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ORIGINAL ARTICLE

Implementation of artificial intelligence technologies in Russian healthcare: results of 2018–2024

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ABSTRACT

Background: Healthcare is one of the priority sectors for the implementation of artificial intelligence (AI) worldwide, including Russia. The key area of AI implementation is the integration of AI-based medical devices into the Unified Digital Framework in the healthcare sector of the constituent entities of the Russian Federation. The aim of this study is to analyze the development and implementation outcomes of AI in the Russian healthcare system in 2018–2024.

Materials and methods: The data regarding AI implementation were extracted from legislation, scientific publications and provided by the Ministry of Health of the Russian Federation and the national technical committee for standardization in the AI technologies.

Results: In Russia, 77% of AI-based medical devices are intended for medical image analysis. Between 2018 and 2024, 69% of investments in the development and implementation of AI solutions in healthcare came from state sources. Scientific research in this field is actively progressing: research institutions under the Russian Ministry of Health are implementing 215 AI-related healthcare projects. A total of 21 national and pre-liminary technical standards in the field of AI for healthcare have been

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developed and approved. In 2023, the deployment of AI-based medical devices began across the Russian regions. As of 01.01.2025, a total of 412 AI-based medical devices had been implemented, of which 83% are used for image analysis and 16% for electronic health record analysis.
Conclusion: A set of measures is being developed to actively introduce AI into healthcare, including the legal frameworks, attracting investments, conducting research and developing new products.

Key Words: artificial intelligence; medical devices; medical images; electronic health record; EHR

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Introduction

The introduction of artificial intelligence (AI) technologies is one of the key areas of digital transformation of healthcare. The prospect of AI technologies is due to several factors at once: the accumulation of a large amount of data, including widespread implementation of electronic health records (EHR) and digital diagnostics, the development of machine learning methods, the availability of high-performance graphics accelerators, etc. The accumulated experience in the development and application of various AI systems, as well as the results of research in this area demonstrate that AI technologies can significantly contribute to increasing the efficiency of healthcare organizations and rational use of available financial and human resources, improve healthcare management and offer new digital services for patients [1, 2].

The President of Russia V.V. Putin has repeatedly given various instructions regarding the development and implementation of AI technologies in healthcare[1]. According to the "National Strategy for the Development of Artificial Intelligence in Russia until 2030 (as amended in 2024)", the main goals of AI development in healthcare are:

1. Development of a comprehensive system of legal regulation, including ensuring the safety of using AI technologies.
2. Support for organizations developing AI technologies.
3. Support for research and development to achieve pioneering advancements in AI.
4. Enhancing competency levels and raising awareness about AI technologies.
5. Promoting the adoption of AI technologies.

The objective of this paper was to study the results of the development of artificial intelligence technologies in healthcare in the Russian Federation based on the results of 2018–2024.

Materials and methods

The sources of data for the study were scientific publications and reports of the Ministry of Health of the Russian Federation on the topic of creation, development and implementation of software using artificial intelligence technologies, as well as current regulatory legal acts on this

[1] List of assignments following the conference "Journey into the World of Artificial Intelligence" dated January 29, 2023 No. Pr-172. (In Russian) Accessed 01.08.2025. http://www.kremlin.ru/acts/assignments/orders/70418

issue. In addition, information provided by subordinate scientific centers of the Ministry of Health of the Russian Federation, as well as data from the national technical committee responsible for standardization in the field of AI technologies, were used to collect data.

Results

Creating basic conditions for the implementation of AI technologies

In 2011–2024, the Russian Ministry of Health implemented two major projects: "Development of the Unified State Information System in Healthcare" and "Creation of a Unified Digital Framework in Healthcare Based on the Unified State Health Information System".

Through these activities, all the necessary basic conditions were created for the subsequent introduction of AI technologies, including equipping healthcare facilities with computer equipment, introducing healthcare information systems of healthcare organizations and state healthcare information systems in the constituent entities of the Russian Federation.

The main information technology infrastructure has been created in Russian regions. More than 1 million automated workplaces of medical staff are connected to healthcare information systems, a secure data transmission network has been implemented. State and municipal healthcare organizations and systems of the regions of the Russian Federation use healthcare information systems to organize and provide medical care to citizens and ensure information interaction with the Unified State Health Information System, including the widespread maintenance of EHR, central archives of medical images, an electronic method of information exchange in the field of compulsory health insurance, etc.

The Russian Ministry of Health transfers the healthcare system to paperless document management. This process includes the development of structured electronic medical documents. To ensure the transition of the healthcare system to paperless electronic document management, 126 types of structured electronic medical documents have been developed since 2019, which provide more than 80% of the needs of healthcare organizations for organizing paperless medical document management in all types of medical activities.

The transition of the healthcare industry to electronic document management provided conditions for the formation of large structured databases, the use of which contributed to the accelerated development and implementation of artificial intelligence technologies.

