and estimated proportion (P = 0.5), the calculated minimum sample size was also approximately 384 individuals. This consistency supports the adequacy of the calculated sample size under both known and indeterminate population assumptions.

Minimizing Bias in Data Collection

Given the potential for bias in self-administered online surveys and the public health importance of antibiotic misuse, a standard confidence level of 95% was adopted in accordance with common practice in cross-sectional public health research. To further address potential response bias, incomplete questionnaires, and variability in response quality, the calculated minimum sample size was doubled, yielding a final target sample size of approximately 768 participants. Increasing the sample size beyond the minimum requirement was intended to enhance representativeness, improve statistical power, and increase the precision of estimates within a large and heterogeneous population across multiple countries.

Study Procedures

Participants were recruited through a public online campaign using Google Forms. The survey link was disseminated via social media platforms (Facebook, WhatsApp, and Twitter), parenting groups, university networks, and healthcare-related online communities across the Arab countries. No financial incentives were offered. To reduce selection bias, the link remained open for 5 months and was shared periodically across diverse community groups.

The questionnaire used in this study was adapted from a previously validated tool developed by Panagakou et al. (2011) for a similar cross-sectional study conducted in Greece [31]. The adapted version was translated into Arabic and subsequently validated by Zyoud et al. (2015) in a Palestinian population to ensure linguistic and contextual appropriateness [33]. It consisted of structured items covering sociodemographic, knowledge, attitudes, and practices related to antibiotic use and resistance in pediatric URTIs. Participants were asked if they had a child who had previously suffered from upper respiratory tract infections (URTIs) to assess their prior experience and subsequent behavior regarding antibiotic use. This variable refers to the history of infection rather than a diagnosis at the time of participation.

Data Analysis

Data were entered using Microsoft® Excel and analyzed with Stata 14.2 (Stata Corp LP, College Station, TX, USA). Descriptive statistics were reported as means ± standard deviations for continuous variables and frequencies (percentages) for categorical variables. Chi-square tests assessed associations between categorical variables. Stepwise logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for predictors of incorrect responses to questions such as "Are antibiotics the first-line treatment for URTIs in children?" Independent variables included age, sex, urban/rural residence, education, income, health insurance status, medical field affiliation, parenthood, and healthcare access. A *p-value* < 0.05 was considered statistically significant. All independent variables, including socio-demographic data (such as age, gender, educational level, and income) and professional background, were self-reported by the participants using the structured online questionnaire.

Although stepwise models have limitations such as potential overfitting, its use was appropriate in this hypothesis-generating context and allowed identification of the strongest predictors. The results are interpreted cautiously, and future studies should validate these findings using theory-driven models.

Given the heterogeneity of the participating Arab countries in terms of culture, healthcare access, and insurance systems, we examined country-level differences by introducing country dummy variables during preliminary regression testing. However, these variables did not materially change the effect sizes or significance of the main predictors and were therefore excluded from the final parsimonious model. Nonetheless, country-level distributions are reported, and interpretation acknowledges contextual variability.

Data Handling

All data were entered as recorded, without alteration. Each entry was double-checked against the original questionnaire to resolve discrepancies. The original unedited data were preserved to ensure integrity. Coding, entry, and analysis were performed by the research team to ensure data fidelity and reproducibility. Ethical approval was obtained prior to data collection.

Results

Demographic Characteristics

A total of 2,172 adults from Egypt, Jordan, Yemen, Iraq, Saudi Arabia, Kuwait, Morocco, Palestine, and Sudan completed the survey. The mean age was 31 ± 9 years (range: 21-62). Most participants resided in urban areas (78.91%), held university-level education (79.97%), and reported moderate family income (77.90%). More than half (53.18%) had a background in healthcare. Approximately 35.05% lacked health insurance, 14.96% reported poor access to healthcare, and 41.90% had children (Tab. I). Although the required sample size was 768, the actual collected data reached 2,172 thereby substantially increasing the statistical power of the study. Participants were classified into six groups (Tab. II) based on combined family income and healthcare-related education or employment: (Group 0) Low family income level and no working or studying in a medical field, (Group 1) Low family income level and working or studying in a medical field, (Group 2) Moderate family income level and no working or studying in a medical field, (Group 3) Moderate family income level and working or studying in a medical field, (Group 4) High family income level and no working or studying in a medical field, (Group 5) High family income level and working or studying in a medical field.

General Knowledge

The primary source of antibiotic-related information was physicians (67.68%), followed by pharmacists (17.36%), with similar patterns across groups (Tab. III).

Tab. I. Demographic profile (n = 2,172).

Characteristics	%	N
Female	79.93%	1,736
Age		
Mean ± s.d. range (min-max)	30.97 ± 8.88 21-62	
Habitants of Town	78.91%	1,714
Country		
Jordan Yemen Egypt Iraq Sudan Palestine Kuwait Morocco Saudi Arabia	23.11% 20.86% 18.37% 17.82% 13.77% 2.49% 1.7% 0.97% 0.92%	502 453 399 387 299 54 37 21 20
Educational status		
Postgraduate education High school University stage	13.90% 6.12% 79.97%	302 133 1,737
Family income level		
High Moderate Low	9.35% 77.90% 12.75%	203 1,692 277
Insured (Government health insurance or Private health insurance)	64.96%	1,411
Access to health care system (medium-very good)	85.04%	1,847
Work or study in medical field	53.18%	1,155
Children	41.90%	910
Having a child that suffered from URTIs (i.e. colds, ear, asthma, etc.)	6.72%	146

Tab. II. Distribution of subjects interviewed in the six groups.

Groups	N	%
Group 0	116	5.34
Group 1	161	7.41
Group 2	821	37.80
Group 3	871	40.10
Group 4	80	3.68
Group 5	123	5.66

When asked whether antibiotics are the first-line treatment for pediatric upper respiratory tract infections (URTIs), 66.62% answered correctly (*i.e.* disagreed). Group-level differences were statistically significant ($p<0.001$), with the highest accuracy in participants with both high income and medical knowledge (Group 4: 92.50%; Group 5: 92.68%) and the lowest in Group 0 (51.72%). Respondents with medical backgrounds more accurately identified antibiotics from a drug list ($p<0.001$). Misidentification was more common among participants without medical training (Fig. 1).

A large majority (87.06%) acknowledged the potential side effects of antibiotics. Additionally, 69.61% disagreed with initiating antibiotics solely due to high fever, with significant differences across groups ($p=0.010$) (Tab. IV).

The most commonly cited risks were antibiotic resistance (75.37%) and weakened immunity (74.49%). Group 5 showed the highest awareness of resistance risk (92.68%). About 74.35% recognized that most respiratory infections are viral in origin and do not require antibiotics (Tab. V).

Logistic regression identified high income (OR=0.15, 95% CI: 0.09-0.25), university education (OR=0.66, 95% CI: 0.53-0.83), and medical training (OR=0.72, 95% CI: 0.60-0.87) as protective factors against the misconception that antibiotics are the first treatment for URTIs (Tab. VI). Age, sex, and parenthood were not significant predictors ($p>0.06$).

Similarly, predictors of awareness about antibiotic resistance included high income (OR = 0.44, 95% CI: 0.29-0.67) and medical background (OR = 0.68, 95% CI: 0.56-0.83). Other variables were not statistically significant and were excluded from the final model (Tab. VII).

Attitudes

Regarding symptoms, 39.81% of respondents reported fever and 34.07% reported earache in children as reasons to use antibiotics, often exceeding 70% usage in these cases (Tab. VIII).

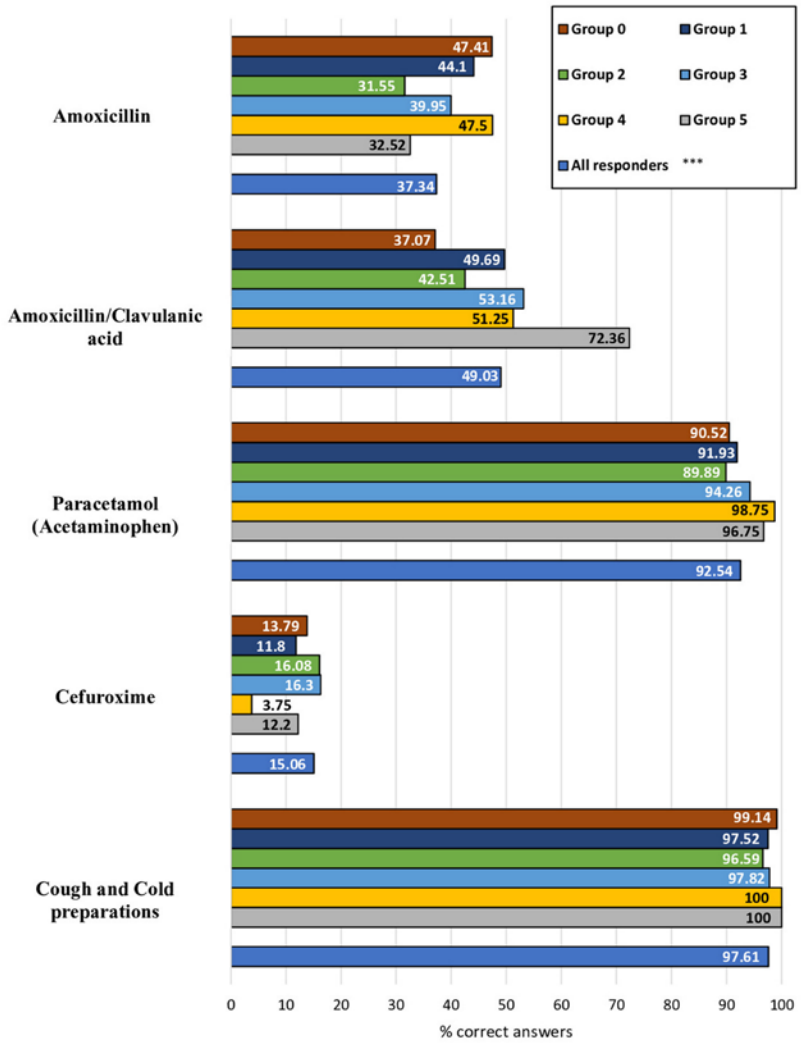
Pediatricians were consulted for fever (73.02%) and earache (68.28%). When asked what medications they expected for pediatric URTIs, 78.59% expected analgesics/antipyretics, 51.93% antitussives, and 49.82% antibiotics (Fig. 2).

Antibiotics were sometimes used by self-administration for reasons such as prior prescriptions (57.69%), pharmacist recommendations (33.66%), perceived mild illness (29.42%), time/cost barriers (27.39%), and non-

Tab. III. Percentage of respondents reporting their primary source of information on the appropriate use of antibiotics, overall and by group.

	Physician	Pharmacist	Radio, Television and internet	Scientific newspaper and magazine	Others	Relatives and friends
Group 0	62.07	16.38	10.34	2.59	2.59	6.03
Group 1	62.73	12.42	6.21	7.45	8.70	2.48
Group 2	62.36	23.02	5.72	3.29	1.71	3.90
Group 3	72.33	14.70	3.79	3.79	3.21	2.18
Group 4	73.75	13.75	7.50	0.00	5.00	0.00
Group 5	78.05	8.13	11.38	0.81	1.63	0.00
All	67.68	17.36	5.62	3.50	2.99	2.85

Fig. 1. Which of the following do you think is an antibiotic? Percentage of correct answer.



professional advice (7.32%) (Tab. IX).

A total of 84.53% agreed that antibiotics are often overused, with significant group differences ($p < 0.001$) (Tab. X).

Practices

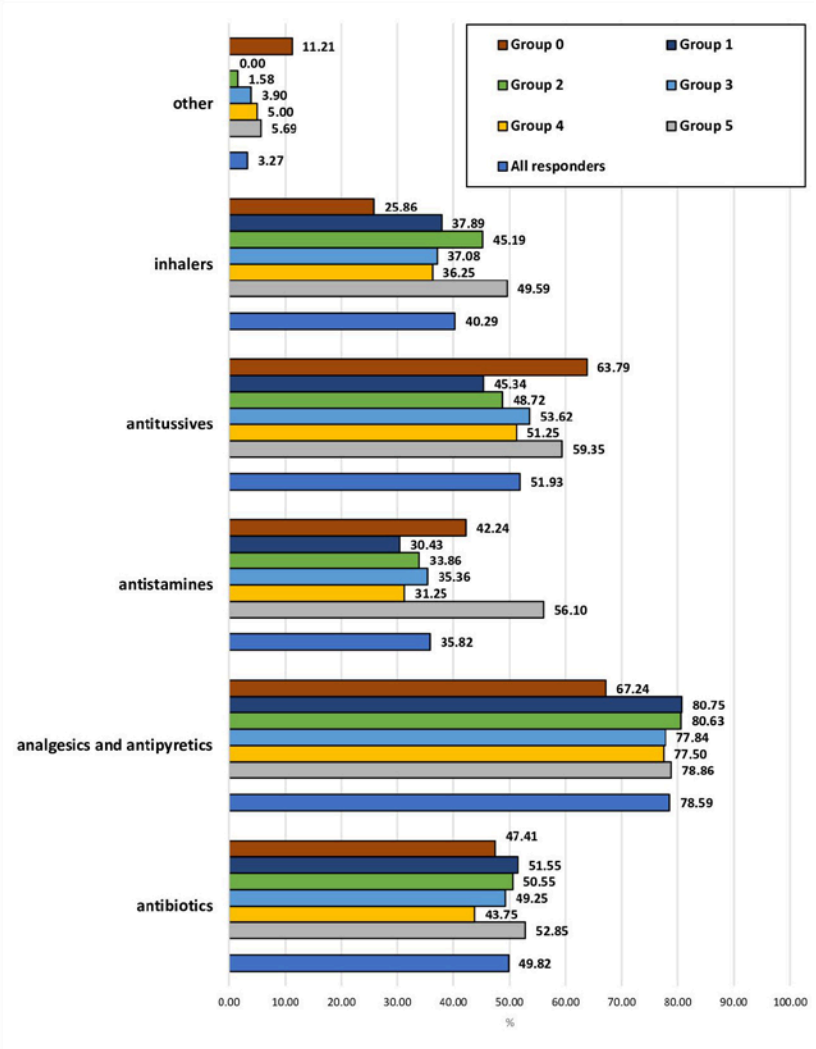
Approximately 42.03% of participants consistently asked pediatricians whether antibiotics were needed before administration. Only 21.69% expressed opposition to unnecessary prescriptions, with significant variation across groups ($p<0.001$). Over 50% reported consistent adherence to the pediatrician's instructions when administering antibiotics (Tab. XI).

Discussion

This study assessed adult knowledge regarding antibiotic use for pediatric URTIs across nine Arab countries (Jordan, Yemen, Egypt, Iraq, Sudan, Palestine, Kuwait, Morocco, Saudi Arabia). The predominantly female sample (79.93%) aligns with previous research [31-33]. Participants were grouped by socioeconomic and educational status to explore impacts on knowledge. Physicians were the main information source, consistent with earlier findings [31, 33-39, 42]. Two-thirds recognized that antibiotics are not the first-line treatment, with the highest awareness among those with higher income and medical backgrounds, similar to findings from studies conducted in Oman, Greece, Malaysia, Saudi Arabia, and Palestine [37]. Awareness of side effects was high; 69.61% opposed using antibiotics solely for fever, consistent with existing literature [31, 33, 35, 38, 40]. However, a Jordanian study found that over two-thirds believed fever warranted antibiotics [36], and 37% of Turkish parents thought viral infections could be treated with antibiotics [41]. Regarding risks, 75.37% identified antibiotic resistance as a major concern, aligned with international reports [31, 33, 35-40]. High education and reliance on healthcare professionals likely contribute to these positive outcomes.

Attitudes: Despite sound knowledge, many participants

Fig. 2. participants expectations for Pediatrician-Recommended Treatments for Upper Respiratory Infections: Affirmative Response Percentage.



believed antibiotics were necessary for fever (39.81%) and earache (34.07%), with over 70% seeking pediatric consultation for such symptoms–mirroring findings from Oman and Saudi Arabia [42, 43]. Expectations for medication during URTI episodes included analgesics/antipyretics (78.59%), antitussives (51.93%), and antibiotics (49.82%). Elbur et al. reported higher antibiotic expectations (>50%) but lower for analgesics (33%) and antitussives (25.8%) [43]. Self-medication was often influenced by prior prescriptions (57.69%), pharmacist recommendations (33.66%), and mild illness perception (29.42%), similar to findings from UAE and Saudi Arabia studies [33, 43-45]. Additional reasons included time and financial constraints, as well as non-professional advice. A majority believed antibiotics are overused, with significant group differences (G3: 95.93%; $p<0.001$), supporting prior findings [31, 35, 43]. Higher socioeconomic and educational status correlated with reduced self-medication [47-49].

Practices: Only 42.03% regularly questioned the necessity of antibiotics, comparable to 30% in Greece [31] but lower than in Cyprus and Jordan [35, 36]. Most participants reported adherence to pediatrician instructions, reflecting strong trust in healthcare providers, with similar adherence rates documented in Malaysia, Palestine, and Saudi Arabia [33, 37, 39].

Limitations: Despite the diverse participation from various Arab countries, several limitations must be acknowledged. First, the study relied on self-reported data, which may introduce social desirability bias. Additionally, the retrospective nature of questions regarding children's past infections may have led to recall bias, potentially affecting the accuracy of participants' responses.

Regarding the methodology, a significant limitation is the inability to determine a formal response rate; since the survey was distributed via social media using snowball sampling, the total number of individuals reached (the denominator) remains unknown. Furthermore, while the study covered nine countries, the uneven sample size distribution and the lack of a uniform denominator prevented us from performing reliable comparative

Tab. IV. Percentage of participants with knowledge regarding upper respiratory tract infections in children, overall and by group.

	Strongly agree/agree	Uncertain	Disagree/strongly disagree
All children should be given antibiotics when they have a fever (high temperature)			
All	27.67	2.72	69.61
Group 0	31.03	0.86	68.11
Group 1	24.85	3.73	71.42
Group 2	29.1	3.78	67.12
Group 3	27.9	2.18	69.92
Group 4	28.75	0	71.25
Group 5	16.26	1.63	69.61
Children with flu symptoms get better faster when they are given antibiotics			
All	32.91	2.81	64.28
Group 0	38.79	4.31	56.9
Group 1	32.92	3.1	63.98
Group 2	40.32	2.68	57
Group 3	27.21	2.99	69.8
Group 4	31.25	3.75	65
Group 5	19.51	0	80.49
Respiratory infections re often caused by a virus and do not require antibiotics			
All	74.35	4.74	20.91
Group 0	77.59	0.86	21.55
Group 1	81.99	6.21	11.8
Group 2	74.06	4.99	20.95
Group 3	74.51	4.59	20.9
Group 4	65	0	35
Group 5	68.29	8.95	22.76
Antibiotics do not have side effects			
All	9.25	3.69	87.06
Group 0	16.38	2.59	81.03
Group 1	12.42	2.49	85.09
Group 2	8.52	3.78	87.7
Group 3	8.96	3.67	87.37
Group 4	7.5	6.25	86.25
Group 5	6.5	4.07	89.43
Excessive use of antibiotics reduces their effectiveness and leads to bacterial resistance			
All	77.72	2.76	19.52
Group 0	75	0	25
Group 1	85.72	0.62	13.66
Group 2	79.41	1.71	18.88
Group 3	76.58	3.9	19.52
Group 4	71.25	0	28.75
Group 5	70.73	8.94	20.33
Using antibiotics can prevent complications from upper respiratory infections			
All	65.83	6.08	28.09
Group 0	72.41	2.59	25
Group 1	76.4	4.35	19.25
Group 2	65.65	7.92	26.43
Group 3	64.06	4.94	31
Group 4	60	3.75	36.25
Group 5	63.41	8.94	27.64
Scientists will be able to produce antibiotics capable of treating the types of bacteria that are resistant to the antibiotics currently available			
All	66.58	13.95	19.47
Group 0	69.83	14.66	15.52
Group 1	68.33	18.01	13.66
Group 2	66.86	15.35	17.79
Group 3	65.45	11.6	22.96
Group 4	81.25	13.75	5
Group 5	57.72	15.45	26.83

Tab. V. Percentage of respondents reporting perceived risks associated with antibiotic use, overall and by study group.

	All	Group 0	Group 1	Group 2	Group 3	Group 4	Group 5
Harming the liver	43.00	48.28	49.69	45.19	39.38	48.75	36.59
Harming the kidney	48.80	46.55	49.07	49.70	49.60	48.75	39.02
Hurting the stomach	38.67	42.24	36.02	38.73	38.81	37.50	38.21
Increased resistance of bacteria to antibiotics	75.37	75.00	83.85	70.16	76.12	77.50	92.68
Allergies	31.49	30.17	33.54	27.77	33.52	38.75	35.77
Weakened immune system	74.49	80.17	73.29	75.03	73.94	63.75	78.05
It has no risk	0.51	0	0.00	0.24	0.46	6.25	0.00
Other	10.08	4.31	8.07	7.43	12.28	6.25	22.76

Tab. VI. Logistic Regression Analysis of Demographic Variables Predicting Antibiotic Preference for Child Upper Respiratory Infections.

	OR	St. error	*p*	IC 95%
Family income level	0.15	0.04	0.000	0.09-0.25
Work or study in medical field	0.72	0.07	0.001	0.60-0.87
Educational status	0.66	0.08	0.000	0.53-0.83
Health insurance	0.79	0.08	0.012	0.64-0.95
Original residence	0.79	0.09	0.037	0.63-0.99
Access to health services	0.78	0.10	0.058	0.61-1.01

Tab. VII. Logistic Regression Analysis of Demographic Variables Predicting Drug Resistance Risk: Negative Response.

	OR	St. error	*p*	IC 95%
Family income level	0.44	0.09	0.000	0.29-0.67
Work or study in medical field	0.68	0.07	0.001	0.56-0.83
Educational status	0.79	0.10	0.051	0.62-1.00

analyses between specific nations or regions.

It should also be noted that while preliminary models adjusted for country-level effects using dummy variables – showing no significant impact on the results – inherent differences in healthcare systems, national guidelines, and cultural prescribing norms across the Arab world may still influence KAP outcomes.

Finally, Future studies should aim to include more diverse socio-economic groups to ensure a more comprehensive understanding of antibiotic use across all segments of the population. Moreover, subsequent research should explore country-specific determinants in greater depth to identify unique cultural and regulatory influences on parental behaviors.

Conclusion

This cross-sectional study assessed adults' knowledge, attitudes, and practices regarding antibiotic use for pediatric URTIs across diverse Arab populations. While healthcare professionals are the primary information source and antibiotic overuse is recognized, misconceptions about antibiotic necessity for fever and earache persist, with some self-medication reported. Compliance with medical advice remains generally high. These findings highlight the crucial role of healthcare providers and the urgent need for targeted interventions to improve public understanding and behavior. Further qualitative and longitudinal research is recommended, including underrepresented Arab countries. Addressing antibiotic resistance requires coordinated efforts from healthcare stakeholders to curb irrational antibiotic use and safeguard their efficacy.

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Tab. VIII. Percentage distribution of participants according to reported frequency of antibiotic prescription (Never-Always) for selected child symptoms, overall and by group.

	Never 0-5%	Sometimes 5-30%	Often 30-70%	Most of the times 70-95%	Always 95-100%
Colds					
All	37.85	30.70	16.62	8.84	5.99
Group 0	37.94	35.34	19.83	5.17	1.72
Group 1	32.30	42.24	13.04	9.94	2.48
Group 2	36.18	25.82	19.48	12.67	5.85
Group 3	39.49	30.31	16.19	6.89	7.12
Group 4	48.75	37.50	1.25	0.00	12.50
Group 5	37.40	42.28	12.20	4.87	3.25
Runny nose					
All	50.28	27.95	17.27	3.04	1.46
Group 0	47.41	33.62	11.21	5.17	2.59
Group 1	56.52	26.09	12.42	4.97	0.00
Group 2	42.39	32.76	20.46	2.44	1.95
Group 3	54.54	24.91	16.65	3.10	0.80
Group 4	56.25	26.25	7.50	2.50	7.50
Group 5	63.41	15.45	18.70	2.44	0.00
Dry throat					
All	37.25	32.50	18.51	9.76	1.98
Group 0	39.66	31.03	21.55	5.17	2.59
Group 1	42.85	20.50	32.30	3.11	1.24
Group 2	33.25	33.62	19.00	11.21	2.92
Group 3	38.69	33.41	16.88	9.64	1.38
Group 4	45.00	25.00	10.00	18.75	1.25
Group 5	39.02	40.65	11.38	8.13	0.82
Cough					
All	29.01	33.70	18.60	15.65	3.04
Group 0	25.86	27.59	25.00	18.97	2.58
Group 1	35.40	33.54	21.74	9.32	0.00
Group 2	23.38	32.16	20.83	19.61	4.02
Group 3	30.65	37.44	15.84	13.20	2.87
Group 4	50.00	21.25	15.00	12.50	1.25
Group 5	35.77	31.71	15.45	13.82	3.25
Vomiting					
All	38.26	27.76	16.80	12.20	4.98
Group 0	33.62	27.59	6.90	25.86	6.03
Group 1	43.48	20.50	13.66	18.63	3.73
Group 2	35.81	23.75	20.22	14.13	6.09
Group 3	39.15	32.49	14.36	9.18	4.82
Group 4	36.25	30.00	31.25	0.00	2.50
Group 5	47.15	29.27	15.45	7.32	0.81
Fever					
All	12.57	26.29	25.83	21.50	13.81
Group 0	9.48	23.28	23.28	32.76	11.20
Group 1	6.83	13.66	28.57	36.02	14.92
Group 2	10.72	23.02	24.24	24.60	17.42
Group 3	13.55	30.54	27.44	15.27	13.20
Group 4	26.25	33.75	18.75	21.25	0.00
Group 5	19.51	32.51	28.46	15.45	4.07
Pain in the ear					
All	6.58	26.71	32.64	21.22	12.85
Group 0	3.45	22.42	26.72	20.69	26.72
Group 1	3.11	16.15	42.24	21.11	17.39
Group 2	5.36	27.41	30.33	23.01	13.89
Group 3	7.58	26.75	34.56	21.13	9.98
Group 4	22.50	27.50	31.25	12.50	6.25
Group 5	4.88	39.02	28.46	16.26	11.38

Tab. IX. Percentage of participants reporting factors leading to self-administration of antibiotics for their child, overall and by study group.

All	Group 0	Group 1	Group 2	Group 3	Group 4	Group 5
Because the pediatrician previously prescribed the same medicine for your child and for the same current symptoms						
57.69	63.79	59.01	56.15	56.95	56.25	66.67
Because the pharmacist recommended a specific antibiotic						
33.66	31.03	41.61	24.71	32.26	28.75	31.71
Because you thought your child's condition was not serious						
29.42	23.28	24.22	29.6	31.11	25	31.71
Because you do not have enough time to visit the doctor, or not having enough money						
27.39	22.41	39.75	27.89	27.1	30	13.01
Because a relatives or neighbors recommended giving a specific antibiotic						
7.32	11.21	7.45	5.72	8.61	2.5	8.13

Tab. X. Percentage distribution of parents' attitudes and behaviors regarding antibiotic use, overall and by study group.

	Strongly agree/agree	Uncertain	Disagree/strongly disagree
Do you think antibiotics are used too much and unnecessarily?			
All	84.53	2.72	12.75
Group 0	86.21	3.45	10.34
Group 1	72.67	0.00	27.33
Group 2	81.73	3.90	14.37
Group 3	86.80	2.18	11.02
Group 4	92.50	0.00	7.50
Group 5	95.93	3.25	0.82
Did you change your pediatrician because he didn't prescribe the antibiotics for your child as you wanted?			
All	15.66	19.98	64.37
Group 0	6.03	30.17	63.80
Group 1	11.18	21.74	67.08
Group 2	20.22	18.88	60.90
Group 3	14.81	20.55	64.64
Group 4	10.00	1.25	88.75
Group 5	9.76	23.58	66.66
Have you changed your pediatrician because at every visit he prescribes antibiotics?			
All	50.86	21.55	27.58
Group 0	54.66	8.70	36.65
Group 1	57.00	11.94	31.06
Group 2	58.78	12.28	28.94
Group 3	75.00	2.50	22.50
Group 4	49.59	21.95	28.46
Group 5	50.86	21.55	27.58
Do you give your child leftovers from the previous antibiotic when he has the same previous symptoms?			
All	22.6	13.77	63.63
Group 0	25.00	25.00	50.00
Group 1	27.95	14.29	57.76
Group 2	23.26	14.86	61.87
Group 3	21.59	12.51	65.90
Group 4	30.00	1.25	68.75
Group 5	11.39	12.20	76.42
Do you think that most upper respiratory infections can be resolved without the use of antibiotics because they go away on their own?			
All	72.75	5.11	22.14
Group 0	73.27	6.90	19.82
Group 1	63.35	3.73	32.92
Group 2	72.84	5.85	21.31
Group 3	73.36	4.94	21.70
Group 4	87.50	1.25	11.25
Group 5	69.91	4.07	26.02

Tab. X. (*follows*).

	Strongly agree/agree	Uncertain	Disagree/strongly disagree
Do you think parents and pediatricians should be informed about using antibiotics wisely?			
All	94.66	0.64	4.7
Group 0	97.41	0.00	2.59
Group 1	86.34	0.62	13.04
Group 2	95.00	1.46	3.53
Group 3	94.83	0.11	5.05
Group 4	100.00	0.00	0.00
Group 5	95.93	0.00	4.07

Tab. XI. Percentage distribution of parental practices and behaviors regarding antibiotic prescription for children, overall and by study group.

	Never 0-5%	Sometimes 5-30%	Often 30-70%	Most of the times 70-95%	Always 95-100%
Do you ask the doctor whether or not it is necessary to prescribe antibiotics for your child?					
All	5.61	12.29	18.09	21.96	42.03
Group 0	8.62	19.83	18.97	12.93	39.66
Group 1	9.94	12.42	19.25	17.39	40.99
Group 2	3.65	10.48	16.81	22.41	46.65
Group 3	4.71	12.86	17.45	25.37	39.61
Group 4	20.00	12.50	21.25	20.00	26.25
Group 5	7.32	13.01	26.83	10.57	42.28
Would you like the doctor not to prescribe antibiotics for your child?					
All	2.67	14.92	26.75	33.98	21.69
Group 0	0.00	24.14	25.86	22.41	27.59
Group 1	1.24	13.66	29.19	34.78	21.12
Group 2	4.02	13.89	30.21	34.10	17.78
Group 3	2.64	13.89	24.23	38.00	21.24
Group 4	0.00	22.50	25.00	16.25	36.25
Group 5	0.00	17.07	20.33	26.02	36.59
Do you directly ask the doctor to prescribe antibiotics for your child?					
All	39.00	34.02	14.41	7.27	5.29
Group 0	32.76	43.97	5.17	12.93	5.17
Group 1	35.40	32.92	16.15	11.18	4.35
Group 2	39.34	30.21	17.17	8.65	4.63
Group 3	39.15	36.51	14.01	5.05	5.28
Group 4	48.75	25.00	5.00	7.50	13.75
Group 5	39.84	39.84	11.38	3.25	5.69
Do you fully follow all your pediatrician's instructions and advice when using the antibiotic?					
All	0.86	1.72	8.62	33.62	55.17
Group 0	0.62	4.35	4.35	34.78	55.90
Group 1	0.73	4.26	10.60	28.50	55.91
Group 2	0.57	2.53	16.65	27.55	52.70
Group 3	0.00	2.50	8.75	20.00	68.75
Group 4	0.00	4.07	11.38	19.51	65.04
Group 5	0.86	1.72	8.62	33.62	55.17
Do you think your pediatrician is prescribing an antibiotic for your child just because you asked for it?					
All	39.96	30.06	16.85	7.37	5.76
Group 0	40.52	30.17	14.66	10.34	4.31
Group 1	42.86	34.78	9.32	6.83	6.21
Group 2	41.66	25.94	19.61	7.67	5.12
Group 3	38.46	32.72	16.76	6.77	5.28
Group 4	38.75	22.50	20.00	7.50	11.25
Group 5	35.77	37.40	8.94	7.32	10.57

Ethics approval and consent to participate:

At the beginning of the questionnaire, participants were presented with a detailed consent form outlining the study's aims, procedures, risks, benefits, and data privacy measures. Only participants who agreed to the consent statement were able to proceed with the survey. informed consent was obtained from all participants. Ethical approval for this study was obtained from the Ethics Committee of Tanta University (approval code: 36264PR105/2/23).

Competing interests statement

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Authors' contributions

MK: made all over the study, preparing the proposal, receiving ethical approval, completing the questionnaire preparation and revision, collecting the data, handling the data, performing the statistical analysis, writing, revising, and reviewing the final manuscript.
EM, AK, AN, RG: participated in the literature review, writing the protocol, collecting the data, preparing and revising the questionnaire, and writing the manuscript. All authors participated in performing the statistical analysis and writing and revising the Results section of the manuscript. MS: participate in Perform statistical analysis, writing and revising results section, and revising discussion section of the manuscript.
MA, EN: Participation in the literature review and writing of the manuscript.
AF, NM, SR: Participated in the literature review, collected the data, and revised the manuscript. SS: Supervised the whole process of the research and revised the manuscript.
All authors read and approved the final manuscript.

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Non comunicable diseases

Association between the condition of living alone and the presence of depressive symptoms in adults in Peru: an analysis of nationally representative survey data

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Keywords

Loneliness • Depression • Social Determinants of Health • Home environment • Peru

Summary

Introduction. *Depression is a major public health problem that affects quality of life, social functioning, and overall well-being. Among the social factors potentially related to depressive symptoms, living alone has gained increasing attention, although findings have been inconsistent across settings. In Peru, where household composition and social support dynamics may differ from those reported in other contexts, evidence on this association remains limited. Therefore, this study aimed to determine the association between living alone and depressive symptoms in Peruvian adults.*

Methods. *This observational, cross-sectional, and analytical study used secondary data from the 2022 Demographic and Family Health Survey (ENDES), conducted in 30,087 Peruvian adults aged 18 years old and older. The dependent variable was the presence of moderate to severe depressive symptoms (yes/no), measured by the Patient Health Questionnaire-9 (PHQ-9), while the independent variable was living alone (yes/no). Generalized linear models of the Poisson family and log link function, were used to estimate crude and adjusted prevalence ratios (PRs). The analyses were performed in Stata v18.0 with a significant level of 5%.*

Results. *Moderate to severe depressive symptoms was identified in 7.9% of participants, while 7.5% lived in single-person households. In the crude analysis, living alone were associated with a higher probability of presenting depressive symptoms (PR: 1.60; 95% CI: 1.33-1.92; p < 0.001). However, after adjusting for confounding variables, the association ceased to be significant (aPR: 1.01; 95% CI: 0.82-1.24; p = 0.928).*

Conclusion. *Unlike studies where living alone is associated with a higher prevalence of depressive symptoms, in the Peruvian context, no statistically significant association was observed in the adjusted analysis. This finding suggests that other social and cultural determinants may be associated with depressive symptoms among adults living alone in Peru. Understanding these differences is key to the design of mental health prevention and intervention strategies adapted to the specific characteristics of the population.*

Introduction

Depression, defined by the World Health Organization WHO as a "low mood or loss of interest in or pleasure in performing activities, which persists for a prolonged period" [1], affects approximately 280 million people in the world [2]. In Peru, the Epidemiological Bulletin of the National Center for Epidemiology, Prevention and Control of Diseases (CDC) reported 13,105 cases between 2016 and 2021, with Lima concentrating the highest number of episodes (40.1%) [3]. Depression has a high global impact, as it increases the risk of suicide [4], and each year approximately 726,000 people take their own lives; and in 2021, suicide was the third leading cause of death in young people aged 15 to 29 years [5]. In addition, jointly with anxiety disorders, the economic consequences are alarming, with an estimated loss of 12 billion days of lost productivity each year, which is equivalent to almost a thousand billion dollars for the world economy [6]. In the Peruvian context, mental health disorders represent the second largest contributor to years of healthy life lost (DALYs), with 9.8%, equivalent to 17.7 years lost per thousand inhabitants. Of these, disability is responsible for 99.4%, with depression being one of the main mental disorders involved, with a prevalence of 30.1% [7].

Depression is a mental health disorder influenced by genetic, biological, environmental, and psychological factors [8], and living alone stands out as a factor that can contribute to its development or aggravation [9-12]. For instance, a study conducted in South Korea in 2022, using data from the National Health and Nutrition Examination Survey, analyzed 21,618 individuals between the ages of 20 and 80, where it was observed that the prevalence of depressive symptoms was higher in those who lived alone (17.6%) than in those who lived with others (11.1%) [13]. In a U.S. nationally representative survey conducted in April 2020, the weighted prevalence of depressive symptoms was 31.7%, and participants with depressive symptoms were more

likely to live alone (21.5% vs 16.3%; $p = 0.05$) [14]. Conversely, a systematic review published in 2022 that included seven studies (six cohort and one case-control) with a total of 123,859 participants, reported that living alone is associated with an increased risk of depression compared to living together (OR: 1.42; 95% CI 1.19-1.70) [15]. In this sense, international evidence suggests that loneliness may be a key risk factor for depression.

According to the last national census carried out in Peru in 2017, the most common type of household is nuclear (53.9%), followed by extended (20.6%) and one-person (16.8%). Other types of households such as those without a nucleus (6.2%) and composite households (2.5%) have lower percentages. During the 2007-2017 intercensal period, one-person households increased by 74.2%, with an average annual growth rate of 5.7%. In this type of household, the predominant age group is 25 to 49 years old (35.9%), followed by those over 60 years old (35.3%) and a smaller percentage those between 50 and 59 years old (17.2%), 18 to 24 years old (10.2%) and those from 6 to 17 years old (1.4%) [16]. Due to the high prevalence of mental health disorders in our country, it is necessary to consider not only the axes of treatment, but also to explore the influence of other factors, such as living alone, as has been seen in the aforementioned studies. Thanks to the Demographic and Family Health Survey (ENDES), developed by the National Institute of Statistics and Informatics (INEI), reliable and representative data are available at the national level that allow the analysis of both the prevalence of depression and the housing conditions of the population [17]. In this sense, the objective of this study was to estimate the relationship between the condition of living alone and the prevalence of depressive symptoms in the Peruvian population, using nationally representative data from the ENDES.

Methods

Design and population

Observational, cross-sectional, analytical study using secondary data from ENDES 2022. The survey was conducted from January to December 2022, selecting 36,650 households nationwide, of which 35,287 were interviewed, covering urban and rural areas of the 24 departments of Peru, the Constitutional Province of Callao, and the main geographical regions (Metropolitan Lima, Coast, Highlands, Jungle) [18]. Databases and methodological details are available on the INEI website [19] and the National Open Data Platform [20].

Sample

A two-stage cluster sampling was implemented by the INEI. In the first stage, primary sampling units (clusters) were selected using the 2017 Population and Housing Census (CPV 2017) as a reference. In the second stage, secondary sampling units (dwellings) were selected from the sampling frame updated through the mapping and registration of buildings and dwellings [18]. Data were collected by direct interview, conducted by trained personnel, using tablets or printed formats. Three questionnaires were applied: Household (to the head, spouse, or any adult resident), Individual (to all women aged 12-49), and Health (to one household member aged ≥ 15). This study included 30,087 participants aged ≥ 18 who completed the Health Questionnaire (Fig. 1) [17].

Variables

- **Exposure:** Living alone was defined as residing without other family members or a spouse [13], classified as "lives alone" if only one person resided in the household, otherwise "does not live alone."
- **Outcome:** The dependent variable of this study is depression (yes or no), which, according to the

Fig. 1. Flowchart of study participants.

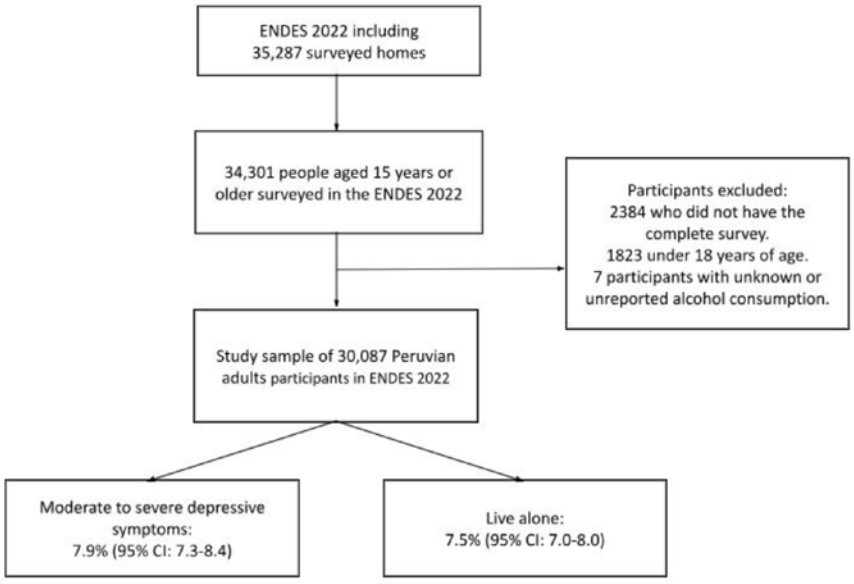
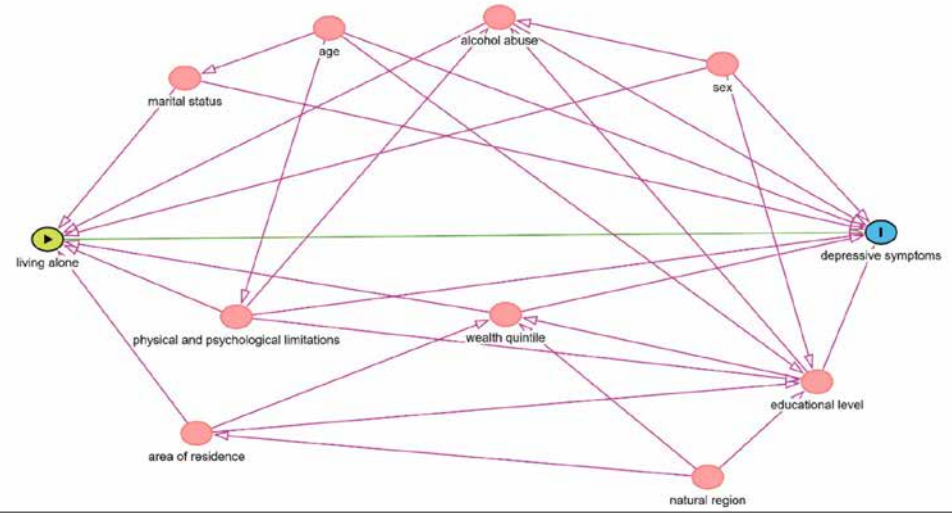


Fig. 2. Directed Acyclic Graph of the association between the condition of living alone and the presence of depressive symptoms.



WHO, is defined as the loss of interest or pleasure in activities for prolonged periods of time. In ENDES 2022, the Patient Health Questionnaire-9 (PHQ-9) was used to explore depressive symptoms in the last 14 days prior to the survey. This questionnaire assesses the severity of depressive symptoms through 9 questions, each with a score ranging from 0 to 3: 0 represents «none,» 1 «several days,» 2 «more than half the days,» and 3 «almost every day». The total score obtained ranges from 0 to 27, allowing participants to be classified into different levels of depressive symptoms: no symptoms (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe (20-27) [21]. A score ≥ 10 identified moderate to severe symptoms. This tool has been validated for Peru [22] and used in previous ENDES-based studies [23, 24].

- **Covariates:** The descriptive analysis included the following variables: sex (male or female); age group (18-24 years, 25-44 years, 45-60 years, and 60 years or older); educational level (no education or initial, primary, secondary, or higher education); marital status (married or cohabiting, single, widowed, divorced or separated); area of residence (urban or rural); natural region (Metropolitan Lima, coast, highlands, jungle); wealth quintile (very poor, poor, medium, rich, very rich); physical and psychological limitations (without limitations or with limitations), defined based on a positive response to one or more of the following: difficulty seeing even with glasses, hearing even with hearing aids, speaking or communicating, moving or walking, understanding or learning, and relating to others due to thoughts, feelings, or behaviors; and alcohol abuse in the last 12 months (yes or no), assessed by the *Composite International Diagnostic Interview* (CIDI 1.1) of the World Health Organization, which determines alcohol abuse according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), as previously reported [25] in another study.

For the adjusted analysis, covariates were selected based on an epidemiological criterion using a Directed Acyclic Graph (Fig. 2) constructed in DAGitty v3.1 to identify relevant variables and relationships. This systematic approach ensured proper control of confounding factors. The final adjustment set included age group, alcohol abuse, educational level, marital status, physical and psychological limitations, sex, and wealth quintile.

Statistical processing and analysis:

A univariate analysis was performed to describe the characteristics of the study population, reporting the absolute and relative frequencies of all the variables of interest. Likewise, the tabulation of the dependent variable in relation to the exposure variable and the selected covariates was carried out, to evaluate the distribution of the outcome in the population studied.

Subsequently, regression analyses were performed using generalized linear models of the Poisson family, using a logarithmic linkage function. These models allowed us to calculate prevalence ratios (PRs) along with their 95% confidence intervals (CIs). Both crude prevalence ratios (which evaluated only the association between living alone and depression) and adjusted (aPR, considering adjustment for possible confounding variables) were estimated. Additionally, the corresponding *p values* were reported to determine the statistical significance of the associations.

All statistical analyses were performed using the Stata v18.0 software, incorporating the weights and the complex sample design of the survey using the svy command.

Ethical considerations

This study used anonymized secondary data from the publicly accessible ENDES 2022 database. As these data do not allow the identification of the participants, there are no associated risks for the respondents. For

these reasons, the project was exempted from ethical evaluation by the Universidad Científica del Sur, through Resolution No. 070-DACMH-DAFCS-U. CIENTIFICA-2025.

Results

After applying the selection criteria, 30,087 participants were included, of which 52.4% were women. The largest age group was 25 to 44 years old (42.8%), and 43.3% had a secondary education level. Most of the participants were married or cohabiting (63.8%), and 81.9% resided in urban areas, mainly in Metropolitan Lima (37.6%). The predominant wealth quintile was the middle, with 21.3%. Regarding physical and psychological limitations, 97.6% of the participants reported no limitations, and 96% did not present alcohol abuse. Additionally, 7.5% of the participants lived in one-person households (Tab. I).

Overall, the percentage of moderate to severe depressive symptomatology was 7.9%. The highest prevalence was observed in women (11.2%), in the age group of 60 years or older (14.2%), and in those without education (18.1%). Among widowed, divorced or separated people, the prevalence was 14%. By area of residence, the highest percentage was in rural areas (8.4%), and, by natural region, in the highlands (10.2%). As for the wealth quintile, the highest prevalence corresponded to the lowest quintile (9.3%). Participants with physical and psychological limitations had a prevalence of 15.8%, those who consumed alcohol excessively 12.2%, and those who lived alone 12.1% (Tab. II).

It was identified that in the study population, living alone was associated with a higher probability of moderate to severe depressive symptoms (PR: 1.60; 95% CI: 1.33-1.92; $p < 0.001$). However, the association was lost after adjustment for confounding variables. (aPR: 1.01; 95% CI: 0.82-1.24; p: 0.928) (Tab. III).

Tab. I. Characteristics of the population of adults over 18 years of age, Peruvians, participants of the ENDES 2022 included in the study (N=30,087).

Characteristics		n	% (95% CI)*
Sex			
	Female	17,247	52.4 (51.4 - 53.4)
	Male	12,840	47.6 (46.6 - 48.6)
Age group (years)			
	18 to 24 years old	4,236	15.7 (15.1 - 16.5)
	25 to 44 years old	16,368	42.8 (41.9 - 43.6)
	45 to 60 years old	6,532	28.4 (27.6 - 29.3)
	60 years and older	2,951	13.0 (12.4 - 13.7)
Level of Education			
	No education	1,207	3.5 (3.2 - 3.8)
	Primary	6,873	19.2 (18.5 - 20)
	High school	12,942	43.3 (42.3 - 44.2)
	Higher	9,065	34.0 (33.1 - 35.0)
Marital status			
	Married or cohabiting	20,508	63.8 (62.8 - 64.7)
	Single	3,969	16.3 (15.5 - 17.0)
	Widowed, Divorced or Separated	5,610	20 (19.2 - 20.8)
Area of Residence			
	Rural	10,627	18.1 (17.7 - 18.6)
	Urban	19,460	81.9 (81.4 - 82.3)
Natural Region			
	Metropolitan Lima	3,513	37.6 (36.5 - 38.6)
	Coast	8,422	25.9 (24.8 - 27)
	Highlands	10,878	24.1 (23.2 - 25.1)
	Jungle	7,274	12.5 (11.8 - 13.1)
Wealth quintile			
	Very poor	9,688	18.3 (17.7 - 19)
	Poor	7,708	20.2 (19.4 - 21)
	Middle	5,624	21.3 (20.4 - 22)
	Rich	4,083	20.5 (19.7 - 21.4)
	Very rich	2,984	19.7 (18.8 - 20.8)
Physical and psychological limitations			
	No limitations	29,516	97.6 (97.3 - 98.0)
	With limitations	571	2.4 (2.1 - 2.7)
Alcohol abuse			
	No	29,003	96 (95.5 - 96.3)
	Yes	1,084	4.1 (3.7 - 4.5)
Living alone			
	No	27,776	92.5 (91.9 - 93.0)
	Yes	2,311	7.5 (7.0 - 8.0)

*Estimates include weights and sample characteristics from ENDES 2022.

Discussion

The aim of this research was to evaluate the association between the condition of living alone and the presence of depressive symptoms in Peruvian adults, using data from ENDES 2022. It was found that 7.9% of the participants presented moderate to severe depressive symptoms, while 7.5% of the respondents lived in a one-person household. In this population, living alone was initially associated with an increased likelihood of moderate to severe depressive symptoms. However, after adjusting for confounding variables, this association ceased to be significant. These results differ from what has been reported in other studies conducted in international contexts, where living alone has been consistently associated with a higher prevalence of depressive symptoms. The absence of this significant association in the Peruvian context could reflect cultural, social, or community support differences in the Peruvian population, highlighting the need to explore specific factors that may be related to this association in different settings.

In the Peruvian adult population, 7.9% had moderate to severe depressive symptoms, consistent with previous research in various contexts, although with some variations. In an epidemiological study in Argentina, depressive disorder prevalence exceeded 8.7%, similar to our finding [26]. Another study in four cities of Argentina, Chile, and Uruguay reported a 14.6% prevalence of major depressive episode, ranging

Tab. II. Frequency of moderate to severe depressive symptomatology according to characteristics of the population of adults over 18 years of age, Peruvians, participants of the ENDES 2022 included in the study (N=30,087).

Characteristics		Moderate to severe depressive symptomatology	
		No (n=27,927)	Yes (n=2160)
		n (%)*	n (%)*
Total		27927 (92.1)	2160 (7.9)
Sex			
	Female	15,615 (88.8)	1,632 (11.2)
	Male	12,312 (95.8)	528 (4.2)
Age group (years)			
	18 to 24 years old	3,971 (92.6)	265 (7.4)
	25 to 44 years old	15,510 (94.9)	858 (5.2)
	45 to 60 years old	5,959 (90.7)	573 (9.3)
	60 years and older	2,487 (85.9)	464 (14.2)
Level of Education			
	No education	1,001 (82)	210 (18.1)
	Primary	6,247 (89.4)	629 (10.6)
	High school	12,068 (91.9)	874 (8.1)
	Higher	8,616 (95)	449 (5)
Marital status			
	Married or cohabiting	19,363 (94)	1,145 (6)
	Single	3,687 (92.2)	282 (7.8)
	Widowed, Divorced or Separated	4,877 (86)	733 (14)
Area of Residence			
	Rural	9,812 (91.6)	815 (8.4)
	Urban	18,115 (92.3)	1,345 (7.8)
Natural Region			
	Metropolitan Lima	3,264 (92.4)	249 (7.6)
	Coast	7,909 (93.3)	513 (6.7)
	Highlands	9,918 (89.8)	960 (10.2)
	Jungle	6,836 (93.4)	438 (6.6)
Wealth quintile			
	Very poor	8,916 (90.8)	772 (9.3)
	Poor	7,140 (91.7)	568 (8.3)
	Middle	5,235 (92.3)	389 (7.7)
	Rich	3,831 (92)	252 (8)
	Very rich	2,805 (93.8)	179 (6.2)
Physical and psychological limitations			
	No limitations	27,462 (92.3)	2,054 (7.7)
	With limitations	465 (84.2)	106 (15.8)
Alcohol abuse			
	No	26,953 (92.3)	2,050 (7.7)
	Yes	974 (87.9)	110 (12.2)
Living alone			
	No	25,887 (92.5)	1,889 (7.5)
	Yes	2,040 (87.9)	271 (12.1)

*Estimates include weights and sample characteristics from ENDES 2022.

from 5.6% to 18.2% [27]. In 27 European countries, prevalence averaged 6.38%, with values between 2.58% and 10.33% [28]. In the U.S., the overall prevalence was 18.5%, with state and county variations [29]. Differences in prevalence may be related to factors such as study design, cultural and socioeconomic conditions, health system differences, measurement instruments, and underreporting due to stigma, limited diagnostic access, or self-perception. In addition, the prevalence of 7.9% found in this study is within the range of previous research. Therefore, it is essential to consider the specific context when interpreting the results and designing mental health strategies.

By comparison, cross-national census-based data show substantial between-country differences in the prevalence of single-person households. In Northern Europe, single-person households account for about 44.7% of all households in Finland and 39.8% in Sweden; similarly high proportions are observed in Germany (42.3%) and France (34.7%), while the share is lower in Spain (25.7%) and the United States (28.4%) [30]. In several Asian settings, the proportion tends to be lower, such as China (13.7%, 2010 data), Indonesia (7.9%, 2020), Thailand (10.0%, 2021) and Viet Nam (8.7%, 2019) [31]. Likewise, in Latin America, census outputs indicate markedly lower levels, including Chile (17.8% of households, 2017) [32] and Brazil (18.8%, 2022) [33]; analyses of Mexico's 2023 census microdata likewise suggest that one-person households account for about 14.0% of households [34]. The differences in the percentages of individuals residing alone may be associated with cultural, economic, and demographic factors between regions. In Northern Europe, the high percentages could be related to stronger social welfare systems and a high quality of life that facilitate independence. In contrast, in Asia and Latin America, traditional family values and economic constraints seem to play a predominant role in the decision to live alone.

Although studies carried out in other countries have found an association between living alone and the presence of moderate to severe depressive symptoms [13-16], the present study did not show such a relationship in the Peruvian population (aPR: 1.01; 95% CI: 0.82-1.24; p: 0.928). This discrepancy could be explained by a variety of contextual, cultural, and sociodemographic factors that influence the characteristics and lifestyles of people living alone in different regions. For instance, a study conducted in Spain on lifestyles found that people who lived alone were less sedentary and spent more time on physical activity compared to those who lived with others. This pattern was attributed to greater flexibility in the organization of their time, as they did not depend on coordination with other members of the household. In addition, the same study observed that alcohol consumption was lower in people who lived alone, which could be related to lower social pressures to consume alcohol in group contexts [35]. In this sense, these behaviors could be associated with the lower prevalence of depressive symptoms in people who live alone in certain contexts, highlighting the importance of exploring lifestyles as possible protective factors in future studies.

However, other mechanisms related to housing conditions could also influence the relationship between living alone and depressive symptoms. A study conducted in Korea showed that both the economic burden of housing costs (OR: 1.92; 95% CI: 1.13-3.24)

Tab. III. Association between living alone and the presence of moderate to severe depressive symptomatology in the population of adults over 18 years of age, Peruvians, participants of the ENDES 2022 included in the study (N=30,087).

Live alone		Bivariate analysis			Adjusted analysis*		
		PR	95% CI	*p-value*	aPR	95% CI	*p-value*
	No	Ref.			Ref.		
	Yes	1.60	1.33 - 1.92	<0.001	1.01	0.82 - 1.24	0.928

*Adjusted for: sex, age group (years), education level, marital status, wealth quintile, physical and psychological limitations, and alcohol abuse. Estimates include the weights and ENDES 2022 sample specifications.
PR: Prevalence ratio. 95% CI: 95% confidence interval. aPR: adjusted Prevalence ratio.

and the number of housing quality items perceived as inadequate (OR: 1.31; 95% CI: 1.19-1.45) were significantly associated with depressive symptoms in one-person households. In contrast, in non-one-person households, only the number of housing quality items perceived as inadequate showed a significant association (OR: 1.34; 95% CI 1.15-1.55) [9]. This suggests that, in addition to psychological or social factors related to loneliness, economic and material aspects are strongly associated with mental health outcomes among those who live alone. These findings highlight the importance of considering cultural, social, and economic differences between populations when analyzing the relationship between living alone and depressive symptoms. It is possible that, in the Peruvian context, factors such as community support, extended family networks, or the lifestyle of those who live alone may be associated with lower levels of depressive symptoms [36-39]. However, this interpretation should be understood as a hypothesis rather than a conclusion derived from the present data, as these variables were not directly measured in this study. Therefore, further research, including qualitative studies, is needed to better understand how these contextual and social dynamics may relate to depressive symptoms among individuals living alone in the Peruvian population.

This investigation, as it is based on secondary data from the ENDES 2022, has some inherent limitations. Among them, the possibility of registration and/or typing errors that could generate information biases. In addition, variables may be affected by memory biases, as respondents may not accurately recall events leading up to the survey. Also, as it is a cross-sectional design, it is not possible to establish cause-and-effect relationships, since the variables studied were not monitored over time. Furthermore, although ENDES uses a probabilistic sampling design and survey weights were applied, some degree of selection bias cannot be entirely ruled out, as the health module is administered to one selected individual per household. However, one of the main strengths of this study lies in the quality of the data used. The ENDES 2022, prepared by the INEI, provides reliable and representative information at the national level, both on depression and on the housing conditions of the Peruvian population, which ensures an objective database that accurately reflects the national reality. This study represents a starting point for future research that allows us to delve into this topic. The fact that we have not found a significant association between living alone and depressive symptoms in the Peruvian context, in contrast to what has been reported in studies carried out in other settings, highlights the importance of investigating other contextual, cultural or social factors that could be modulating this relationship.

Conclusion

In conclusion, after adjusting for potential confounders, the present study did not identify a significant association between living alone and the presence of moderate to severe depressive symptoms in Peru. This finding, in contrast to studies conducted in other countries, suggests that factors such as lifestyle, housing conditions, and cultural or social particularities may be associated with this relationship. These results highlight the need to further explore these contextual factors to better understand how they influence mental health in different environments.

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Conflicts of interest statement

The authors affirm that they have no financial conflicts of interest or personal relationships that could have influenced the content of this article.

Data availability statement

The primary data used for this secondary analysis are available on the INEI website: https://proyectos.inei.gob.pe/iinei/srienaho/index.htm.

Authors' contributions

PCN: Conceptualization, Methodology, Writing - Original draft, Writing - Review & editing, Visualization, Project administration. ACZ: Conceptualization, Methodology, Writing - Original draft, Writing - Review & editing, Visualization, Project administration. AHV: Conceptualization, Methodology, Formal analysis, Writing - Review & editing. DA: Conceptualization,

Methodology, Formal analysis, Visualization, Writing - Review & editing, Supervision, Project administration.

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Non comunicable diseases

Factors Affecting Pap Smear Screening Among Women of Reproductive Age in Owerri West LGA, Imo State, South-Eastern Nigeria

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Keywords

Cervical cancer • HPV vaccine • Pap Smear • Screening uptake

Summary

Introduction. *Cervical cancer remains a significant public health issue and is the second leading cause of cancer-related mortality among women globally. Its burden extends beyond individual health, affecting families, communities, and social systems. This study aimed to identify the factors influencing Pap smear testing among women of reproductive age in Owerri West, Imo State.*
Methods. *This study adopted a descriptive cross-sectional design using 399 respondents selected through a multistage sampling method. Data were collected using a structured questionnaire and analysed with the Statistical Package for the Social Sciences (SPSS), with results presented in frequencies and percentages.*
Results. *Most respondents were married (51.6%), aged 20-29 years (42.9%), predominantly traders (34.6%) and civil servants (34.9%), of Igbo ethnicity (78.0%), and had tertiary education (48.4%). While 44.8% had heard of cervical cancer, they were not familiar with its details. About 59.0% had heard of Pap smear testing, with nearly half (49.3%) receiving the information from healthcare professionals. Despite a relatively high level of awareness, 61.8% had never undergone a Pap smear. Respondents identified several barriers to Pap smear testing, including the belief that the procedure is expensive or embarrassing. Some also associated undergoing the test before sexual activity with a loss of virginity, while others cited the distant location of screening centres as a significant challenge.*
Conclusion. *There is a critical need for increased medical education and public sensitization on cervical cancer and the importance of routine screening to improve uptake and early detection.*

Introduction

Cervical cancer is a major public health concern and one of the leading causes of cancer related deaths among women worldwide. Globally, it ranks as the third most common cause of cancer mortality in women. It is the most frequently diagnosed cancer in 28 countries and the leading cause of cancer deaths in 42 countries most of which are in sub-Saharan Africa and Southeast Asia [1]. In Nigeria, it is a leading cause of cancer related deaths among women. Despite the availability of effective screening methods such as Pap smear testing, uptake of these services remains low. Its epidemiology and health impacts are not only affecting women, but also their families, communities and social institutions [2]. Although cervical cancer is one of the most preventable and treatable forms of cancer, effective prevention relies on HPV vaccination, early detection, and timely management at the early stages. Cervical screening can be properly utilized if awareness is made and the screening services available. Early screening is proven to be cost-effective and a form of control strategy of the disease burden [3]. The aim of cancer screening is to reduce death from the disease. When pre-cancer lesions are detected and remedied, the incidence of cancer cervix decreases [4, 5]. The three cervical cancer screening tests include cervical cytology (Pap smear or Pap test), primary HPV testing and co-testing (HPV testing in combination with cytology) [6]. Regular cervical cancer screening with Papanicolaou (Pap) smear testing has remained an effective public health intervention in the prevention and subsequent reduction of the incidence, morbidity and mortality of cervical cancer disease [7].
Previous research has shown that various factors influence the decision of women to undergo Pap smear testing. Socio-demographic factors, including age, education level, income, and marital status, have been found to be associated with Pap smear utilization [8, 9]. Younger women and those with higher educational attainment and income tend to be more likely to seek cervical cancer screening services. On the other hand, women with lower educational levels and income might face barriers related to awareness and accessibility [10-13]. Cultural beliefs and misconceptions about the Pap smear procedure have been identified as significant

barriers to screening uptake among women in Nigeria: these include religious modesty requirements, need for spousal consent, preference for female healthcare providers, and traditional beliefs about disease causation [14, 15]. In addition to cultural factors, emotional and psychological factors also play a crucial role in influencing women's attitudes towards Pap smear testing [16, 11]. Embarrassment, anxiety, and fear of pain during the procedure have been reported as barriers to screening uptake [17]. Addressing these emotional aspects is essential to creating a supportive and comfortable environment for women during the screening process.

Furthermore, healthcare system-related barriers have been identified as important determinants of Pap smear testing uptake. Access to healthcare facilities and the availability of screening services can significantly impact women's willingness to undergo screening [18]. Limited access to healthcare facilities, particularly in rural areas, may hinder women from accessing screening services, leading to missed opportunities for early detection and prevention of cervical cancer.

Additionally, negative or dismissive attitudes from healthcare providers towards screening can discourage women from seeking cervical cancer screening services. The attitudes and knowledge of healthcare providers also influence women's participation in screening programs. A lack of awareness or inadequate training among healthcare providers on cervical cancer prevention and screening may result in missed opportunities for education and promotion of Pap smear testing [19]. The study aimed to explore and analyse how different factors affect Pap smear testing among women of reproductive age in Owerri West, Imo State, Nigeria.

Methods

Study Design

This community-based descriptive cross-sectional study used a survey approach to examine the factors affecting Pap smear testing among women of reproductive age in Owerri West LGA, Imo State.

Study Population

This study on the factors affecting Pap smear testing among women of reproductive age was targeted at women of reproductive age (21-49).

Inclusion Criteria

The study included all females aged 21 to 49 years who provided informed consent and were present at the study location during the period of data collection.

Exclusion Criteria

The study excluded males, females below 21 years or above 49 years of age, and individuals who did not provide informed consent.

Sample size

The sample size was determined using Taro-Yamane's formula n=N/(1 + N(e)2 with 95% confidence level.
Where:
n = the sample size
N = the population of the study
e = the margin error in the calculation Substituting the values,
we have; n = 43977/1 + 43977(0.0025) n = 399
The total population of reproductive women N in Owerri west during this study was 43977 which suggested a sample size of 399 participants at 5% minimal error (e).

Sampling method

A multistage simple random sampling method was used in selecting the community in the study. Since the communities are of similar characteristics, fifteen communities in the LGA were enlisted on different ballot papers and five of the ballot papers were randomly selected. The selected ones were used to represent the LGA.

Stage 1: *selection of communities*
Simple random sampling technique was used to select four communities from the fifteen communities in Owerri-West Local Government Area of Imo State. This was done via balloting to give each community an equal chance of being selected.

Stage 2: *selection of villages*
This was done through balloting, one village from each of the communities were selected.

Stage 3: *selection of respondents*
In each village, respondents were recruited via simple random sampling technique so that each member of the population has an equal chance of being selected for the sample, and the selection was made completely at random.

Ethical approval and consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The research protocol was reviewed and approved by Federal University of Technology Owerri Ethics Committee and all participants provided informed consent prior to their participation.

Data collection

A pretested questionnaire was used to collect the data and the questionnaire was administered to the literate study participants in the community while the non-literate were asked orally after getting an informed consent. The questionnaire addressed socio-demographic data, knowledge of cervical cancer, knowledge of Pap smear test, the accessibility of Pap smear testing and belief and attitudes of Pap smear testing, then the participants was provided verbally with basic information on cervical cancer and reasons why they should go for Pap smear testing and be questioned verbally on their beliefs on Pap smear testing.

Data Analysis

IBM Statistical Product and Service Solutions

(SPSS) version 25 was used to analyse the data that were produced. The statistical tools employed in the analysis were mean score, and percentage.

Results

A total of 399 questionnaires were distributed and 364 questionnaires were retrieved back and analysed giving a total response rate of 91.9 %.

According to Table I, majority (42,9%) were aged between 21-29 years. More than half of the respondents were married (51.6%), while 34.9% were civil servants. Nearly half (48.4%) had attained tertiary education, and 37.4% had between three to five children.

Tab. I. Socio-demographic Information of Respondents.

Characteristic	Frequency	%
Age (in years):		
21– 29	156	42.9
30 – 39	119	32.7
40 – 49	92	25.3
Total	364	100
Religion:		
Christianity	321	88.2
Islam	34	9.3
Traditional	9	2.5
Others	00	00
Total	364	100
Marital Status:		
Single	157	43.1
Married	188	51.6
Divorced	7	1.9
Widowed	12	3.3
Total	364	100
Occupation:		
Civil servant	127	34.9
Trader	126	34.6
Farmer	41	11.3
Others	70	19.2
Total	364	100
Ethnic Group:		
Yoruba	34	9.3
Hausa	19	5.2
Igbo	284	78.0
Others	27	7.4
Total	364	100
Level of Education:		
No formal education	16	4.4
Primary	68	18.7
Secondary	104	28.6
Tertiary	176	48.4
Total	364	100
Number of children:		
None	73	20.1
1-2	93	25.5
3-5	156	37.4
Above 5	42	11.5
Total	364	100

Table II, indicated that (41.8%) of the respondents reported being aware of what the HPV vaccine is. More than half (57.7%) indicated that the recommended age to begin cervical cancer screening is between 21 and 29 years. A majority (51.6%) knew that cervical cancer can be prevented or detected early through regular screening. Regarding risk factors for HPV, 35.2% identified having multiple sexual partners. Unusual vaginal bleeding was the most commonly identified symptom of cervical cancer (53.0%). The HPV test was the most recognized cervical cancer screening method, mentioned by 45.9% of respondents.

Table III, indicated that 31,3% reported that they were likely to have heard about Pap smear testing. Among those who had heard about it, the most common source of information was from a nurse/doctor (49.3%). In terms of knowledge, the majority (35.4%) were moderately knowledgeable about what a Pap smear is. Regarding uptake, the highest proportion (46.4%) had not undergone the test but were planning to. On frequency, the majority (36.8%) believed the test should be done every 2-3 years. Finally, the most common reason for undergoing the test, as reported by 34.6% of respondents, was to find precancerous cells.

Table IV, showed that 46.4% of respondents had neither visited nor were aware of any nearby Pap smear facility, while 23.1% had visited once. About 37.6% reported the facility was far from their residence, and 28.8% rated availability as poor. The main barrier to access was limited healthcare infrastructure (34.1%), followed by time constraints (26.6%).

Table V, showed respondents' attitudes towards Pap smear testing. While 31.6% were neutral about its importance, 25.0% agreed that it is important for women's health. On their comfort level with undergoing the test, only 23.1% said they were comfortable, while 28.0% agreed that Pap smear testing can help prevent cervical cancer.

Table VI, revealed that many respondents held misconceptions about Pap smears. About 44% strongly believed they're only needed if sexually active. Around 32% found them expensive, and 31% wrongly believed the HPV vaccine replaces the need for testing. While 36% strongly disagreed that Pap smears mean you have cancer, 32% also disagreed that the test is painful. These results highlight key gaps in knowledge and concerns about cost.

Discussion

This study assessed factors influencing the uptake of Pap smear testing among women of reproductive age in Owerri West Local Government Area, Imo State. The findings revealed moderate awareness of cervical cancer and Pap smear testing; however, actual screening uptake remained low. This highlights a persistent gap between knowledge and preventive health behaviour, a pattern widely reported in cervical cancer literature across low- and middle-income countries. The majority of respondents were aged

Tab. II. Respondents' Knowledge on Cervical Cancer.

Variable	Frequency	%
Have you heard about the HPV (Human Papilloma Virus) vaccine? Yes, I am aware of what HPV vaccine is	152	41.8
No, I have never heard of HPV vaccine before	37	10.2
I have heard of HPV vaccine, but I am not familiar with the details	149	40.9
I am not sure what HPV vaccine is	17	4.7
I would prefer not to answer	9	2.5
Total	364	100
Do you know that HPV infection is a major cause of cervical cancer? Yes, I am aware that HPV infection is a major cause of cervical cancer	197	54.1
No, I did not know that HPV infection is a major cause of cervical cancer	29	8.0
I have heard about the link between HPV infection and cervical cancer, but I am not familiar with the details	81	22.3
I am not sure about the relationship between HPV infection and cervical cancer	57	15.7
I would Prefer not to answer	00	00
Total	364	100
What is the recommended age to start cervical cancer screening? Before 21 years old	43	11.8
Between 21 and 29 years old	210	57.7
Between 30 and 39 years old	67	18.4
40 years old or older	29	8.0
I don't know	15	4.1
Total	364	100
Do you know that cervical cancer can be prevented or detected early through regular screening?		
Yes	188	51.6
No	67	18.4
Not sure	109	29.9
Total	364	100
Which of the following increases the risk of developing HPV?		
Early puberty	83	22.8
Multiple sexual partners	128	35.2
Early sexual activity	39	10.7
Failure to use condom	114	31.3
Not exercising	00	00
Total	364	100
Which of the following are symptoms of cervical cancer?		
Unusual vaginal bleeding	193	53.0
Pelvic pain	141	38.7
Headache	16	4.4
Nausea	9	2.5
Dizziness	5	1.4
Total	364	100
Which of the following are types of cervical cancer screening?		
HPV test	167	45.9
Pap smear test	126	34.6
Gold test	14	3.8
Co-test	49	13.5
RDT	8	2.2
Total	364	100

21-29 years, consistent with findings from other Nigerian studies conducted among women of reproductive age [20, 21]. This age group is often considered sexually active, economically productive, and more exposed to health information. Despite this, screening uptake among younger women remains low. Similar observations have been reported in different studies, where younger women perceived themselves as being at low risk for cervical cancer and therefore delayed screening until symptoms appeared [11, 22]. This perception of invulnerability may contribute significantly to poor preventive health-seeking behaviour.

Although 44.8% of respondents had heard of cervical cancer, many lacked detailed knowledge. This was

Tab. III. Respondents' Knowledge of Pap Smear Testing.

Variable	Frequency	%
Source of information about Pap smear **(n = 215);** From a friend	17	7.9
From family members	11	5.1
From nurse/doctor	106	49.3
From School	43	20
From TV/radio/ social media	38	17.7
Total	215	100
Do you know what a Pap smear test is? Very knowledgeable	93	25.5
Moderately knowledgeable	129	35.4
Somewhat knowledgeable	69	19.0
Slightly knowledgeable	48	13.2
Not knowledgeable at all	25	6.9
Total	364	100
Have you ever undergone a Pap smear test? Yes, multiple times	55	15.1
Yes, once	84	23.1
No, but planning to	169	46.4
No, and not planning to	56	15.4
Not applicable	00	00
Total	364	100
Who should undergo a Pap smear test? People with age > 49	64	17.6
Married woman	97	26.6
I don't know	76	20.9
Children	24	6.6
People > 21 < 49	103	28.3
Total	364	100
How often do you think Pap smear testing should be done?		
Annually	63	17.3
Every 2-3 years	134	36.8
Every 3-5 years	81	22.3
Only when there are symptoms or risk factors	67	18.4
Not sure	19	5.2
Total	364	100
Why should Pap smear testing be done?		
Finds cancerous cells	108	29.7
It helps detect pregnancy	11	3.0
Finds precancerous cells	126	34.6
Finds inflammation	67	18.4
I don't know	44	12.1
Total	364	100

Tab. IV. Level of Accessibility to Pap Smear Testing Facilities.

Variable	Frequency	%
How far is the nearest Pap smear testing facility from your residence? Very close	46	12.6
Close	61	16.8
Moderate distance	38	10.4
Far	137	37.6
Very far	82	22.5
Total	364	100
How would you rate the availability of Pap smear testing facilities in your area? Excellent	49	12.6
Good	67	18.4
Average	96	26.4
Poor	105	28.8
Very poor	47	12.9
Not applicable	00	00
Total	364	100
Are you aware of any barriers that may hinder women's access to Pap smear testing facilities? Time constraints	97	26.6
Unreliable road conditions	48	13.2
Limited healthcare infrastructure	124	34.1
High Transportation Costs	71	19.5
Others	24	6.6
Total	364	100
Have you ever faced any difficulties in scheduling an appointment for a Pap smear test? Strongly Agree	79	21.7
Agree	113	31.0
Neutral	62	17.0
Disagree	81	22.2
Strongly Disagree	29	8.0
Not applicable	00	00
Total	364	100

in contrast with a study carried out in Imo and Enugu state Nigeria where most of the respondents had heard about cervical cancer screening and know where it can be conducted [20, 23]. However, this awareness level is substantially higher than the 12.8% documented among women in urban slums in Lagos [13], reflecting the influence of socioeconomic factors and educational attainment on cervical cancer knowledge [11].

In addition, only 41.8% of respondents were familiar with the HPV vaccine, consistent with other Nigerian studies reporting similarly low HPV vaccine awareness [13, 24] While 57.7% knew that the recommended age for cervical cancer screening is between 21 and 29 years, and 51.6% understood that regular screening helps early detection and prevention, this knowledge did not translate into action. This knowledge-practice gap has been consistently documented across Nigerian studies [11, 21]. Although some respondents could identify symptoms such as unusual vaginal bleeding and pelvic pain (53.0%), the ability to recognize symptoms does

Tab. V. Respondents' Attitudes Towards Pap Smear Testing.

Variable	Frequency	%
Do you think Pap smear testing is important for women's health?		
Strongly Agree	82	22.5
Agree	91	25.0
Neutral	115	31.6
Disagree	41	11.3
Strongly Disagree	35	9.6
Total	364	100
How likely are you to recommend Pap smear testing to other women?		
Very Unlikely	39	10.7
Unlikely	43	11.8
Neutral	118	32.4
Likely	91	25.0
Very Likely	73	20.1
Total	364	100
What are your feelings about undergoing a Pap smear test?		
Very comfortable	71	19.5
Comfortable	84	23.1
Neutral	121	33.2
Uncomfortable	53	14.6
Very uncomfortable	35	9.6
Total	364	100
Have you ever felt uncomfortable or embarrassed during a Pap smear test?		
Very Unlikely	37	10.2
Unlikely	57	15.7
Neutral	94	25.8
Likely	53	14.6
Very Likely	59	16.2
Not Applicable	64	17.6
Total	364	100
Do you believe Pap smear testing can help prevent cervical cancer?		
Strongly Agree	84	23.1
Agree	102	28.0
Neutral	88	24.2
Disagree	55	15.1
Strongly Disagree	35	9.6
Total	364	100

not significantly impact screening behavior as cervical cancer is often asymptomatic in early stages [25]. Majority (45.9%) of the respondents identified HPV test as a type of cervical cancer screening, this aligns with the findings of Dozie et al. [20], where knowledge of Pap smear testing was reported at 53.9%. This was also in tandem with studies by Nthiga [26] and Owoeye & Ibrahim [27], which found knowledge level of pap smear at 75% and 56.2%, respectively.

Healthcare professionals were the primary source of information on Pap smear (49.3%). This finding is consistent with other studies that identified medical practitioners and health workers as the major source of information about cervical cancer and Pap smear [28-30]. However, this contrasts with a study in Enugu, Nigeria, where media was the predominant source of information [23]. This highlighted the influence of medical practitioners on awareness level. This suggests that health workers remain a crucial means for disseminating accurate cervical cancer information, especially in areas where media reach is limited.

Although there was high level of knowledge about pap smear testing among the respondents, a considerable large proportion, (61.8%) had not undergone the test. The low uptake of cervical cancer screening as found in this study is in agreement with the 7.1% reported in Imo State [29]. Other studies among women revealed similarly low screening uptake. A lower rate 1.78% and 13.91% was reported in a study conducted in, Anambra State and Lagos State, respectively [28, 31]. This pattern is consistent across Sub-Saharan Africa, where systematic reviews have documented screening uptake rates typically below 20% despite moderate awareness levels [10]. Notably, even health education interventions have shown limited success in improving uptake without addressing structural barriers. A study among market women in Lagos demonstrated significant knowledge increases post-intervention, yet screening uptake remained unchanged, highlighting that knowledge alone is insufficient without addressing systemic and financial barriers [32].

Key barriers identified included the belief that Pap smears are expensive (61.3%), embarrassing (61.0%), and the challenge of distant screening centres (60.1%). These findings are consistent with those of a study conducted in Kenya, where lack of information (77%) and limited understanding of cervical cancer (85.9%) were reported as major impediments to screening uptake [26]. Similarly, another study highlighted lack of awareness (51.58%) and the unavailability of screening facilities (15.84%) as significant reasons for non-participation in cervical cancer screening programs [28]. The financial barrier is particularly significant in Nigeria's health system where out-of-pocket expenditure dominates, and cervical cancer screening is rarely covered by health insurance [33]. Embarrassment stems from cultural norms around modesty and the intimate nature of pelvic examination. A study has documented that 94% of tertiary students cited embarrassment as a barrier, with fear of the procedure and results representing additional psychosocial barriers [34]. Furthermore, the challenge of distant screening centers reflects critical health system failures, as there is no organized routine screening program in Nigeria, and services are concentrated in tertiary hospitals primarily in urban centers [33, 35]. These findings highlight the importance of raising awareness through targeted health education and making screening services easier to access, in order to overcome both misinformation and practical challenges.

Tab. VI. Respondents' Beliefs Towards Pap Smear Testing.

Beliefs	SA (%)	A (%)	N (%)	D (%)	SD (%)
Only Promiscuous Women Get HPV	77 (21.2)	62 (17.0)	67 (18.4)	93 (25.5)	65 (17.9)
A regular Pap test is enough to protect women against cervical cancer.	43 (11.8)	57 (15.7)	63 (17.7)	92 (25.3)	109 (30.0)
If a woman gets the HPV vaccine, she no longer needs the Pap or HPV test.	73 (20.1)	81 (22.3)	54 (14.8)	113 (31.0)	43 (11.8)
Pap smears are painful and uncomfortable	31 (8.5)	44 (12.1)	58 (15.9%)	116 (31.9)	115 (31.6)
Pap smears are expensive	116 (31.9)	107 (29.4)	54 (14.8)	54 (14.8)	34 (9.3)
Undergoing Pap smear means you have cervical cancer	16 (4.4)	27 (7.4)	83 (22.8)	106 (29.1)	132 (36.3)
Pap smears are only necessary if you're sexually active	159 (43.7)	118 (32.4)	45 (12.4)	24 (6.6)	18 (4.9)
Pap smears are embarrassing	106 (29.1)	116 (31.9)	64 (17.6)	51 (14.0)	27 (7.4)
Pap smears are not necessary after menopause	47 (12.9)	59 (16.2)	38 (10.4)	108 (29.7)	112 (30.8)
A pap smear test is the same thing as an HPV test	54 (14.8)	68 (18.7)	58 (15.9)	106 (29.1)	78 (21.4)
If you get a pap test before having sex, it means you're not a virgin.	86 (23.6)	98 (26.9)	59 (16.2)	67 (18.4)	54 (14.8)
If you get an abnormal result from a pap test, it always means you have cancer.	53 (14.6)	62 (17.0)	73 (20.1)	105 28.8)	71 (19.5)

SA= Strongly agreed, A= Agreed, N= Neutral, D= Disagree, SD= Strongly disagreed

Conclusion

The respondents were aware of cervical cancer and the Pap smear test, but screening uptake remained low due to common misconceptions, such as viewing the procedure as embarrassing or expensive, or believing it is unnecessary after receiving the HPV vaccine. Addressing these barriers requires improved public education, routine integration of cervical cancer screening into healthcare services, and regular training for healthcare providers to ensure they offer supportive, patient-centred care. Awareness programs in schools and universities can also play a vital role in increasing knowledge and encouraging early screening.

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Conflict of Interest Statement

The Authors have declared no conflict of interest relevant to the study.

Availability of data and materials

The materials used in this study will be made available on reasonable request by the corresponding author.

Author's Contributions

UWD conceptualized and supervised the study, designed the questionnaire, participated in the analysis, contributed significantly to drafting and revising the manuscript. NFC participated in data collection and analysis, MAN, UGE, IMD, COR performed literature search and synthesis, KCND participated in the statistical analysis, UMC, CCI, OCC, INSD revisited the manuscript and critically evaluated the intellectual contents, all authors read and signed the final version of paper.

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HEALTH TECHNOLOGY ASSESSMENT

Strategic health policy priorities for health technology assessment development in Iran

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Keywords

Health Technology Assessment • Iran • Multi-Criteria Decision Analysis • Capacity Building • Health Policy

Summary

Background. *Health Technology Assessment (HTA) is a key policy instrument for improving the efficiency, equity, and transparency of healthcare resource allocation, particularly in low- and middle-income countries such as Iran. Despite its recognized importance, HTA development in Iran has been hindered by institutional fragmentation, limited capacity, and insufficient financial and data infrastructure. This study aimed to identify and prioritize strategic policy actions for HTA development in Iran using a Multi-Criteria Decision Analysis (MCDA) approach.*

Methods. *A multi-stage, mixed-methods design was employed, including a systematic literature review, 25 semi-structured expert interviews, and pilot testing. Findings from the systematic review and interviews informed the development of a comprehensive checklist of potential HTA development strategies. The checklist was validated through expert panel review and pilot-tested for reliability and usability. Eight evaluation criteria, such as feasibility, alignment with national priorities, equity, cost-effectiveness, and stakeholder acceptance, were applied within an MCDA framework to prioritize the identified strategies. Weighted scores were calculated and normalized to generate a ranked list of priorities. In addition, a structured expert consensus process was used to ensure that no essential criterion was excluded and that all selected criteria reflected both global evidence and local contextual needs.*

Results. *Fifteen strategies were identified and evaluated. Establishing a centralized national HTA body ranked as the top priority (weighted score: 82.25), followed by strengthening HTA workforce capacity (79.75) and securing sustainable funding (78.25). Additional high-priority strategies included promoting public awareness of HTA, integrating HTA into national policy processes, and developing robust data infrastructure. Moderate-priority strategies involved enhancing stakeholder collaboration, strengthening research and innovation, and expanding international partnerships.*

Lower-priority but still important strategies included enhancing transparency, creating context-specific evaluation metrics, involving NGOs, and promoting equitable access to health technologies. Sensitivity analyses with different weighting scenarios showed consistent top-ranked strategies. This confirmed the robustness and reliability of the MCDA model.

Conclusion. *The study proposes an evidence-informed roadmap for HTA development in Iran. It highlights key priorities, including a centralized authority, capacity building, and dedicated funding. These steps can support the institutionalization of HTA and its use in policy decisions. Although focused on Iran, the findings are applicable to other resource-limited settings. The MCDA approach offers a transparent method for priority-setting in HTA systems.*

Introduction

Health Technology Assessment (HTA) has emerged as a key policy instrument for improving the efficiency and equity of healthcare resource allocation, particularly in low- and middle-income countries (LMICs) where financial and structural constraints are more pronounced [1]. In Iran, healthcare expenditure represents approximately 6% of GDP, with out-of-pocket payments accounting for nearly 40% of total health spending [2]. These fiscal pressures, combined with demographic changes, population aging, and persistent disparities in access to care, highlight the urgent need for a more systematic and institutionalized HTA framework [3]. While major urban centers increasingly adopt advanced medical technologies, many rural regions continue to lack essential services, exacerbating inequities and underscoring the importance of evidence-informed decision-making [4]. Various theoretical foundations, including health economics and decision theory, have informed models for HTA implementation in resource-limited health systems [5].

HTA is defined as a multidisciplinary process that examines the medical, economic, social, and ethical implications of health technologies, including medicines, devices, and clinical interventions [6]. By generating robust evidence to guide policy decisions, HTA helps identify cost-effective interventions and supports more transparent and accountable resource allocation [7]. In LMICs such as Iran, where health

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systems face substantial budgetary and infrastructural limitations, HTA can play a particularly transformative role in improving system-wide efficiency and addressing inequities [8]. Complementary approaches such as Multi-Criteria Decision Analysis (MCDA) enable decision-makers to incorporate a broader range of criteria, including ethical and social considerations, into the evaluation process, making them especially valuable in contexts where trade-offs between competing priorities are common [9]. Moreover, MCDA provides a structured way to incorporate stakeholder values and non-economic dimensions of decision-making, which is critical in health systems undergoing rapid transition.

Despite these advantages, efforts to institutionalize HTA in Iran have been constrained by several systemic barriers. These include the absence of a dedicated HTA agency, limited engagement from key stakeholders such as private sector providers and civil society, and fragmented data systems that impede reliable assessment of health technologies [10]. Challenges such as the lack of centralized data repositories reduce the accuracy of economic evaluations, while insufficient stakeholder participation may hinder acceptance and implementation of HTA recommendations [11]. Lessons from other LMICs, such as Thailand, South Africa, and Brazil, demonstrate that HTA can be successfully adapted and institutionalized even in constrained environments, provided that development strategies align with national needs and system capacities [12-14]. Iran's earlier attempts to establish HTA functions, initiated in the mid-2000s, were limited in scope and sustainability, further underscoring the need for a more coherent and institutionalized strategy.

Recognizing these challenges, the Iranian Ministry of Health and Medical Education (MoHME) has emphasized the importance of integrating HTA into national health planning to improve resource allocation and promote equitable access to care [15]. However, existing initiatives have largely been fragmented and lack a structured mechanism for prioritizing development strategies tailored to Iran's institutional and socio-political context [16]. This gap underscores the need for a systematic methodology capable of identifying, evaluating, and prioritizing strategic actions for HTA development [17]. In this regard, MCDA offers several advantages over traditional approaches, such as cost-effectiveness analysis or budget impact analysis, as it allows the incorporation of broader ethical, social, political, and organizational, into the decision-making process [18]. Importantly, MCDA is particularly suited to contexts like Iran, where policy decisions often involve balancing competing objectives, such as fiscal sustainability, equity enhancement, and service expansion, within a politically complex governance structure.

MCDA is particularly well-suited for policymaking environments characterized by complex trade-offs and diverse stakeholder perspectives [19]. Unlike traditional economic evaluation methods, MCDA enables a multidimensional assessment of alternatives based on criteria such as feasibility, equity, social acceptability, and long-term system impact [20]. This makes it highly relevant for Iran, where policymakers must simultaneously address budget constraints, equity concerns, and the challenges of a transitioning health system [8]. For instance, MCDA allows for balancing the pursuit of cost-effective interventions with the ethical imperative of equitable access, an issue especially pertinent in underserved regions [13]. Although the importance of HTA has been increasingly recognized in LMICs, limited evidence exists on how to prioritize HTA development strategies in resource-constrained settings such as Iran [21]. Most prior studies have focused on high-income contexts or have not addressed the specific institutional and societal barriers relevant to Iran [22]. Meanwhile, countries like Thailand, South Africa, and Brazil provide examples of successful HTA institutionalization that can inform Iran's policy trajectory [12-14]. However, these examples also highlight that HTA institutionalization requires strong governance commitment, stable financing, and sustained capacity building, factors that must be critically assessed in Iran's context.

To address this gap, the present study employs an MCDA framework to identify and prioritize strategic actions for HTA development in Iran. By evaluating strategies against criteria such as feasibility, anticipated impact, and alignment with national health priorities, this research aims to generate actionable policy guidance for integrating HTA into the Iranian health decision-making ecosystem. The study also considers the ethical and social implications of HTA, particularly its potential to reduce disparities and improve population health outcomes, which are critical for achieving broad stakeholder support. Furthermore, this research acknowledges that HTA development is inherently shaped by political, organizational, and cultural factors and therefore seeks to provide recommendations that are operationally realistic within Iran's governance structure.

Methods

This study was conducted from May to November 2024 using a multi-stage, mixed-methods design to develop and validate a comprehensive checklist for prioritizing strategies for HTA development in Iran within an MCDA framework. The methodological approach was selected to ensure both theoretical rigor and practical relevance by integrating global best practices with contextual insights from national experts. The process involved four sequential stages: a systematic literature review, expert interviews, checklist development and validation, and pilot testing.

Stage 1: systematic literature review

A comprehensive systematic literature review (SLR) was undertaken to identify criteria and strategic actions used for HTA development in various countries. The review followed PRISMA guidelines to ensure methodological

transparency and reproducibility. Four major electronic databases, PubMed, Embase, Web of Science, and Scopus, were searched for studies published between 1990 and November 2024. The search strategy incorporated a combination of keywords and MeSH terms such as "health technology assessment," "HTA framework," and "HTA development" to allow for an inclusive search of both foundational and contemporary literature. Eligible studies were peer-reviewed articles, guidelines, and technical reports published in English that focused on HTA development, implementation, or evaluation strategies. Studies that lacked actionable criteria for HTA development or were irrelevant to LMIC contexts were excluded. Disagreements regarding study inclusion were addressed through consensus discussions, with a senior HTA expert (MaB) serving as arbitrator when needed. Data were analyzed thematically using MAXQDA 13 software to code, categorize, and synthesize key themes. A third author (SA) arbitrated unresolved discrepancies. The extracted items were consolidated into a preliminary list, forming the foundation for further contextualization during subsequent stages.

Stage 2: contextualization through expert interviews

To contextualize the preliminary checklist for Iran's healthcare system, 25 semi-structured expert interviews were conducted using an interview guide specifically developed for this study. The inclusion of 25 experts is consistent with the typical size of HTA expert communities in LMICs, where specialized expertise is often limited, and reflects established sample ranges reported in previous methodological HTA studies. Derived from the SLR findings, the guide included open-ended questions to assess the relevance of each preliminary item and to allow experts to propose additions or modifications based on their professional experience. Experts were selected through purposive sampling to ensure diverse perspectives across regions, sectors, and expertise levels. Participants included policymakers, healthcare administrators, clinicians, and academics from both the public and private sectors. The interview guide was reviewed by two independent HTA researchers and piloted with two experts before data collection. Ethical approval was obtained from the Institutional Review Board of Lorestan University of Medical Sciences, and informed consent was secured from all participants. Interviews (60-90 minutes each) were conducted either in person or virtually, depending on participants' availability. All interviews were audio recorded with consent, transcribed verbatim, and analyzed using MAXQDA 13. Two researchers independently coded the transcripts, and discrepancies were resolved through iterative discussions to ensure analytic rigor. The final interview guide is available in Table. S1.

Stage 3: development and validation of the comprehensive checklist

Insights from the SLR and expert interviews were synthesized to produce a comprehensive checklist intended to guide HTA development in Iran. To establish content validity, the checklist was reviewed by a panel of 10 experts representing diverse HTA-related backgrounds, including policymakers, healthcare managers, academic researchers, and clinicians. Panel members assessed the checklist's clarity, completeness, and relevance, ensuring that it reflected both theoretical principles and practical requirements for HTA institutionalization. Panel feedback was systematically collected, analyzed, and incorporated into successive versions of the checklist. Recommendations to add missing items or refine existing ones were carefully integrated to ensure alignment with Iran's health system needs and contextual realities. This iterative refinement process ensured that the final checklist maintained conceptual clarity while avoiding redundancy and excessive overlap across items.

Stage 4: pilot testing and final refinement of the checklist

A pilot test was conducted with seven HTA experts and policymakers who had not participated in earlier stages to evaluate the checklist's reliability and practical usability. Participants were asked to apply the checklist to a hypothetical or historical HTA development scenario related to Iran, such as prioritizing new technologies or addressing regional disparities. Structured discussions and written evaluations were used to collect feedback on the checklist's content, format, and usability. Based on these insights, minor revisions were made to enhance clarity and practicality. Reliability testing confirmed strong internal consistency (Cronbach's alpha > 0.8) and inter-rater agreement (Cohen's kappa > 0.7). The finalized checklist was subsequently disseminated to a broader group of 83 HTA experts and policymakers nationwide via a secure online platform. Dissemination through an online platform facilitated broader geographic and institutional representation, thereby improving the validity of the final scoring results.

Explanation of scoring levels

A structured three-level scoring system was developed to evaluate HTA development strategies. Scoring categories were defined through expert consensus, reflecting each item's potential impact on cost-effectiveness, equity, and feasibility:

- High (85-100): strategies offering exceptional value, with strong evidence for reducing healthcare costs and improving population health; well-established and closely aligned with HTA goals;
- Moderate (60-84): strategies demonstrating meaningful improvements in efficiency and outcomes but requiring certain enabling conditions for optimal implementation;
- Low (40-59): Strategies with limited or uncertain effectiveness, often experimental or niche-specific.

This scoring structure was selected to balance discriminatory power with interpretability, ensuring that participants could meaningfully differentiate between high- and low-impact strategies.

Statistical analysis

The MCDA framework was applied to integrate criterion scores and expert-assigned weights, producing a composite score for each item. Criterion weights were calculated as the mean of participant-assigned importance ratings. The composite score for each item was computed using the formula:

Weighted Score (Item) = ∑ (Mean Score for Strategies × Weight for Criterion)

To support cross-item comparison, composite scores were normalized to a 0-100 scale. This quantitative approach enabled transparent and rigorous ranking of HTA development strategies by incorporating both performance scores and the relative importance of each criterion.

The eight MCDA criteria were identified through a combined process of systematic literature review and expert interviews, ensuring both theoretical grounding and contextual relevance. All initially identified criteria were subsequently reviewed and finalized through a structured expert consensus process, and no key criterion considered essential by experts was excluded. Additional criteria, such as political feasibility and organizational readiness, were discussed during the early stages of expert consultation; however, they were excluded due to substantial conceptual overlap with existing criteria and the need to maintain parsimony within the MCDA model. To evaluate robustness, sensitivity analyses were conducted by varying each criterion weight by ± 10% from its baseline value rather than by absolute shifts, ensuring proportional adjustment relative to the original weighting structure. The ranking of top-priority strategies remained unchanged across all tested scenarios, demonstrating the stability of the MCDA outputs. Because MCDA inherently involves subjective judgments in scoring and weighting, the use of multiple expert groups, iterative consensus-building, and sensitivity testing helped mitigate subjectivity and enhance the reliability of the final prioritization results.

Results

The systematic literature review and expert interviews yielded a total of 15 strategies for advancing HTA development in Iran, covering a broad spectrum of activities aimed at strengthening HTA capacity and supporting its integration into the national healthcare system. The search process and extracted items are presented in the supplementary material (Tabs. S2-S3, Fig. S2). The identified strategies include conducting HTA-related research and innovation, developing comprehensive HTA guidelines, creating context-specific evaluation metrics, enhancing data infrastructure, improving stakeholder collaboration, ensuring equitable access to health technologies, establishing a centralized HTA authority, fostering international partnerships, integrating HTA into national policy processes, involving non-governmental organizations (NGOs), raising public awareness of HTA, securing sustainable funding, strengthening regulatory frameworks, improving transparency and accountability, and expanding training and capacity-building for HTA professionals.

Tab. I. Mean weights of evaluation criteria for HTA development strategies in Iran.

Criteria	Weight
Cost-effectiveness	0.20
Equity in access	0.15
Feasibility of implementation	0.15
Impact on health outcomes	0.15
Stakeholder acceptance	0.15
Budget impact	0.10
Alignment with national priorities	0.05
Ethical and social acceptability	0.05

To assess these strategies, eight evaluation criteria were identified based on participant feedback: alignment with national health priorities, budget impact, cost-effectiveness, ethical and social acceptability, equity in access, feasibility of implementation, impact on health outcomes, and stakeholder acceptance. Definitions of all criteria are provided in the supplementary material (Tab. S3). Table I displays the mean weights assigned to each criterion, reflecting participants' perspectives on the relative importance of various dimensions of HTA development. Alignment with national priorities and feasibility received the highest weights, emphasizing the importance of practical, context-sensitive strategies for Iran's healthcare environment. These weighting patterns underscore the extent to which policymakers prioritize institutional feasibility and national alignment over purely economic considerations when evaluating HTA development options.

Using the MCDA framework, weighted scores were generated for each strategy and used to rank priorities (Tab. II). The assessment across the eight criteria is illustrated in Figure 1, which presents a heatmap visualizing the performance of each strategy. Darker intensities represent stronger alignment with a given criterion. Strategies such as establishing a centralized HTA body, building professional capacity, and securing dedicated funding scored consistently high across multiple dimensions, suggesting their foundational importance for effective HTA institutionalization in Iran.

Among all strategies, establishing a centralized HTA body emerged as the top priority (weighted score: 82.25). This highlights the need for a unified governance mechanism to coordinate HTA activities and ensure methodological and procedural consistency. Training and capacity building for HTA professionals ranked second (79.75), underscoring the need to develop local technical expertise to sustain HTA functions. Securing dedicated funding for HTA activities ranked third (78.25), reflecting the importance of financial stability for long-term system development.

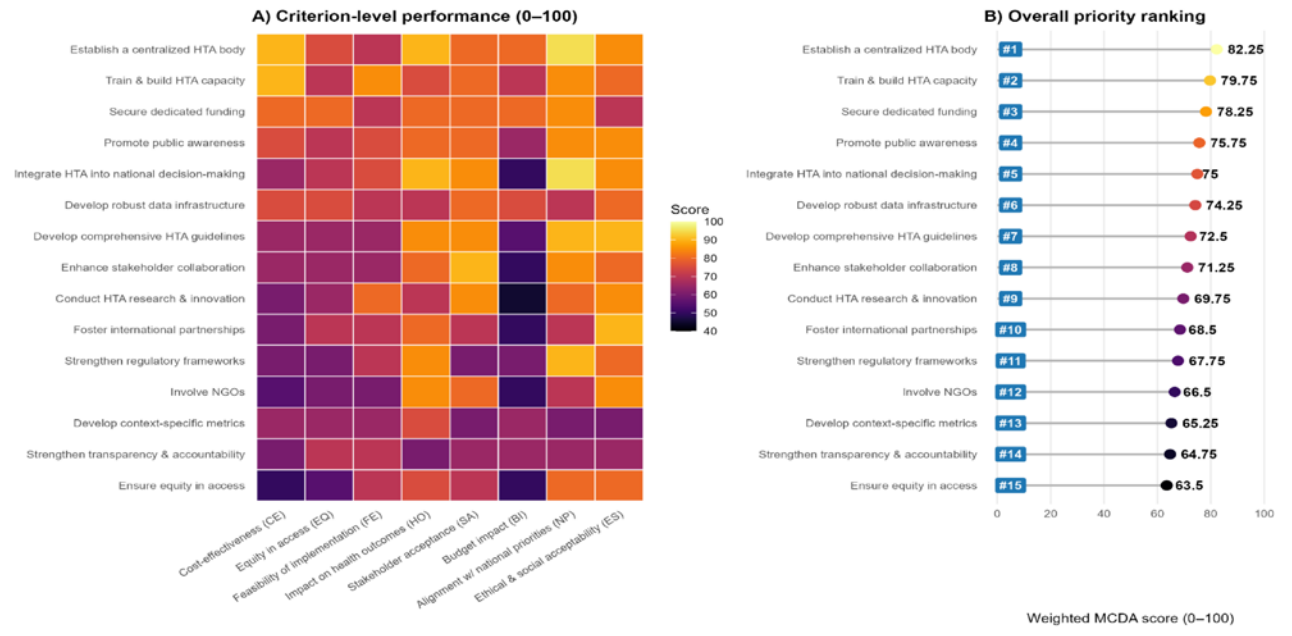
Other high-priority strategies included promoting public awareness of HTA (75.75), integrating HTA into national

Tab. II. Mean Scores of HTA development strategies in Iran based on evaluation criteria.

Strategy	CE	EQ	FE	BI	SA	HO	NP	ES
Establish a centralized HTA body	90	75	70	80	80	90	95	85
Train & build HTA capacity	90	70	85	70	80	75	85	80
Secure dedicated funding	80	80	70	80	80	80	85	70
Promote public awareness	75	70	75	65	80	80	85	85
Integrate HTA into national decision-making	65	70	75	50	85	90	95	85
Develop robust data infrastructure	75	75	70	75	80	70	70	80
Develop comprehensive HTA guidelines	65	65	65	55	85	85	90	90
Enhance stakeholder collaboration	65	65	65	50	90	80	85	80
Conduct HTA research & innovation	60	65	80	45	85	70	80	85
Foster international partnerships	60	70	70	50	70	80	70	90
Strengthen regulatory frameworks	60	60	70	60	60	85	90	80
Involve NGOs	55	60	60	50	80	85	70	85
Ensure equity in access	50	55	70	50	70	75	80	80
Develop context-specific metrics	65	65	65	65	60	75	60	60
Strengthen transparency & accountability	60	70	70	65	65	60	65	65

CE: cost-effectiveness; EQ: equity in access); FE: feasibility); BI: budget impact; SA: stakeholder acceptance; HO: health outcomes; NP: alignment with national priorities; ES: ethical & social acceptability)

Fig. 1. MCDA performance map and overall ranking of HTA development strategies in Iran.



Panel A presents a heatmap of criterion-level performance scores (0-100) for each HTA development strategy across eight evaluation criteria. Darker blue shades indicate higher performance scores; Panel B displays the overall weighted MCDA scores and priority ranking of strategies. Points represent weighted composite scores, horizontal lines indicate relative score magnitude, and blue labels denote final rank order (rank 1 indicates the highest priority. The x-axis is standardized from 0 to 100 to facilitate comparison across strategies).

policymaking processes (75.00), and developing a robust national data infrastructure (74.25). Moderate-priority strategies included enhancing stakeholder engagement (71.25), strengthening HTA research and innovation (69.75), and expanding international partnerships (68.50). Lower-priority strategies, though still relevant, included strengthening regulatory frameworks (67.75), involving NGOs (66.50), developing context-specific evaluation metrics (65.25), improving transparency and accountability (64.75), and ensuring equitable access to health technologies (63.50).

The prioritization patterns illustrated in Figure 1 underscore the central role of governance, capacity building, and sustainable financing as prerequisites for effective HTA institutionalization in resource-constrained settings. Figure 1 summarizes the results of the MCDA by illustrating both criterion-level performance and overall prioritization of HTA development strategies. As shown in Panel A, foundational strategies such as establishing a centralized HTA body, strengthening workforce capacity, and securing dedicated funding demonstrated consistently high performance across

multiple criteria, particularly feasibility, alignment with national priorities, and impact on health outcomes. Panel B presents the overall weighted MCDA scores, highlighting the establishment of a centralized HTA body as the highest-ranked priority, followed by capacity building and sustainable funding. The clear separation observed between top- and lower-ranked strategies indicates a high level of expert consensus regarding the foundational requirements for HTA institutionalization in Iran.

Sensitivity analysis

A sensitivity analysis was performed to test the robustness of the MCDA results by systematically varying the weights assigned to the evaluation criteria. Multiple weighting scenarios, including ±10% proportional adjustments to each criterion, were simulated to reflect alternative stakeholder priorities. Unlike earlier exploratory analyses, the proportional adjustment approach ensured that changes to individual criteria remained consistent with the baseline structure of Table 1, thereby preventing artificial inflation or distortion of relative weights. For example, the weight for "alignment with national health priorities" (baseline = 0.05) was varied within a proportional ± 10% range (0.045-0.055), with corresponding adjustments applied to the remaining criteria. Similar sensitivity tests were conducted for feasibility, equity, cost-effectiveness, and other criteria.

Across all weighting scenarios, the top-ranked strategies, establishing a centralized HTA body, strengthening HTA workforce capacity, and securing sustainable funding, remained unchanged, demonstrating the stability of the results. For instance, even when the weight for feasibility was reduced by 10%, or when the weight for equity was increased by 10%, the top three rankings remained identical, indicating that the prioritization is not overly sensitive to small changes in criterion importance.

Additionally, a threshold analysis identified the minimum weight required for each criterion to influence the ranking. For example, cost-effectiveness needed to increase to at least 0.25 of total weight before it could override the influence of feasibility or national alignment in determining top priorities, highlighting the structural dominance of feasibility-related considerations in Iran's HTA context.

These findings collectively confirm the robustness of the MCDA model and demonstrate that the prioritization outcomes are not dependent on a narrow set of assumptions. Expanding the analysis to incorporate additional weighting scenarios and a wider range of stakeholder perspectives, particularly comparing results with international HTA systems such as Thailand and South Africa, could further enhance interpretability and policy relevance. Moreover, explicitly examining trade-offs, such as tensions between feasibility and equity, would enrich the policy discussion and better align the findings with global HTA best practices.

Discussion

This study applied an MCDA framework to identify and prioritize strategies for strengthening HTA in Iran, with the results emphasizing the fundamental importance of capacity-building and structural reforms. Strategies such as establishing a centralized HTA body, investing in professional training, and securing dedicated funding emerged as the highest-ranked priorities. These findings underscore the need for institutionalization, stable financing, and systematic capacity development as

Tab. III. Roadmap for short-, medium-, and long-term strategies for HTA development in Iran.

Timeline	Strategic objectives	Key policy actions	Responsible organizations
Short-term (1-2 years)	Establish governance foundations for HTA	• Create a centralized national HTA body via MoHME decree or legislation • Define mandate, governance structure, and operating procedures • Begin dedicated budget allocation for HTA activities	MoHME, Parliament, IFDA, National Insurance Organizations, Universities
Medium-term (3-5 years)	Integrate HTA into routine policy processes	• Embed HTA into technology approval, benefits package design, pricing & reimbursement • Develop national HTA guidelines and context-specific evaluation metrics • Strengthen data infrastructure (registries, cost data, utilization databases) • Expand stakeholder engagement mechanisms	MoHME, IFDA, Insurance Council, National Data Center, Professional Associations
Long-term (5+ years)	Institutionalize HTA and expand its social legitimacy	• Link HTA outputs to annual resource allocation and priority-setting cycles • Implement HTA-based equity-focused interventions • Develop participatory HTA models (community-based, deliberative panels) • Strengthen transparency & accountability mechanisms	MoHME, HTA Authority, Parliament Budget Office, NGOs, Universities, International Partners

essential prerequisites for embedding HTA into Iran's health decision-making processes. In particular, the consistent ranking of these foundational strategies across multiple weighting scenarios indicates that they represent core system requirements rather than optional enhancements.

The prioritization of establishing a centralized HTA body as the top-ranked strategy is consistent with international experiences, where national HTA agencies have played a pivotal role in coordinating activities and ensuring methodological consistency in decision-making [23]. Thailand provides a well-studied example: the establishment of a dedicated HTA body under its Ministry of Public Health has facilitated the evaluation of health technologies and informed national benefit-package decisions. Thailand's achievements, underpinned by strong political commitment, international partnerships, and deliberate investments in capacity building, offer several relevant lessons for Iran [24]. Similarly, South Africa's efforts to integrate HTA into national policy processes have advanced the adoption of cost-effective interventions and reduced inequities in access to healthcare [25]. These cases highlight that long-term political commitment, dedicated financial resources, and sustained technical capacity are indispensable components of successful HTA institutionalization.

China's experience further illustrates how HTA development can be closely tied to broader health sector reforms aimed at improving efficiency and equity. The creation of a centralized HTA mechanism in China has facilitated systematic evaluation of clinical and economic evidence and strengthened alignment with national priorities [26]. International collaborations have also played a key role in expanding China's HTA capacity, highlighting the value of global partnerships for resource-limited settings like Iran [27]. Turkey has likewise established a formal HTA structure that informs national policy, and its experience further demonstrates the benefits of leveraging international collaborations and institutional partnerships to build capacity [28].

Egypt has focused its HTA development efforts on building local technical expertise and embedding HTA into decision-making processes, supported by international organizations [29]. Jordan has also made progress by establishing a centralized HTA body that guides national evaluation efforts and policy decisions [30]. Both cases underscore the importance of political support and sustained financial investment, factors that are equally critical for Iran. These examples also demonstrate that HTA development is not a linear process; instead, it evolves through iterative cycles of institutional learning, stakeholder negotiation, and policy adaptation.

Malawi offers an instructive example from sub-Saharan Africa. Although some HTA-related functions exist within national bodies such as the Ministry of Health Senior Management Team and the Pharmacy and Medicines Regulatory Authority, these mechanisms remain fragmented and informal [7, 11]. Institutionalizing HTA in Malawi would require stronger political will, dedicated financing, and systematic capacity building, challenges that mirror Iran's context. In India, a national HTA initiative has been established to promote the generation of local evidence for decision-making, illustrating the importance of developing context-specific HTA frameworks in large and diverse health systems [31].

Indonesia has integrated HTA into its national health insurance system to support decision-making on medicines and medical devices, demonstrating the importance of aligning HTA with universal health coverage (UHC) reforms [32, 33]. Brazil, through its national HTA commission, has underscored the need for stakeholder involvement and transparency, elements that can enhance trust and legitimacy in HTA processes [34]. Other South American countries, including Colombia and Argentina, have used HTA to guide decisions on the adoption of new technologies within public health programs [35]. These countries have invested in capacity-building initiatives and institutionalizing HTA processes, highlighting the value of long-term commitment and stakeholder engagement [36]. Taken together, these international experiences demonstrate that HTA development requires context-sensitive strategies that align with institutional capabilities, political environments, and health system goals [37]. Conversely, countries lacking centralized HTA bodies frequently face fragmented processes and limited progress, a challenge also encountered in Iran [38]. Context-specific evaluation methods and capacity-building initiatives have been recommended in such settings [8], emphasizing the relevance of tailored approaches for Iran's socio-political and economic environment. Furthermore, international evidence suggests that failure to build strong governance structures and institutional accountability mechanisms can lead to HTA systems that function symbolically rather than substantively, an important cautionary insight for Iran.

The findings of this study provide a clear roadmap for HTA development in Iran. In the short term, establishing a centralized HTA authority, investing in workforce development, and securing dedicated funding should be prioritized [1]. These foundational steps would help lay the groundwork for a stable and effective HTA system. Over the longer term, enhancing stakeholder engagement and addressing equity issues will be critical for ensuring the ethical and social acceptability of HTA recommendations [5]. Importantly, the prioritization results reveal systematic trade-offs: strategies with high cost-effectiveness did not always score strongly on equity or feasibility, suggesting that policymakers will need to balance technical optimization with social and political realities.

The highest-ranked strategies, establishing a centralized HTA body and investing in professional training, offer actionable pathways for integrating HTA into national decision-making [39]. Creating such a body would require legislative support and dedicated resources, but it could serve as a central institution for coordinating activities, setting national priorities, and ensuring

consistency in HTA methodologies [7]. It would also strengthen stakeholder engagement, which is essential for the acceptability and uptake of HTA recommendations. Likewise, building a skilled HTA workforce is vital for sustaining system functions over time. Training programs could be developed in collaboration with academic institutions, international organizations, and established HTA agencies in other countries [40]. Integrating HTA into university curricula would also help create a pipeline of competent professionals [29]. However, workforce expansion must be accompanied by institutional reforms that clarify career pathways, ensure retention, and create incentives for technical excellence. Ensuring sustainable financing is another priority. Dedicated funding sources could include government budgets, public-private partnerships, or international grants [41]. Participation in global health initiatives may also provide opportunities to secure financial resources for HTA development [8]. Lower-priority strategies, such as strengthening transparency, improving regulatory frameworks, and promoting equity, are nonetheless essential for enhancing the legitimacy and fairness of HTA processes [42]. Pilot initiatives, such as community-based HTA or participatory decision-making approaches, could support progress in these areas [43]. These lower-ranked strategies, while not immediate priorities, represent important long-term commitments necessary to ensure the social and ethical robustness of HTA institutionalization.

This study contributes to the growing evidence base on HTA development in LMICs by offering a comprehensive framework for prioritizing strategies tailored to Iran's context. Beyond identifying immediate priorities, it provides insights relevant to other countries with similar institutional and economic challenges. Nonetheless, the study has limitations. Potential biases may have arisen from expert selection, and the MCDA approach inherently involves some subjectivity, particularly in weight assignments. Although multiple layers of triangulation and consensus-building were used to mitigate subjectivity, MCDA outputs inevitably reflect stakeholder perspectives and therefore should be interpreted as one input, rather than the sole determinant in policymaking. Future research could address these limitations by employing alternative multi-criteria approaches, such as Delphi or the analytic hierarchy process to validate results. Comparative studies across multiple LMICs could also deepen understanding of how contextual differences shape HTA development trajectories and enhance the generalizability of MCDA-based prioritization frameworks.

Policy implications

The prioritized strategies identified in this study offer a clear, actionable roadmap for integrating HTA into Iran's health system. Operationalizing these strategies requires coordinated action across key governmental and technical institutions. In the short term (1-2 years), the MoHME should initiate the establishment of a centralized HTA authority through formal legislation or ministerial decree, defining its mandate, governance structure, and relationships with insurance organizations and regulatory bodies. Concurrently, universities and professional associations should begin developing standardized HTA training programs and accredited courses to expand the national HTA workforce. Establishing early-phase pilot units within selected medical universities or major insurance organizations could provide an initial testing ground for HTA processes before nationwide rollout.

In the medium term (3-5 years), HTA processes should be embedded within routine decision-making frameworks of MoHME, the Iranian Food and Drug Administration (IFDA), and major health insurance organizations. Strengthening national data systems, including clinical registries, cost databases, and technology utilization records, will be critical for enabling high-quality HTA analyses. Expanding stakeholder engagement mechanisms, such as consultation platforms with clinicians, NGOs, patient groups, and private-sector actors, will enhance transparency and foster broader acceptance of HTA recommendations. Developing standardized HTA submission pathways for industry and establishing formal consultation procedures can further institutionalize these mechanisms and reduce ambiguity in evidence requirements.

In the long term (5+ years), integrating HTA into national priority-setting cycles and health sector budgeting can promote more equitable and efficient allocation of resources. Institutionalizing periodic evaluation of HTA performance and adopting participatory models, such as community-based HTA or deliberative decision-making, can further strengthen social legitimacy. Aligning Iran's HTA system with successful international experiences, particularly in LMICs, will support ongoing capacity building, benchmarking, and collaboration. Long-term sustainability will also require embedding HTA into regulatory and reimbursement cycles, ensuring that all major clinical or technological investments undergo systematic assessment before approval or inclusion in benefit packages. Taken together, these policy actions provide a feasible implementation pathway that can enhance governance, transparency, and evidence use within Iran's health system. A summarized roadmap outlining the recommended short-, medium-, and long-term actions for HTA development in Iran is presented in Table III to provide policymakers with a clear implementation pathway.

Limitations

While this study provides important insights into HTA development strategies in Iran, several limitations must be acknowledged. First, relying on expert opinions introduces potential bias, as participants' perspectives may reflect their institutional backgrounds and prior experiences. Future studies would benefit from including a broader range of stakeholders, such as patients, civil society groups, and community representatives, to capture a more diverse set of views.

Second, the use of hypothetical scenarios during pilot testing may not fully reflect the complexities of real-world HTA implementation. Applying the prioritized strategies in practical settings or conducting case studies could provide stronger evidence of feasibility and impact. Additionally, the generalizability of these findings is constrained by Iran's unique socio-political and economic context. However, the findings may still help inform HTA development pathways in other resource-limited settings with comparable governance structures and implementation challenges. Future comparative research across multiple LMICs could further clarify which elements of HTA system design are universally applicable and which require tailoring to local institutional realities. Finally, although the MCDA framework offers a systematic and transparent approach to priority setting, it involves subjective judgment in assigning weights to criteria. Although sensitivity analyses demonstrated robustness, further empirical validation using complementary methods, such as Delphi processes, analytic hierarchy process (AHP), or real-world implementation studies, would strengthen the evidence base. Moreover, as HTA systems evolve, periodic reassessment of criteria weights may be necessary to reflect shifting national priorities, technological advances, and stakeholder expectations.

Conclusion

This study offers a structured and evidence-informed framework for prioritizing HTA development strategies in Iran. By highlighting foundational actions, such as establishing a centralized HTA authority, strengthening workforce capacity, and securing sustainable funding, the findings provide a roadmap for integrating HTA into national health decision-making processes. Effective implementation of these strategies has the potential to enhance efficiency, equity, transparency, and overall health system performance. The prioritization results also underscore the importance of aligning HTA system development with broader health sector reforms, ensuring that institutional, financial, and human resources evolve in parallel. Furthermore, the MCDA approach applied in this study demonstrates its value as a practical and adaptable tool for guiding policy decisions in resource-constrained environments. Beyond Iran, the prioritized strategies and methodological approach may also inform HTA development in other low- and middle-income countries facing similar governance constraints and resource limitations. As LMICs increasingly adopt evidence-informed health policies, structured priority-setting tools such as MCDA can provide a transparent and participatory foundation for technology adoption and reimbursement decisions. Overall, this research contributes to both the national policy discourse and the global understanding of HTA institutionalization in LMICs, offering actionable insights for policymakers, practitioners, and researchers seeking to strengthen the use of evidence in health system reform. Continued investment in HTA governance, capacity, and data systems will be essential to ensure that the momentum generated by this study translates into long-term improvements in health outcomes and resource allocation.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of Lorestan University of Medical Sciences (IR.LUMS.REC.1402.310). All methods were carried out in accordance with the ethical principles of the Declaration of Helsinki. All participants were informed about the study objectives, assured of confidentiality, and provided written informed consent before participation. Participation was voluntary, and participants could withdraw at any time without consequences.

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Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author upon reasonable request.

Competing interests statement

The authors declare that they have no competing interests.

Authors' contributions

MaB, SA, AB: conceptualized the study. MaB, MeB, AB, SS: contributed to data acquisition and analysis. All authors: participated in data interpretation. MaB, SS, MM: drafted sections of the manuscript, and all authors reviewed, revised, and approved the final version; MM: editing. All authors are accountable for the accuracy and integrity of the work.

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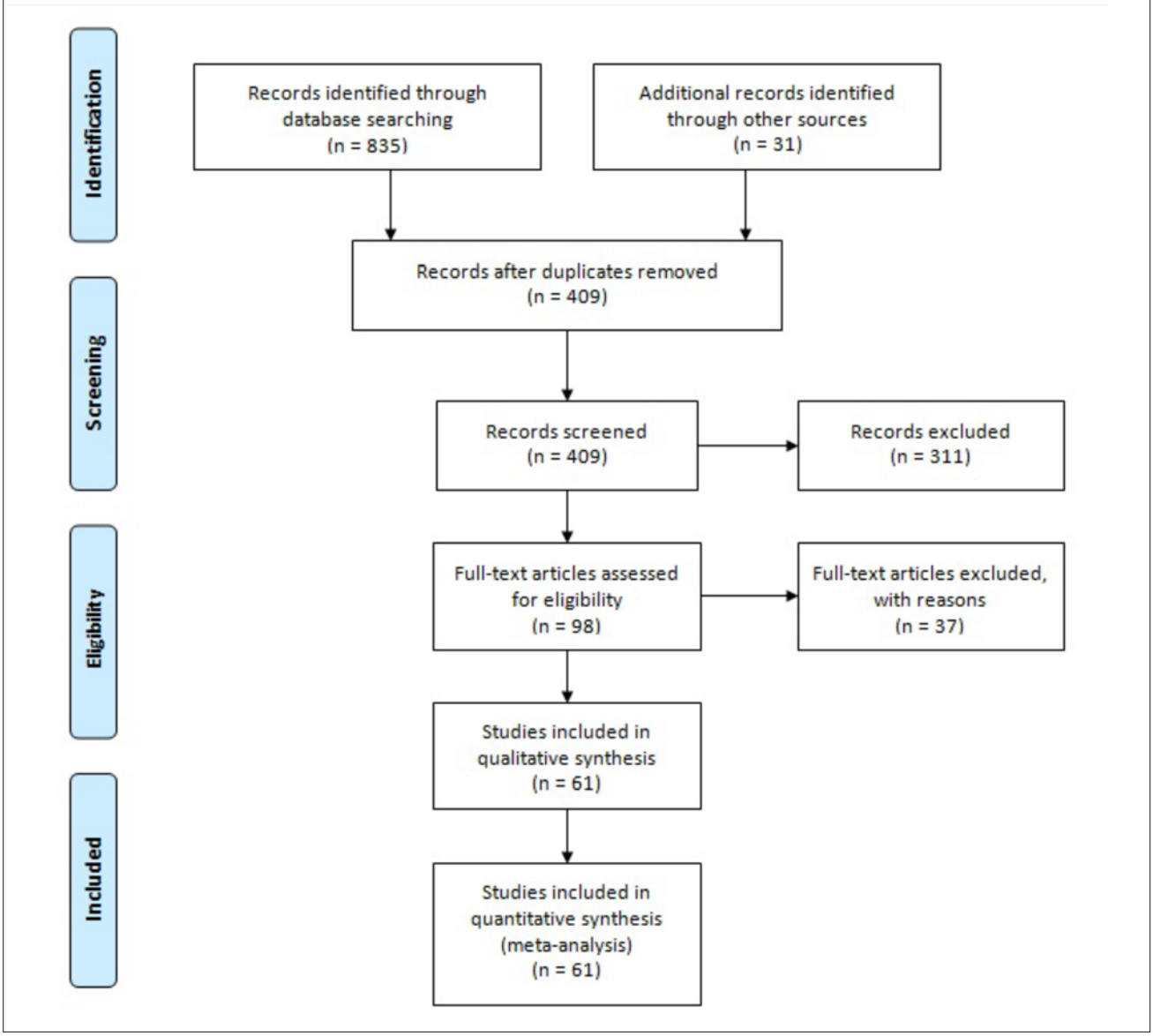
Supplementary material

Fig. S1. Study search process and key findings.



Tab. S1. Interview guide for prioritizing HTA development strategies in Iran.

Interview Guide for Prioritizing HTA Development Strategies in Iran
Introduction: Thank you for participating in this study. The purpose of this interview is to gather your expert insights on the relevance and applicability of strategies for Health Technology Assessment (HTA) development in Iran. Your input will help refine and prioritize these strategies to better align with Iran's healthcare system and priorities.
Section 1: background Information
1. Can you briefly describe your professional background and experience with HTA or healthcare policy?
2. In your opinion, what are the most pressing challenges for HTA development in Iran?
Section 2: evaluation of HTA development strategies
1. Based on our preliminary findings, we have identified 15 strategies for HTA development in Iran. I will now share these strategies with you. For each strategy, please evaluate its relevance and applicability to Iran's healthcare system using the following criteria:
• Alignment with national health priorities
• Budget impact
• Cost-effectiveness
• Ethical and social acceptability
• Equity in access
• Feasibility of implementation
• Impact on health outcomes
• Stakeholder acceptance
Strategies:
• Establishing a centralized HTA body
- How relevant is this strategy to Iran's context?
- What are the potential challenges or barriers to implementing this strategy?
• Training and capacity building for HTA professionals
- How critical is this strategy for sustaining HTA initiatives in Iran?
- What specific areas of training should be prioritized?
• Securing dedicated funding for HTA activities
- How feasible is this strategy given Iran's current healthcare financing system?
- What funding mechanisms would you recommend?
• Promoting public awareness of HTA
- How important is public awareness for the success of HTA in Iran?
- What methods would be most effective for raising awareness?
• Integrating HTA into national policy and decision-making
- How can HTA be effectively integrated into Iran's policy-making processes?
- What are the potential barriers to this integration?
• Developing a robust data infrastructure
- How critical is data infrastructure for HTA development in Iran?
- What steps should be taken to strengthen data systems?
• Enhancing stakeholder collaboration
- Which stakeholders should be involved in HTA development, and how can their collaboration be improved?
• Conducting HTA research and innovation
- What areas of HTA research should be prioritized in Iran?
• Fostering international partnerships
- How can international partnerships support HTA development in Iran?
• Ensuring equity in access to health technologies
- How can equity be ensured in the implementation of HTA strategies?
• Involving non-governmental organizations (NGOs)
- What role can NGOs play in HTA development in Iran?
• Developing context-specific evaluation metrics
- What specific metrics should be developed for Iran's context?
• Strengthening transparency and accountability
- How can transparency and accountability be improved in HTA processes?
• Strengthening regulatory frameworks
- What regulatory changes are needed to support HTA development?
2. Are there any additional strategies that should be considered for HTA development in Iran?
Section 3: Prioritization and Scoring
1. Based on your experience, how would you prioritize the strategies in terms of their potential impact on cost-effectiveness, equity, and feasibility in Iran?

▶

Tab. S1. *(follows).*

2. For each strategy, please assign a score (0–100) based on the following criteria:
• with national health priorities
• Budget impact
• Cost-effectiveness
• Ethical and social acceptability
• in access
• Feasibility of implementation
• Impact on health outcomes
• Stakeholder acceptance
3. Are there any specific conditions or challenges in Iran that might affect the implementation of these strategies?
Section 4: additional Insights
1. Do you have any additional suggestions or recommendations for improving the prioritization of HTA development strategies in Iran?
Thank you for your time and valuable insights. Your contributions will significantly enhance the development of a contextually relevant HTA framework for Iran.

Tab. S2. Main findings.

• Health Technology Assessment (HTA) is increasingly being adopted in low- and middle-income countries (LMICs) to support healthcare decision-making. Traditionally led by high-income countries (HICs), HTA is now gaining traction in least-developed and lower-middle-income countries (LLMICs) to optimize resource allocation and improve patient outcomes. However, the implementation faces challenges such as limited funding, insufficient local expertise, and fragmented processes.
• Governments and policymakers must prioritize investments in capacity-building and institutional frameworks to sustain HTA as a strategic decision-making tool. Strengthening these aspects can ensure that HTA remains relevant and effectively supports healthcare policy decisions in LLMICs.
• Multi-sectoral collaborations are crucial for the successful development of HTA in LLMICs. Many countries lack formal HTA agencies, making partnerships with universities, international organizations, and non-governmental entities essential. These collaborations facilitate knowledge sharing, technical assistance, and policy advocacy.
• Engaging the private sector in HTA discussions can enhance the efficiency and sustainability of health interventions. Policymakers should create regulatory frameworks that support transparent and evidence-based decision-making by fostering strong linkages between HTA stakeholders.
• Despite progress in HTA adoption, gaps remain in its application for disinvestment – phasing out ineffective or obsolete health interventions. Many health systems still allocate resources to low-value technologies, limiting cost-effectiveness. Addressing these inefficiencies is essential for optimizing resource utilization.
• Early HTA, which evaluates health technologies before large-scale implementation, is underutilized in many LMICs. To strengthen HTA's impact, governments should incorporate mechanisms for continuous reassessment and refine disinvestment strategies to ensure funds are directed toward high-impact healthcare solutions.
• Most HTA applications in LLMICs focus on evaluating pharmaceuticals and medical devices, often overlooking system-level interventions. These include health service delivery models, referral pathways, and workforce training. Expanding HTA beyond technology-based solutions can yield significant public health benefits.
• Governments should integrate HTA into national health planning processes to guide policy decisions that enhance healthcare efficiency, equity, and access. This broader application of HTA can improve overall health system performance.
• For HTA to reach its full potential in LLMICs, it must align with universal health coverage (UHC) objectives. Sustainable funding, political commitment, and technical capacity-building are critical for institutionalizing HTA in health policy frameworks.
• Regional cooperation can facilitate the exchange of best practices and accelerate HTA adoption. Future efforts should focus on integrating HTA with financial planning, expanding its scope to include social and ethical considerations, and developing long-term strategies for evidence-informed policymaking.
• Adaptive Health Technology Assessment (aHTA) offers a practical solution for LMICs to implement evidence-based healthcare decisions despite resource constraints. Adaptive methods, such as expedited reviews, international data adaptation, literature synthesis, price benchmarking, and simplified modeling, can help policymakers make timely decisions.
• These approaches allow countries to leverage existing global evidence while customizing it to their local healthcare contexts. For health systems looking to establish HTA, starting with adaptive methods can provide an initial framework to build capacity and institutionalize robust decision-making processes over time.
• Despite its advantages, aHTA has limitations. A major challenge is the transferability of international data, as healthcare costs, patient demographics, and clinical guidelines vary across regions. Without proper adaptation and validation, reliance on global evidence may lead to suboptimal policy decisions.
• Additionally, aHTA does not always foster long-term capacity building in health economics and policy analysis, which are essential for sustainable HTA institutionalization. To mitigate these challenges, health systems should invest in training local experts and data collection efforts to transition from adaptive to full-scale HTA processes.

▶

Tab. S2. *(follows).*

• HTA should not replace traditional HTA but serve as a complementary tool within a broader evidence-based policy framework. LMICs can use aHTA strategically to assess well-established technologies and prioritize cost-effective interventions while allocating resources for comprehensive HTA evaluations when dealing with complex technologies.
• To implement aHTA effectively, governance structures and standardized processes should be established to enhance transparency and credibility. Collaborating with international HTA agencies and academic institutions can bridge technical capacity gaps.
• Engaging a wide range of stakeholders, including clinicians, policymakers, and patient representatives, can improve the contextual relevance of aHTA recommendations. Integrating aHTA findings into national health policy discussions will ensure meaningful contributions to healthcare priority setting.
• HTA has proven to be a critical tool for improving healthcare decision-making in LMICs. Countries that have successfully integrated HTA, such as Thailand and Brazil, have achieved significant cost savings and improved resource allocation.
• However, many LMICs still face barriers in implementing HTA, including limited institutional capacity, lack of funding, and weak regulatory frameworks. To address these barriers, health systems should consider flexible and adaptive HTA approaches that enable pragmatic decision-making while building long-term institutional capacity.
• Agile leapfrogging is one strategy that allows LMICs to bypass traditional, resource-intensive HTA processes and instead adopt adaptive methodologies. This approach enables HTA assessments of entire health benefit packages rather than individual technologies.
• Localization of HTA processes is essential for shifting decision-making authority from external donors to national institutions. Greater country ownership enhances accountability, ensures alignment with local needs, and reduces dependency on external funding.
• Regional collaboration can address challenges such as data scarcity and technical expertise shortages. Instead of establishing separate HTA agencies in each country, regional networks can pool resources, share best practices, and conduct joint evaluations of health technologies.
• The case studies of Thailand's HITAP and the UK's NICE highlight that HTA is not just a technical process but also a policy tool requiring institutional support, stakeholder engagement, and political commitment. Countries must integrate HTA into national health policies to improve efficiency and equity.
• Ultimately, the sustainability of HTA depends on long-term political commitment and institutionalization. Governments must commit to funding HTA activities, embedding them in policy structures, and ensuring systematic application in decision-making. By doing so, LMICs can achieve efficient, evidence-based healthcare investments that improve population health outcomes.

Tab. S3. Definitions and details of evaluation criteria for HTA development strategies.

Criterion	Definition
Alignment with National Health Priorities	The extent to which the strategy aligns with Iran's overarching health goals, policies, and priorities, ensuring that HTA development supports the country's most pressing healthcare needs and objectives.
Budget impact	The financial implications of implementing the strategy, including its potential to affect healthcare expenditures, resource allocation, and the overall budget of the healthcare system.
Cost-effectiveness	The degree to which the strategy provides value for money by comparing the costs of implementation with the health benefits achieved, ensuring efficient use of limited resources.
Ethical and social acceptability	The extent to which the strategy adheres to ethical principles and is socially acceptable to stakeholders, including patients, healthcare providers, and the general public.
Equity in access	The degree to which the strategy promotes fair and equitable access to health technologies across different population groups, reducing disparities and ensuring inclusivity.
Feasibility of implementation	The practicality of implementing the strategy within Iran's healthcare system, considering factors such as available resources, infrastructure, technical capacity, and political will.
Impact on health outcomes	The potential of the strategy to improve health outcomes, such as reducing morbidity and mortality, enhancing quality of life, and addressing key health challenges in the population.
Stakeholder acceptance	The level of support and approval for the strategy among key stakeholders, including policymakers, healthcare providers, patients, and other relevant groups, ensuring broad-based buy-in and collaboration.

History of Medicine and Ethics

Equity in the allocation of hospital beds in Iran: a systematic review and meta-analysis

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Keywords

Equity • Hospital beds • Systematic review • Iran

Summary

Background. *Equitable access to healthcare is a fundamental human right. As capital intensive infrastructures, hospitals consume 40-50% of health expenditure in low and middle-income countries. However, inequities in the allocation of hospital beds compromise efficiency, accessibility and outcomes. This study aimed to systematically review and meta-analyze the available evidence on the allocation of hospital beds in Iran and to quantify the inequality with established indices.*
Methods. *A systematic review has been done in accordance with the principles of PRISMA, and the search process was conducted in international (PubMed, Scopus, Web of Science, EMBASE, CINAHL, DOAJ, MEDLine) and Iranian (SID, BKNS, Magiran) databases, and studies published from 2000 to 2025 in English and Persian language. Eligible studies reported quantitative measures of the allocation of hospital beds using inequality indices. Study quality was evaluated by using the Joanna Briggs Institute checklist. Meta-analysis was conducted using random effects and quality effects models, with heterogeneity being tested by Cochran's Q, I2, and H2.*
Results. *Thirty studies were eligible for inclusion (16 English, 14 Persian). Eight studies contributed 18 effect sizes for meta-analysis. The pooled Gini coefficient was 0.24 (95% CI: 0.20-0.28), and this indicates relative equity across the country, though heterogeneity was very high (I2 = 96.3%). Quality-effects modelling produced a very similar, higher estimate 0.26 (95% CI: 0.21-0.30). At the provincial level, Gini values were found to be between 0.229 (South Khorasan) and > 0.50 (Sistan and Baluchestan, Bushehr), showing the existence of important regional differences. City level inequalities were greater where values of 0.46 and 0.68-0.70 were found in Tehran and Shiraz, respectively, compared to those in Shanghai and Shenyang.*
Conclusion. *While there is national equity in the allocation of hospital beds in Iran there are significant sub-national (provincial and urban) inequities. Addressing these requires equity-focused planning, monitoring and prioritization of disadvantaged regions.*

Introduction

Providing access to health services has been recognized as a fundamental human right [1]. Hospitals as the vital columns of national health systems, are fundamental to the provision of care and to the provision of equitable access to health care services. However, the building and maintenance of hospital infrastructure, particularly bed capacity, is one of the most capital-intensive investments in health care [2]. Hospitals in most low and middle-income nations account for more than 35% of spending on health, underscoring the fact that they are a significant expenditure [3]. Conversely, inefficiencies in the use of resources is often accompanied by wastage estimated to be between 20 and 40 percent which erodes systems performance as well as long-term viability [4]. Due to high capital investments, the structure of hospitals involves region-specific, evidence-based planning to optimally utilize these resources to achieve maximum value for the resources invested [5].
The importance of equitable bed allocation at hospitals is best seen in instances such as the ongoing coronavirus (COVID-19) pandemic, where studies have shown a direct link between lower mortality rates and bed availability [6, 7]. Enhancement in the capacity of the hospital beds in any particular area automatically aids in the movement of specialized staff personnel in medicine, sophisticated medical equipment and other support facilities. Thus, it remains one of the most important parameters for measuring the allocation of fairness in healthcare services [8]. Hence, comparison of the hospital bed index in the regions through the size of their populations is important to establish regions with weak access to healthcare services and to undertake focused allocation of services to regions in want [9]. Nonetheless, no solitary ideal value remains acceptable for the hospital bed index per head of population as this indicator stretches over nations in light of public health culture, disease prevalence, as well as the health system's structure [10]. However, in a country with one health system, the hospital bed indicator can continue to be one of the most important indicators of balanced allocation of resources in regions. Thus, unequal allocation of hospital beds causes wastage of resources as well as migration of patients to cities with superior facilities, aggravating health system problems [11].
Various studies have been done on the allocation of

hospital beds among provinces or within cities of one province. However, these investigations have used diverse indices and methodological approaches, leading to heterogeneous results as regards equity in the allocation of hospital beds [12-14]. Such inconsistency poses problems in drawing a clear assessment in order to support an evidence-based decision making. Consequently, systematic monitoring of the allocation of health resources and the provision of correct evidence for policy makers are imperative [15]. There is a general consensus that implementation of evidence-based health policy-making is gaining momentum in a situation with limited resources like low and middle income countries since high quality and context specific evidence may be used to guide decision makers to tackle problems related to inequalities and resource allocation [16]. Due to the heterogeneity and methodological differences in current literature on hospital bed allocation, a meta-analysis will overcome inconsistencies and will be capable f giving strong evidence to make decisions [17]. The proposed study will address the knowledge gap by undertaking a systematic review and meta-analysis of the allocation of the bed in hospitals in Iran. This is aimed at evaluating equity in the access to hospital beds and giving concrete evidence to health policymaking.

Methods

This systematic review was designed and conducted in 2025, and the results are reported following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines [18].

Search Strategy

The searches were conducted in two international and Iranian databases, including articles published between January 1, 2000, to June 30, 2025. The international databases were Medline, Pubmed, Embase, Cinahl, Directory of open Access journals, Web of Science and Scopus and Iranian databases were SID, Barakat knowledge network system (BKNS), Magiran. Search terms used were: ('Distribution' OR 'Allocation' OR 'Rationing') AND ('Hospital facilities' OR 'Hospital beds' OR 'Hospital resources' OR 'Physical resources' OR 'Healthcare resource') AND 'Iran'. To ensure that no relevant articles were omitted, the resources located were critically reviewed, and studies that were deemed suitable for inclusion based on manual review of the title and abstract were added to the shortlist. The searches were performed independently by two authors, and if any difference occurred between the two, the third party was consulted as the arbitrator and any difference was resolved.

Inclusion and Exclusion Criterion

Included studies were quantitative studies reporting the allocation of hospital beds at the national (inter-provincial), provincial (intra-provincial) or urban level with inequality measures (*e.g.,* Gini coefficient, Coefficient of Variation). We excluded studies that were qualitative in nature, letters to the editor, lacking hospital bed allocation data, as well as those analyses localized to special beds (due to limited comparability and heterogeneity in the allocation logic of beds).

Assessing the Quality of Articles

Two researchers independently extracted the data and conducted the article quality assessments. In case of any disagreement during the data extraction or quality assessment process, a third researcher's opinion was sought to resolve the conflict and reach a consensus. The researchers were blinded to the authorship of the studies to prevent any potential bias in the evaluation process. Two researchers independently assessed the quality of the studies included in the final analysis The quality of the articles was assessed using the Joanna Briggs Institute (JBI) checklist for cross-sectional studies. This checklist consists of 8 criteria. Each article was scored based on these criteria and assigned one of the following values: conformity (Y), nonconformity (N), unclear (U), and items not applicable to the article (N/A). Studies were then categorized based on the percentage of conformity: studies with less than 50%, 50-70%, and greater than 70% conformity were categorized as low, medium, and high quality, respectively [19].

Statistical Analysis

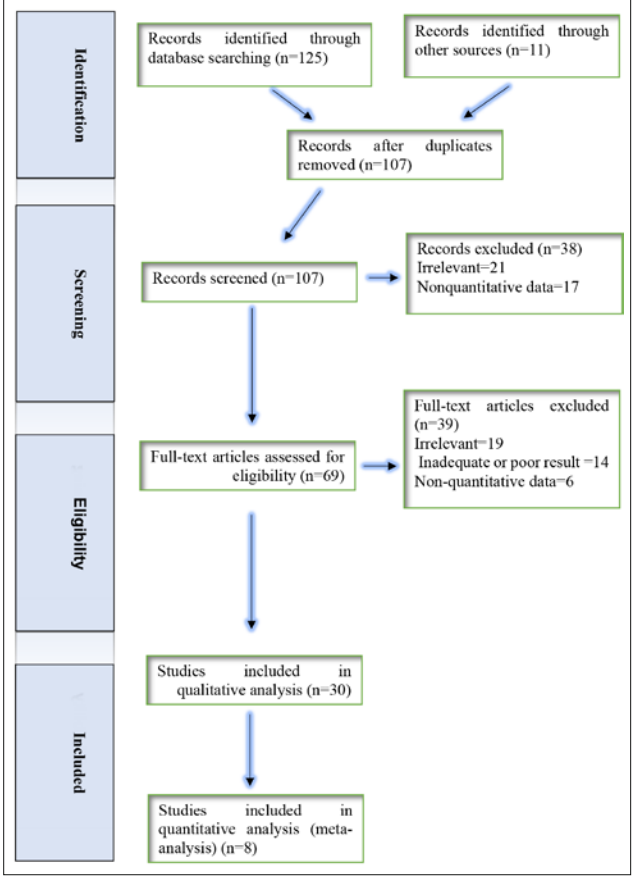
The search included international and Iranian databases, looking for articles published from January 1, 2000 to June 30, 2025. Studies in English and Persian were considered eligible for inclusion. Overall, eight studies met the criteria for the meta-analysis; however, because several studies reported the Gini coefficient at more than one time point, a total of 18 effect sizes were analysed. Each reported Gini coefficient for a distinct time point was treated as a separate effect size to preserve temporal information and document changes in inequality over time, while also reflecting study-specific heterogeneity across different periods. Given the anticipated high heterogeneity, we did not conduct subgroup analysis or meta-regression due to the insufficient number of studies available for meaningful exploration of the sources of heterogeneity. The latest version of the Cochrane Handbook suggests a minimum of 10 studies per examined covariate in metaregression [20]. To obtain these estimates, we used both a conventional random-effects model (inverse variance weighting) and a quality-effects model. The heterogeneity between studies was evaluated with Cochran's Q statistic, I2 index and H2 statistic. All analyses have been performed using Stata, version 18 (StataCorp, College Station, TX, USA).

Results

Study selection

The selection process is shown in Figure 1. In all, 136

Fig. 1. PRISMA flow diagram of the study.



records were found (125 by searching the database and 11 by manual search). After eliminating 29 duplicates, there were 107 unique records to screen. Title and abstract evaluation resulted in 69 articles for full text review, out of which 30 articles met the inclusion criteria and were included in the qualitative synthesis (16 in English and 14 in Persian). Among these, 8 studies, specifically looking at national level of equity in the allocation of hospital beds, were included in the meta-analysis.

Study characteristics

The included studies addressed the allocation of hospital beds at the level of different administrative levels: inter-provincial, 8 studies [14, 21-27]; intra-provincial, 18 studies [13, 28-44]; city-level, 3 studies [45-47] and within or across universities of medical sciences, 1 study [12]. Overall, most studies were on provincial-level allocation and comparatively fewer studies examined the allocation on national-level. This imbalance is likely the result of both the limited data available combined with the lack of comprehensive nationwide statistics.

Quality assessment

The methodological quality of the included studies was appraised using the JBI checklist, which has been validated for appraisal of both quantitative and qualitative research in terms of design, methodology, sampling and validity of results [48]. Based on this assessment, 4 studies were determined to be high quality, 18 were medium quality and 8 were low quality. The low-quality studies were excluded from the quantitative synthesis.

Measures of inequality

Among the 33 articles that were included in the final analysis, 32 used the Gini coefficient (or one of its variants) to assess hospital bed allocation. The Gini coefficient, which comes from the Lorenz curve, is generally accepted as the best measure of fairness in the allocation of resources [49]. The index ranges between 0 to 1, where 0 indicates absolute equality and 1 absolute inequality. Conventionally, values < 0.2 represent complete equality; 0.2-0.3, notable equality; 0.3-0.4, inequality; 0.4-0.6, substantial inequality; and > 0.6, absolute inequality" [50, 51]. In addition to the Gini coefficient, a few studies also reported other measures such as the Robin Hood, Gastwirth and Concentration indices. These complementary indicators were not widely applied but were included in Table I.

Meta-analysis Interpretation

A total of 8 eligible studies were included in meta-analysis. Since most of these studies reported Gini coefficients for multiple time periods (*e.g.,* 2006, 2011, and 2016), each figure was treated as an effect size. Therefore, 18 effect sizes were included in a final analysis. Considering all the values reported made it possible to capture the temporal variation and study-specific heterogeneity, and thus allow a more complete and realistic evaluation of the allocation of hospital beds.

Primary analysis (inverse-variance model).

Using the standard random effects model with inverse-variance weighting, a pooled Gini coefficient of 0.24 (95% CI: 0.20 to 0.28) was estimated (Fig. 2). This estimate implies a notable equity in the allocation of hospital beds across provinces. However, heterogeneity was very high (Cochran's Q = 619.54, df = 17, $p < 0.001$; I2 = 97.3%; H = 6.037). These values mean that virtually all of the observed variability is due to real differences between studies and not chance. Given this high degree of inconsistency, the use of a random-effects model was appropriate, as it accounts for the within- and between-study variance and provides a more realistic pooled estimate [52, 53].

Complementary analysis (quality-effects model).

To further compensate for the methodological rigor, we also used a quality-effects model, as suggested by Doi and Thalib [54]. In this approach, study weights were adjusted based on quality scores based on the Joanna Briggs Institute (JBI) checklist, thus reducing the effect of statistically precise but methodologically weaker studies. The pooled Gini coefficient was 0.26 (95% CI: 0.21 to 0.30) (Fig. 3) under this model. Although broadly

Tab. I. Characteristics of the studies included in the final analysis.

Row Writer – Year – Language	Study Quality	Purpose of Study	Region/ Scope	Inequality Measure	Result
Jalilian 2025 English	Medium	To assess the correlation between the allocation of hospital beds and COVID-19 mortality in South Khorasan Province	South Khorasan	Gini Index	Gini = 0.229 → Equality (2022)
Rezaei 2024 English	High	Investigate trends in healthcare resource allocation inequality in Bushehr province	Bushehr	Gini, CI & RH Index(68, 69),	Gini = 0.47 (2012), 0.48 (2015), 0.49 (2019), 0.47 (2022) → Severe inequality
Behzadifar 2024 English	Medium	To examine the inequality in hospital bed allocation in Lorestan province	Lorestan	Gini Index	Gini = 0.27 (2023) → Equality
Mosadeghrad 2022 Persian	Low	To measure equity in the geographical allocation of hospital beds in Fars province	Fars	Gini Index	Gini = 0.30 (2016) → Inequality
Majiri 2022 Persian	Low	Evaluate inequality in the allocation of healthcare resources in Sistan and Baluchestan	Sistan & Baluchestan	Gini Index	Gini = 0.505 (2014), 0.262 (2015), 0.287 (2016), 0.287 (2017), 0.279 (2019), 0.345 (2022) → Inequality
Khammarniyeh 2021 English	Medium	To assess the equity in the allocation of health resources in Southeast Iran	Sistan & Baluchestan	Gini Index	Gini = 0.526 (2020) → Severe inequality
Mosadeghrad 2020 Persian	Low	To examine equity in the geographical allocation of hospital beds in Zanjan province	Zanjan	Gini Index	Gini = 0.26 (2016) → Equality
Mosadeghrad 2020 Persian	Low	To assess the geographic allocation of hospital beds in Khuzestan province	Khuzestan	Gini Index	Gini = 0.33 (2016) → Inequality
Mosadeghrad 2020 Persian	Low	To measure equity in the geographical allocation of hospital beds in Tehran province	Tehran	Gini Index	Gini = 0.299 (2016) → Equality
Daroudi 2019 Persian	Low	Assess equity in hospital bed allocation in Mazandaran	Mazandaran	Gini Index	Gini = 0.28 (2016) → Equality
Mosadeghrad 2020 Persian	Medium	To examine equity in the allocation of hospital beds across Iran	Iran	Gini Index	Gini = 0.107 (2016) → Complete equality
Mokhtaripayam et al. 2019 English	High	Investigate trends in the allocation of health sector resources in Iran	Iran	Gini Index	Gini = 0.107 (2006); 0.116 (2011); 0.147 (2016) → Equality weakened, but still relatively fair
Ebrahimzadeh 2019 English	Medium	To assess equity in the allocation of hospital beds in Gilan Province	Gilan	Gini Index	Gini = 0.23 (2016) → Equality
Chavehpour 2019 English	Medium	To investigate the socio-economic disparities in the allocation of hospital beds in 5 major cities of Iran	5 Metropolitan Cities	Gini Index	Gini = 0.58 (Tehran), 0.53 (Mashhad), 0.56 (Isfahan), 0.59 (Shiraz), 0.54 (Tabriz) → (2016) Severe inequality
Haghdoost 2018 Persian	High	To evaluate the number and allocation of hospital beds in the country in 2015 and estimate the required hospital beds until 2025	National (Univ.)	Coefficient of Variation	CV = 36% (2016) → High variability
Lotfi 2018 English	Medium	To evaluate the equality of health resources allocation (human resources, hospital beds, and medical centers) among the provinces of the country in 2014	Iran	Gini Index & Robin Hood Index	Gini = 0.14 → Equality; RH = 6.7 → Inequality (2014)
Nouraei Motlagh 2018 Persian	Medium	To estimate the equality between physical and human resources in the health sector among the cities of Lorestan province from 2006 to 2014	Lorestan	Gini Index	Gini = 0.49 (2006); 0.49 (2007); 0.49 (2008); 0.50 (2012); 0.51 (2013); 0.51 (2014) → Severe inequality

▶

Tab. I. *(follows).*

Row Writer – Year – Language	Study Quality	Purpose of Study	Region/ Scope	Inequality Measure	Result
Feyzabadi 2018 Persian	Medium	To evaluate the inequality trend in the allocation of human force and healthcare facilities in Iran from 2006 to 2015	Iran	Gini Index	Gini = 0.45 (2006); 0.30 (2011); 0.42 (2015) → Fluctuating, yet severe inequality
GolpariPour 2018 Persian	Low	Evaluate the inequality in the allocation of hospital resources in West Azerbaijan province before and after the Health System Reform Plan	W. Azerbaijan	Hall-Tiedman Index	Hall-Tiedman Index = 0.129 (2013); 0.153 (2016); Inequality worsened after Health Transformation Plan
Chavehpour 2017 English	Medium	To evaluate the spatial allocation of public and private hospitals in Tehran	Tehran	Gini Index	Gini (2011) Public Sector = 0.6 Private Sector= 0.8 → Absolute inequality
Hatam N 2016 English	Medium	To explore the allocation of hospital beds in Shiraz and surrounding regions	Shiraz	Gini Index	Gini = 0.68 (2014) → Absolute inequality
Rezaei 2016 English	Medium	To evaluate the allocation of physicians and hospital beds in Iran in 2001, 2006, and 2011	Iran	Gini Index	Gini = 0.16 (2001); 0.15 (2006); 0.13 (2011) → Equality
Rezaei 2016 English	Medium	To evaluate the inequality of health resources allocation in Kermanshah province from 2005 to 2011	Kermanshah	Gini Index	Gini = 0.47 (2005), 0.45 (2006), 0.45 (2007), 0.46 (2008), 0.46 (2009), 0.44 (2010), 0.40 (2011) → Severe inequality but improved over time
Ramandi 2016 English	High	To evaluate the allocation of physicians, staff, paramedics, and hospital beds	Iran	Gini Index	Gini = 0.52 (2006), 0.59 (2007), 0.59 (2008), 0.58 (2009), 0.57 (2010), 0.58 (2011), 0.58 (2012), 0.57 (2013) → Severe inequality with fluctuations
Masoudi Asl 2015 English	Medium	To evaluate the allocation of hospital beds across 22 regions of Tehran	Tehran	Gini Index	Gini = 0.46 (2010-2012) → Severe inequality
Sari 2015 English	Medium	To evaluate the inequality of physical and human resources in the health sector among the provinces of the country from 2001 to 2011	Iran	Gini Index & Gastwirth Index(70)	Gini = 0.158 (2001), 0.13 (2011) → Improved Gastwirth = 0.25 (2001), 0.20 (2011) → Improved
Rezaei 2015 English	Medium	To evaluate the access and need to hospital beds and physicians among the provinces of the country during 2001-2011	Iran	Gini Index & Robin Hood Index	Gini = 0.16 (2001); 0.13 (2011) → Equality Robin Hood = 7% (2001); 5% (2011) → Redistribution improved
Rezaei 2015 Persian	Medium	To evaluate the inequality trend in the allocation of resources in the health sector in the cities of Kurdistan province during 2006 – 2016	Kurdistan	Gini Index	Gini = 0.34 (2006); 0.30 (2016) → Inequality improved
Mostafavi et al. 2013 Persian	Low	To assess the allocation of specialist physicians and hospital beds in West Azerbaijan Province	West Azerbaijan	Gini Index	Gini = 0.51 (2012) → Severe inequality
Zandian 2012 Persian	Medium	To measure inequality in the allocation of health resources in Ardabil Province	Ardabil	Gini Index	Gini = 0.60 (2001); 0.59 (2008) → Severe inequality

References in parentheses indicate previous studies that also applied these indices and were used to guide interpretation (64, 65 & 66).

consistent with the inverse variance estimate, the wider confidence interval reflects sensitivity of results to quality and methodological diversity of studies.

Summary of findings

Taken together the two approaches indicate a remarkable equity in the allocation of hospital beds across Iranian provinces. While the inverse variance model is a statistically more precise estimate, the quality effects model adds complementary information by highlighting the importance of methodology in determining results. Accordingly, the final interpretation is based largely

Fig. 2. Forest plots of the pooled Gini coefficients for hospital bed allocation across Iranian provinces. Inverse variance (Random-effects).

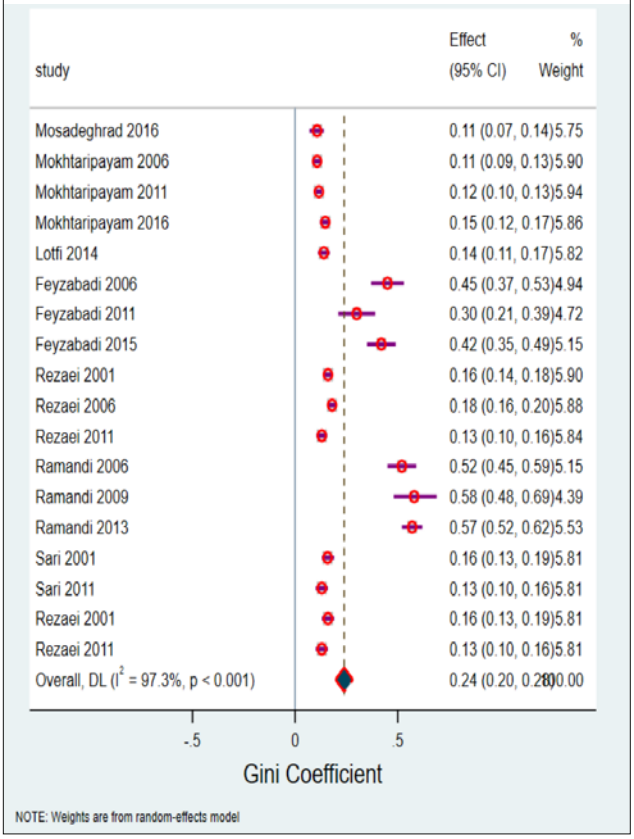
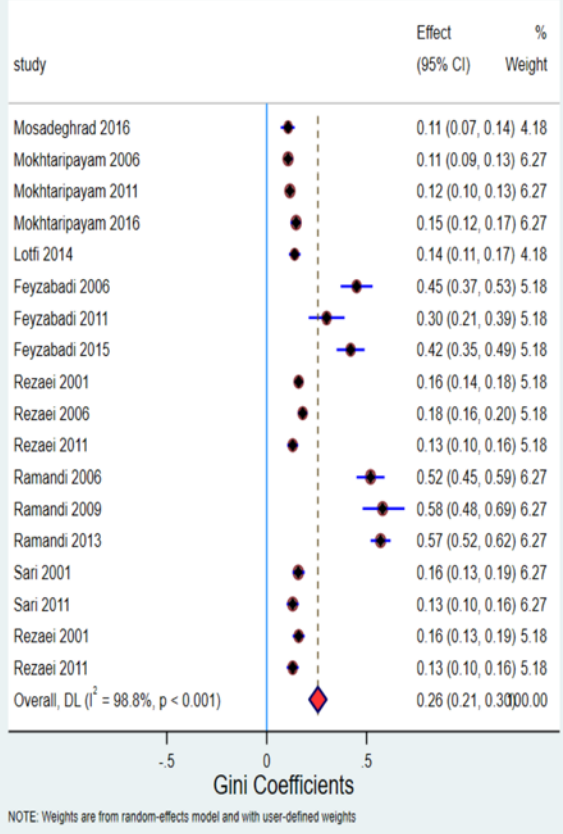


Fig. 3. Forest plots of the pooled Gini coefficients for hospital bed allocation across Iranian provinces. Quality-weighted (Random-effects).



(a) Random-effects model with inverse-variance weighting. The pooled estimate was 0.24 (95% CI: 0.20 to 28). (b) Random-effects model with quality-based weighting (red). The pooled estimate was 0.26 (95% CI: 0.21 to 0.30).Each horizontal line represents the 95% confidence interval (CI) for a reported effect size, labeled by the author and year of data collection. The diamond at the bottom of each panel indicates the pooled estimate with its CI. The wider CI in the quality-effects model reflects the reallocation of weights according to methodological rigor (JBI checklist) rather than statistical precision.

on the inverse variance random effects model with the quality-based model reported as a robustness check.

Intra-provincial studies

Eighteen studies looked at equity of hospital bed allocation within provinces. Reported Gini coefficients were quite different, ranging from 0.229 for South Khorasan (2022) to 0.526 for Sistan and Baluchestan (2020). Most provinces, such as Tehran (0.299, 2016), Fars (0.300, 2016), Zanjan (0.260, 2016) and Gilan (0.230, 2019) reported significant equity allocations. However, severe inequality was identified in Sistan and Baluchestan where Gini coefficients were more than 0.50 in several years and in Bushehr (0.47, 2012-2022). Due to the high heterogeneity in scope, indicators and study design, these studies within provinces were not included in the meta-analysis. Nevertheless, they are important contextual evidence as they reveal that maldistribution of resources is not uniform between provinces and whereas some provinces have relatively equitable resource allocation, other provinces, especially disadvantaged areas such as Sistan and Baluchestan, Lorestan and Kurdistan, show persistently inequitable allocation.

City-level studies

Three studies measured the allocation of hospital beds in large cities. Reported Gini coefficients varied from 0.46 in Tehran to 0.68-0.70 in Shiraz and another study in five metropolitan cities reported more than 0.55. These results suggest substantial to absolute inequality, and are consistent with a concentration of hospital resources in affluent urban districts.

Discussion

Importance of Equity in Resource Allocation

Population health improvement involves more than the absolute increase in resources for health; rather, it requires an equitable allocation of resources [55]. Even if hospital beds are increased, but the resources are not distributed evenly across populations, the improvement in population health is not guaranteed [28]. Evidence from developed as well as developing health systems indicates that maldistribution is linked with reduced accessibility

and efficiency of the delivery of services and increased health disparities, especially in disadvantaged areas [56]. Equity in allocation policies is therefore required to become a fundamental principle of health systems planning, and the benefits from augmented resources must be translated into measurable health outcomes for all population groups [57].

National-Level Findings

At the national level, our meta-analysis of eight eligible studies resulted in a pooled Gini coefficient for hospitalization beds of 0.24 (95% CI: 0.20-0.28), which suggests a notable equity of hospital beds allocation between provinces. However, heterogeneity was extremely strong [I2 = 97.3%], indicating that there were large differences in scope, data quality and methodology. Studies also confirm that data collected from hospitals in Iran suffer from quality issues due to problems such as lack of coherence and integration in information systems and the absence of standardized indicators [58, 59]. To allow robustness, we also complemented the classical random-effects model with a quality-effects model [54]. Hence, by weighting studies according to methodological strength, the effect of weaker studies is minimized. The estimate obtained from the quality-effects model was slightly larger (0.26); however, the congruity between the two models demonstrates the consistency and robustness of the overall interpretation.

International Comparison

Iran's pooled Gini coefficient (0.24) is roughly comparable to the Gini coefficient of South Korea, which had a Gini index for all hospital beds increased slightly from 0.269 in 2008 to 0.273 in 2012, which is a moderate level of inequality, despite the rapid expansion of their health systems [60]. However, the overall bed capacity is much different: in 2022, South Korea had about 12.8 beds per 1,000 people (56) compared to 1.65 in Iran in the same year [61], compared to 1.65 in Iran in the same year [62]. This difference highlights the fact that in situations of low total capacity, equity of access assumes greater importance: even small inequalities can have a powerful limiting effect [4], whereas in high capacity systems such as South Korea, the impact of imbalance is less severe.

By comparison, Iran's performance continues to exceed the unusually equitable level reported for China in 2014 (0.07), owing to far-reaching reforms and massive public investment since 2009 [63]. The same is true in other countries, including Saudi Arabia: the Saudi national Gini index in 2022 was 0.15, a fully equal national allocation by conventional standards [64].

Intra-Provincial Disparities

Subnational analysis shows more dramatic differences. The Gini coefficients within the provinces varied from 0.229 (South Khorasan, 2022) to higher than 0.50 (Sistan and Baluchestan, 2020), and maldistribution remained an unwavering and recurrent pattern in Bushehr, while relatively uniform allocation was observed in Tehran, Fars, Zanjan, and Gilan. These disparities are located in structurally deprived areas like Sistan and Baluchestan, Lorestan and Kurdistan where geographic and socioeconomic barriers contribute to health inequities. A similar pattern was noted in Saudi Arabia where at the national level there was equity while at the regional level there were inequities between areas with high population density such as Makkah and Jeddah and those with low population density such as Al-Jouf and the Northern region [64].

Intra-Urban Inequalities

The disparities are even further marked at the city level with Gini coefficients ranging from 0.46 in Tehran to 0.68-0.70 in Shiraz, and above 0.55 in a number of other metropolitan regions. These trends represent a clustering of hospital resources in high income neighborhoods and under-servicing of peripheral or disadvantaged communities. Comparable estimates for Shanghai (0.33-0.34) and Shenyang (0.52-0.68) indicate that differences between Iranian metropolitan areas are very high by global standards [65, 66].

Policy Implications

The research suggests equity based allocation beyond the national level. Intra-provincial and intra-urban disparities clearly indicate the need to focus on poor provinces and deficient urban areas. In addition, the ability to incorporate systematic monitoring of equity into health planning could identify inequities early and inform corrective response.

Moreover, in the Iranian context where a significant share of outpatient specialty and sub-specialty services are provided by the private sector [67], the inequities in hospital bed allocation far transcend inpatient provision. Where there is not enough bed space, specialists have a smaller motivation to start private practices because there is not the infrastructure for admitting and managing patients. As a result, populations in these areas are left without access to hospital-based services as well as specialist out-patient care. This indicates that maldistribution of beds in hospitals can create a domino effect of inequity throughout the health system, at the same time undermining access to equitable basic and specialized services.

For future research, it is recommended to explore the underlying factors of hospital bed and health resource distribution and propose strategies to create an enabling environment for equitable distribution through appropriate policies.

Conclusion

In conclusion, this study demonstrates that although, allocation of hospital beds at the national level is relatively even, there are considerable intra-provincial and intra-urban disparities in Iran. Ensuring equal access to hospital care among all population groups

requires equity-focused resource allocation and strategic monitoring of health system performance.

Strengths and Limitations

This study is one of the first systematic reviews to systematically evaluate the allocation of hospital beds in Iran using national and subnational evidence. However, there are some limitations. First, there was considerable heterogeneity between studies (I2~96%) as a result of variability in data sources, definitions, and time periods. Specifically, some studies focused on active beds (beds currently in use and providing services to patients), while others examined static beds (beds that have been built and have operational permits). This difference in the definitions and types of beds contributed to further heterogeneity in the study results. Second, the majority of included studies were cross-sectional, which limited causal inferences. Third, because of the small number of studies included in the meta-analysis (eight studies, 18 effect sizes), a formal test of publication bias could not be performed. Lastly, studies with mixed methods were summarized narratively across provinces and cities because of heterogeneity of methods.

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Conflict of interest statement

The authors declare no conflict of interes.

Authors' contributions

MK was responsible for the conceptualization and leadership of the study; MJ, HR contributed to the methodology, formal analysis, and supervision; all authors were involved in writing the original draft and reviewing and editing the manuscript.

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History of Medicine and Ethics

The history of smallpox vaccination in Italy: the vaccination campaign in the Ligurian Republic between the end of the Ancien Régime and the advent of the Napoleonic period (1797-1805)

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Keywords

history of smallpox • vaccination campaign • Medical Emulation Society • Ligurian Republic (1797-1805)

Summary

In 1798, Edward Jenner publicized his technique of smallpox vaccination, thus making obsolete what had been for centuries the most effective weapon against smallpox: variolation. News of this sensational breakthrough spread quickly throughout Europe, reaching Italy, and particularly Genoa, then the capital of the Ligurian Republic (1797-1805).
Indeed, the first vaccinations in Italy were carried out in Genoa, and several doctors there, first individually and then collectively (within the "Medical Emulation Society"), went on to implement and spread the practice of vaccination.
Although it was only with the annexation of Liguria to the French Empire that the practice became more structured and more widely implemented, this period still marked an extremely prolific time for medical science in the Genoa area.

Introduction

Human beings have always sought to defend themselves against pathogens by exploiting whatever knowledge of hygiene and sanitation was available to them. Of the many diseases that afflicted humans for millennia, one of the most noteworthy is smallpox [1, 2]. However, unlike other diseases, such as plague or cholera, smallpox has been less intensively studied by scholars.
According to the historian Alberto Tanturri [3], this relative disinterest has been due to the modest impact that smallpox had at the demographic level [4-8], to the less systematic nature of the measures implemented in order to combat it [9-15] and the limited impact that the disease had on social behaviour [16, 17].
The pathway leading up to the definitive eradication of smallpox was very long (starting more than two centuries ago), and it was only in 1980 that the World Health Organization declared the disease to be extinct [18].

From variolation to Jenner's vaccination

Smallpox (term formed by combining the words small and pox used to distinguish it from the great pox or syphilis) is a highly contagious disease and is fatal in nearly 50% of cases. Caused by a virus belonging to the Variola family, it can be contracted by inhaling the air exhaled by an infected person (while coughing or simply breathing).
The initial symptoms of the disease are fever, malaise, headache and coughing, while the more distinctive skin lesions develop within 12-15 days.
These lesions are initially papular, but subsequently transform into vesicles and then into pustules, which leave permanent scars. For the first 7-10 days after being infected, the person is particularly contagious and therefore at high risk of transmitting the disease to others [19].
Since ancient times, people have always tried to limit the complications of smallpox by implementing a series of measures.
The oldest technique that we know of, and which proved quite effective [1], originated in Asia and in some parts of Africa around the 2nd century BC [20], and is known as 'variolation' or 'inoculation'. Indeed, this approach involved inoculating a healthy individual with material taken from the pustules of a subject infected with a mild form of smallpox (Variola minor).
In this way, a less dangerous (and therefore less lethal) form of the disease was deliberately caused, which rendered the person immune to the more lethal form.
This practice, however, made the "variolated" subject a vehicle for the spread of the disease and, furthermore, exposed him/her to the risk of contracting other diseases, such as tuberculosis [21] and syphilis, or of developing bacterial infections such as septicaemia [1].
Although variolation can be considered completely obsolete today, it nevertheless remained for a long time

the only way to prevent the disastrous and lethal effects of smallpox.

The first news regarding the practice of variolation reached Europe only at the beginning of the 18th century through the reports of some physicians from Istanbul [22] such as Emanuel Timoni (1670-1718) and Jacopo Pylarini (1659-1718) [1]. It was, however, the determination of a woman, Lady Mary Wortley Montagu (1689-1762), that brought this practice to the attention of European medicine.

In 1717, a few weeks after arriving in Istanbul with her husband, who had been appointed the new ambassador of the United Kingdom, she wrote to a friend telling of this method of preventing the disastrous, if not lethal, effects of smallpox. Remembering her own terrible experience of smallpox, Lady Montagu had her son inoculated in March 1718. The outcome was successful and, on returning to London in April 1721, she also had the procedure performed on her daughter, who was just 3 years old [1, 23].

Having been convinced of the effectiveness of this practice, the Princess of Wales, Caroline of Brandenburg-Ansbach, had her two daughters "variolated" in 1722.

From then on, variolation began to spread throughout the European courts. It was especially in the 1750s, following a spate of smallpox deaths among royal families, that the practice spread rapidly, even reaching the American continent.

Among those who underwent variolation were: the Empress Maria Theresa, Frederick II of Prussia (who also ordered his soldiers to undergo the same treatment) [24], Louis XVI of France, Catherine II of Russia and, finally, all the soldiers of the Continental Army led by George Washington [1].

The practice also spread to Italy, particularly the Republic of Venice [25-29], the Kingdom of Naples [3, 30, 31, 32, 33], the Grand Duchy of Tuscany [22, 28, 34] and Austrian Lombardy [28].

In this latter region, the spread of variolation was celebrated by two great intellectuals of the time:

- in 1765, Giuseppe Parini wrote an ode entitled "L'innesto del vaiuolo" ("The inoculation of smallpox") [35] and
- the following year Pietro Verri published an article entitled "Sull'innesto del Vaiuolo" ("On the inoculation of smallpox") in the periodical "Il Caffè" [36].

A more effective method of preventing smallpox was developed only in 1796 by the English physician and naturalist Edward Jenner (Berkeley 1749-1823). Jenner's method of immunization, which he called vaccination, involved inoculating healthy individuals with pus taken from skin lesions on cows or humans affected by cowpox, a disease that was much less dangerous than human smallpox.

In this way, the individual would also develop immunity to the much more dangerous and lethal form of smallpox.

Today, we know that Jenner was not actually the first to use vaccine material to immunize people against smallpox; indeed, many English doctors in rural areas were aware of this approach [1].

Nevertheless, Jenner had the undisputed merit of conferring scientific status on this practice (by empirically demonstrating that vaccination elicited immunity to smallpox) and of spreading it systematically through the publication of his pamphlet "An Inquiry into the Causes and Effects of the Variolae Vaccinae, [...]" in 1798 [37].

This innovative technique soon spread from England to European countries, including Italy. Among the Italian pioneers of Jenner's method, we may mention:

- the Ligurian physician Onofrio Scassi (Cogoleto 1768 - Genoa 1836), who is deemed to have been the first to practise smallpox vaccination in Italy [38], and
- the Lombard Luigi Sacco (Varese 1769 - Milan 1836), the first doctor to use vaccine material harvested in Italy [30]. Although recent studies have focused primarily on these and other prominent figures in the medical field, less well-known participants in the first vaccination campaigns in Italy also deserve attention.

The present article will therefore attempt to shed light on the work of a small group of doctors who worked to spread vaccination in the area of Genoa between 1797 and 1805.

The spread of vaccination in the Ligurian Republic

With the fall of the Republic of Genoa, on June 1797, the aristocratic government that had ruled Liguria since the 16th century came to an end, being replaced by the Ligurian Republic (1797-1805) (Fig. 1).

On paper at least, this latter professed to be more democratic, more representative and based on the sovereignty of the people [39, 40]. It was precisely within the brief and fragile political-institutional reality of this government that several doctors undertook the first smallpox vaccinations.

News of the first vaccination campaigns launched in European countries reached Genoa in October 1800, when an article in the local Gazzetta reported that 30,000 people in Vienna, Hanover, Paris and Geneva had already been vaccinated with 'cowpox pus' from England [41].

On 1st November, this first article was followed by the publication of a letter from the Genoese doctor Onofrio Scassi [42]. In it, the illustrious doctor praised Dr Jenner for his sensational discovery and reported that, since the previous April, he had managed (with the help of William Batt and the Genevan doctor Odier [43, 44]) to obtain some vials of 'vaccine pus' from Geneva, which he had used to vaccinate 10 children.

He concluded by asserting that "those who have had the vaccine can rest assured that they will not get smallpox", and adding (probably to rebut some false rumours that were circulating) that "the vaccine is not [...] contagious" [30, 41].

A few months later, on March 5, 1801, a small pamphlet entitled "Sulla Vaccina di Jenner" (On Jenner's Vaccine) was published by the doctor William Batt (originally from the United Kingdom but resident in Genoa since 1771) [45]. In its eight pages, Batt launched into a long

Fig. 1. Map of the Ligurian Republic and Northern Italy in 1799: taken from The Cambridge Modern History Atlas, Cambridge University Press, London, 1912.

dissertation on the efficacy of vaccination to protect people "in the future against smallpox infection" [45] and recounted his own experience as a vaccinator.

He ended by inviting "Doctors and other persons who are able to inform themselves of the truth on this matter", to spread the practice of vaccination, and assured them that "inoculation of the Vaccine confers perfect lifelong protection against Smallpox" [45].

Regarding the advantages of undertaking vaccination campaigns, he also mentioned, as a virtuous example to be followed, the decision of the Government of the Ligurian Republic to carry out vaccination in the Pammatone Hospital [45].

Probably as a result of this invitation to spread the practice of vaccination and the government's decision to implement vaccination campaigns at the Pammatone Hospital, about 20 Genoese doctors (including W. Batt, L. Marchelli, B. and G. Mojon [46], A. Mongiardini, O. Scassi and D. Viviani [47, 48]) [49] founded the Società Medica di Emulazione ("Medical Emulation Society") in May of the same year [39, 50].

The newly formed association was "composed of Professors dedicated to the health arts"; it was intended to serve as a place where men involved in the health field could "communicate to each other their insights and the felicitous results of their observations" and also spread the practice of smallpox vaccination [51].

Within a few months, the Society was already in the news; on July 11, an article in the "Gazzetta Nazionale" reported that the Society had sent a long letter to the Government Commission "presenting a sample of its early works" [52] and shortly afterwards, at a Society meeting on July 23, 1801, the work of a member, the surgeon Luigi Marchelli, on the inoculation of the vaccine was approved.

Luigi Marchelli had already declared himself a supporter of vaccination in a short article in the "Gazzetta Nazionale" on July 11, 1801. In the article, in addition to refuting some false rumours regarding the efficacy and safety of vaccination, he passionately appealed to "Parents who are still hesitant" to have their young children vaccinated [52].

That article was followed, on July 23, by the presentation and publication of a "Memoir on the Inoculation of the Vaccine" [53]. In it, Marchelli compared the impact of smallpox to that of the plagues of the past [54] and embarked on a long narrative on the origins of the disease and the remedies used over the centuries to combat it, finally arriving at the method devised by Jenner, "a man forever worthy of humanity's esteem" [53].

After this extensive historical preamble, Marchelli went on to provide a detailed description of the two main ways of inoculating the vaccine material ("with fresh pus, that is to say from arm to arm" or "by threads" [53]) and the instruments required, all accompanied by four very detailed illustrative plates (Figs. 2-5).

Finally, he analysed some clinical cases that had particularly intrigued him among the 132 subjects he had vaccinated from March 27, 1801 until that time.

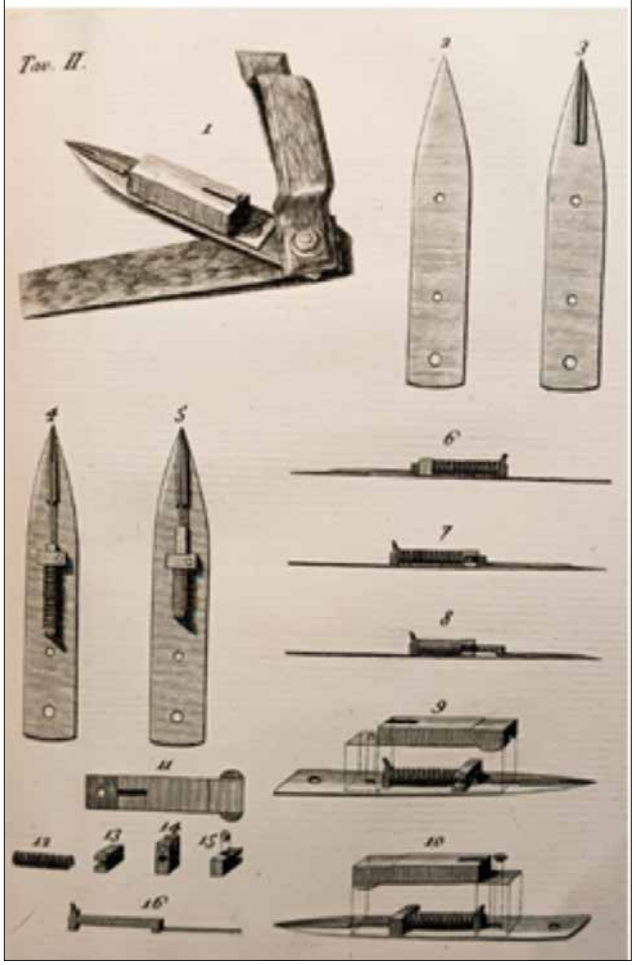
The work of spreading the practice of vaccination continued in August 1801. Indeed, on August 15, the "Gazzetta Nazionale" carried a new article, which reported that the vaccine was making "further progress every day in Liguria: indeed, we are counting many hundreds of vaccinated people in a short time" thanks also to the fact that "Jenner's work on the vaccine has been known in Genoa for three years" [55].

However, one should not think that vaccination was supported by all the doctors in Genoa, then the capital of the Ligurian Republic. Indeed, an article dated September 19, 1801, which was also published in the "Gazzetta Nazionale", mentioned "doctors who do not believe in the effectiveness of vaccination, and who arouse fears that it has harmful consequences", the aim of the article being to encourage parents to have their children vaccinated before it was too late.

Moreover, the various medical societies throughout Europe rebutted all the theses of these "opposition doctors", affirming that:

Fig. 2. Plate I illustrated the point at which to inoculate the vaccine.

Fig. 3. Plate II illustrated all the characteristics of the instrument with which inoculation was performed.



1. The true vaccine protects against smallpox;
2. The vaccine is not at all contagious;
3. The vaccine does not have any bad consequences" [56].

Unfortunately, however, the article did not have the desired effect; just over two months later, smallpox broke out in Genoa and some areas of Liguria, causing "considerable slaughter" [57].

Fig. 4. Plates III showed the evolution of the disease.

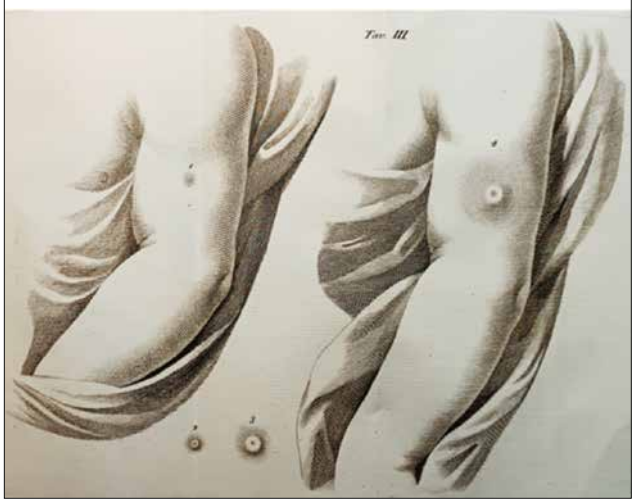
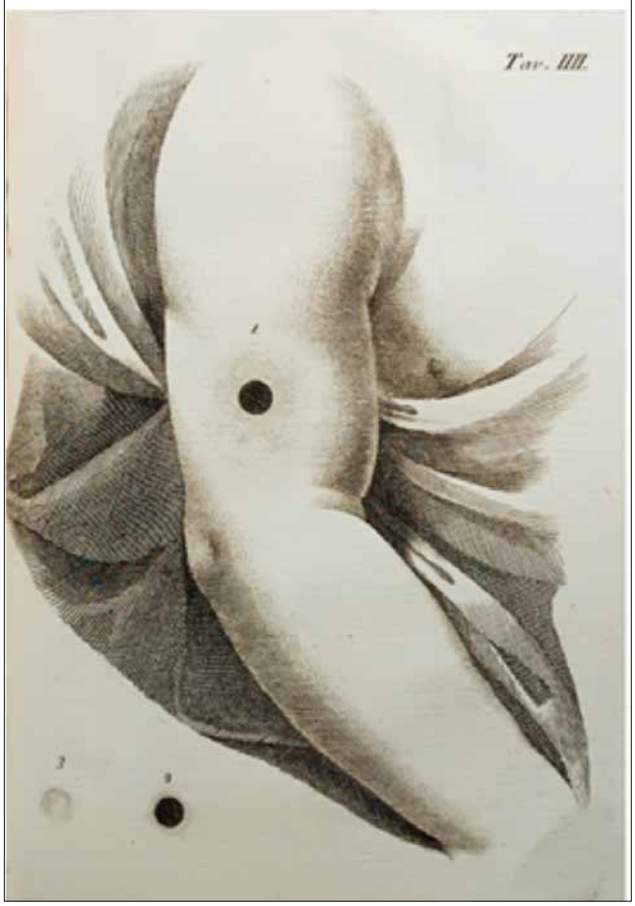


Fig. 5. Plate IV showed the evolution of the disease.



It was during that terrible health crisis that the Medical Emulation Society held its first meeting, directed by President Mongiardini and Secretary Marchelli. In his introductory speech, the President explained that the Society had been founded to emulate other medical societies scattered throughout Europe.

Among the Society's objectives, he also cited that of "especially encouraging Ligurians to take advantage of Jenner's discovery and protect themselves from the all-too-deadly smallpox" [51]. Precisely for this purpose, the Society used its own funds to finance the publication of several works in favour of vaccination until 1814, the year of its dissolution.

With the arrival of the new year, 1802, publications in favour of Jenner's method continued to proliferate.

On June 12, an article entitled "To the detractors of vaccination" appeared in the local Gazette. Signed by two illustrious Genoese scientists, B. Mojon and Dr. M. Covercelli, it aimed to "demonstrate the usefulness and safety of the procedure" [46].

On August 24, William Batt published, at the Medical Society's printing house, a short pamphlet entitled "The necessary distinction between vaccination and the errors or negligence of those who practise it" [58].

In this pamphlet, in addition to pointing the finger at some detractors of the innovative method [58], Batt described in detail all the steps (as they had been explained by

Jenner) to be carried out in order to correctly immunize the patient and the symptoms that the patient should develop in the days following inoculation.
Batt again took up the same arguments in another publication on September 15, less than a month later. In his memoir "On the origin of Vaccine inoculation" [59], he reiterated once again "the preservative efficacy of the vaccine" and then went on to translate into Italian the first part of Jenner's work entitled "On the origin of the inoculation of the vaccine".
And not even a month later, on October 13, 1802, Batt again intervened on the public scene with a short piece entitled "To the editors of the Osservatore", in which he gave the lie to some fake news on vaccination that had been printed in that newspaper by an "anonymous slanderer" [60].
This time, however, a reply to the frontal attack by the doctor of English origin came from a Genoese doctor, Giuseppe Pedemonte, who maintained "the inefficacy of the vaccine in protecting against smallpox" [61].
Notwithstanding the opponents of Jenner's method, however, the practice of vaccination spread to the neighbouring areas of the Ligurian Republic (albeit with greater difficulty) thanks to a few far-sighted doctors.
A perfect example of such commendable figures was Francesco Buffa, a doctor working in Ovada (today a small town near Alessandria in Piedmont, but at that time a territory of the Republic); between 1802 and 1807, he successfully vaccinated 72 young girls and boys between 4 months and 10 years of age [62].
Despite the harsh temperatures that characterized the winter of 1803, Genoa was spared a new smallpox epidemic, but still had to face an "epidemic of catarrhal disease", which caused several deaths in the city; this episode was narrated in a memoir written by the doctors De Ferrari, Landò and Mojon in June of the same year and presented publicly on August 11 of the following year during an open session of the Society [63].
On that occasion, the introductory speech was given by President Mongiardini, who mentioned the numerous "enemies" and "obstacles" that the Society had encountered in those two years of activity.
It had, nevertheless, always remained faithful to its objectives, namely "to fight [...] diseases, to alleviate the discomforts of old age and of civil life itself" by devoting to its homeland, the Ligurian Republic, "its vigils, its efforts, its very thoughts" [64].
In September of that same year, the Gazzetta Nazionale printed an article concerning a possible miraculous and involuntary effect of smallpox vaccination.
According to the Italian doctor Eusebio Valli [65], since smallpox had replaced bubonic plague as the deadly disease of the time, he resolved to discover whether smallpox vaccination would also be effective against the plague. He therefore set out to demonstrate that "the vaccine virus also protects against the plague, as it does against smallpox, both because the vaccinated person becomes unassailable, and because the plague loses much of its strength and its malignity in a vaccinated body" [66].
Unfortunately, however, as we know today, this is far from true: first of all because the plague is not caused by a virus, but by a bacterium (Yersinia Pestis), which was discovered in 1894 by the doctor Alexandre Yersin (1863-1943).
While the Ligurian capital was spared by smallpox in the freezing winter of 1803, this was not the case in the following winter, that of 1804.
Indeed, on that occasion, in addition to the more common "intermittent fevers", "sthenic diseases [...] some coughs, rheumatism and [...] measles", smallpox also appeared.
Fortunately, as narrated in the report drawn up – again – by doctors De Ferrari, Landò and Mojon, "the epidemic that reigned was one of the most benign, and few fell victim to that disease" [67].
One of the reasons for the low number of deaths was, undoubtedly, the result of the vaccination campaign that was implemented in Genoa as early as 1800. In this regard, an article published in the "Gazzetta Nazionale" on July 14 did not fail to underline that the epidemic provided overwhelming and definitive proof of the "preserving virtue of the vaccine, since none of the vaccinated individuals were attacked" [68].
Until 1805, smallpox vaccination continued to be – albeit in an increasingly "disorderly" manner [69] – the fruit of individual action taken by some far-sighted doctors, who read about, appreciated and put into practice Jenner's sensational discovery. Indeed, vaccinations were never directly managed by the local health administration [70], the Central Health Commission, which had been established in 1799 [71].
Only after the fall of the Ligurian Republic in June 1805 and the subsequent annexation of Liguria to the French Empire of Napoleon Bonaparte (1805-1814) was the practice of vaccination more widely implemented and structured [72].
Indeed, the implementation of smallpox vaccination constituted the most significant health policy undertaken by the Napoleonic authorities, both in the Empire and in all the other states under its influence [73].
In each of the newly established departments of Liguria, vaccination committees were created (in constant communication with the central committee in Paris) thanks to the participation of many of the Genoese doctors of the Medical Emulation Society [74].
However, despite the enormous efforts made by the Society and the French administration to spread vaccination even in the most rural areas of Liguria, "the war against smallpox was, at least temporarily, won by the disease", as demonstrated by the very severe smallpox epidemic that struck Genoa in 1829 [39].

Conclusion

While veritable vaccination commissions were created in some European countries, such as France [75, 76], Germany [77, 78] and Denmark [79], as early as the early 19th century [80, 81], the government of the Ligurian Republic almost entirely abandoned this task to

the free initiative of some far-sighted doctors, who, first individually and then collectively (within the Medical Emulation Society), devoted themselves to vaccinating as many people as possible.
It is difficult to quantify the work of these few doctors in terms of precise numbers and during the entire period of the Ligurian Republic:

- firstly, because it is unlikely that the lists of vaccinees drawn up by individual doctors (a practice, moreover, not obligatory) have come down to us;
- secondly, because the documents drawn up by the Society itself (which monitored vaccination developments) have reached us in a fragmentary manner.

Nevertheless, the huge number of printed documents produced in those years in the Ligurian capital enable us to appreciate and admire the commitment and energy that this small group of doctors – united by their love of science and their homeland – devoted to spreading smallpox vaccination in Genoa during the years of the Ligurian Republic.

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Authors' contributions

EB: conceived the study. EB, MM: designed the study; drafted the manuscript; performed a search of the literature; revised the manuscript; conceptualization and methodology; investigation and data curation; original draft preparation; review; editing. All authors have read and approved the latest version of the paper for publication.

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