Development of a comprehensive system of legal regulation

The main guidelines, requirements, and approaches to the legal regulation of AI in the Russian Federation are defined in the "Concept for the Development of Regulation of Artificial Intelligence and Robotics", approved by Order of the Government of the Russian Federation No. 2129-r of 19.08.2020[2].

Based on the approaches and recommendations of the International Medical Device Regulators Forum, AI systems in Russia were divided into 2 main groups: AI-based medical devices (AI MDs), intended for use by medical personnel in the direct provision of medical care and AI services that are not medical devices (MDs) [3].

[2] Order of the Government of the Russian Federation No. 2129-r of 19.08.2020 on approval of the "Concept for regulating artificial intelligence and robotics until 2024". (In Russian). Accessed 01.08.2025. http://publication.pravo.gov.ru/Document/View/0001202008260005

In 2019, the Russian Ministry of Health and the Federal Service for Surveillance in Healthcare (Roszdravnadzor) created an interdepartmental working group tasked with developing amendments to the current legal regulation of medical devices in terms of AI technologies. The working group included representatives of expert and research organizations subordinate to the Ministry of Health and Roszdravnadzor, representatives of developer companies and experts in the field of AI technologies. The key principles of the working group's work were to develop a consolidated position on the main approaches to legal regulation in order, to enable the introduction of safe and effective AI MDs to the market, and avoid the creation of excessive regulatory barriers as well as leave room for investment and the creation of new products. Due to the activities of this working group, in 2020–2021, amendments were made to the national legislation of the Russian Federation, allowing the marketing authorization of AI systems as AI MDs. During 2023–2024, targeted changes were constantly made to the current legal acts aimed at reducing the time of authorization of new AI MDs while simultaneously strengthening post-authorization monitoring of the solutions. At the same time, similar regulatory approaches were implemented in the legislative acts of the Eurasian Economic Commission.

In order to speed up and simplify the introduction of AI MDs to the market, amendments were made to the legislation in 2024 that simplify the marketing authorization of MDs and minimize the number of refusals. Thus, the period for marketing authorization of MD from the moment of applying with Roszdravnadzor is projected to be 10 working days.

The new authorization rules also introduce a simplified procedure for making changes to the documents contained in the authorization dossier for AI MDs. This allows developers of such products to update the registration dossier when releasing new versions, provided that the changes do not affect the intended purpose and/or the principle of operation of the AI MD. Furthermore, this applies only if the AI MD includes a built-in function for automatic transmission of information on processed data and the outcomes of the MD's operation to the automated information system of the registration authority, in accordance with the procedure established by that authority. In such cases, and where the information stipulated by the procedure for reporting adverse events is also transmitted, the amendments may be made without conducting an assessment of the quality, efficacy, and safety of the MD.

For 2025 and the planning period of 2026 and 2027, provisions have been included on financing expenses related to the use of clinical decision support systems in the provision of medical care using AI.

The Russian Ministry of Health, with the active participation of the head specialists of the Russian Ministry of Health, has developed a Code of Ethics for the Use of Artificial Intelligence in Healthcare.

The Industry Code of Ethics for the Use of Artificial Intelligence in Healthcare is intended to regulate the ethical aspects of the development, implementation and use of AI technologies in the field of healthcare, including a set of principles and recommendations that apply to all stages of the life cycle of an AI system. Artificial intelligence, like any technology, carries risks, which is why the development of the Code is due to the need to:

- protect the interests of people, individual groups and each person, whose rights and freedoms are considered the highest value;
- develop a responsible approach among AI community members;
- strengthen patient, physician and public trust in AI.

The Code of Ethics reflects the point of view of the professional and academic community on the current challenge of strategic

development of the healthcare system, is based on concepts important to the healthcare community, and reflects the roles, rights and responsibilities of all participants. Thus, the use of artificial intelligence in the healthcare system will take place in a single terminological field and taking into account the needs of all participants in the process.

Following the provisions of the Code of Ethics will increase Russians' trust in this technology and help developers of artificial intelligence systems create safe and competitive solutions that are necessary for the industry.

Of course, an important direction in the development of regulation was the creation in 2019 of the "Artificial Intelligence in Healthcare" subcommittee within the "Artificial Intelligence" technical committee for standardization. Thanks to the activities of this subcommittee, a set of national standards in the field of artificial intelligence for healthcare has been created in Russia, including 4 National Standards in 2021, 7 – in 2022, 3 – in 2023, 7 – in 2024 (total 21 National Standards) and a preliminary technical standard.

The documents regulate many key aspects of the creation and verification of the AI, including procedures for preparing datasets for machine learning and validation of the AI, technical and clinical tests, basic provisions and requirements for the AI for radiation diagnostics, clinical decision support systems, predictive analytics, etc.

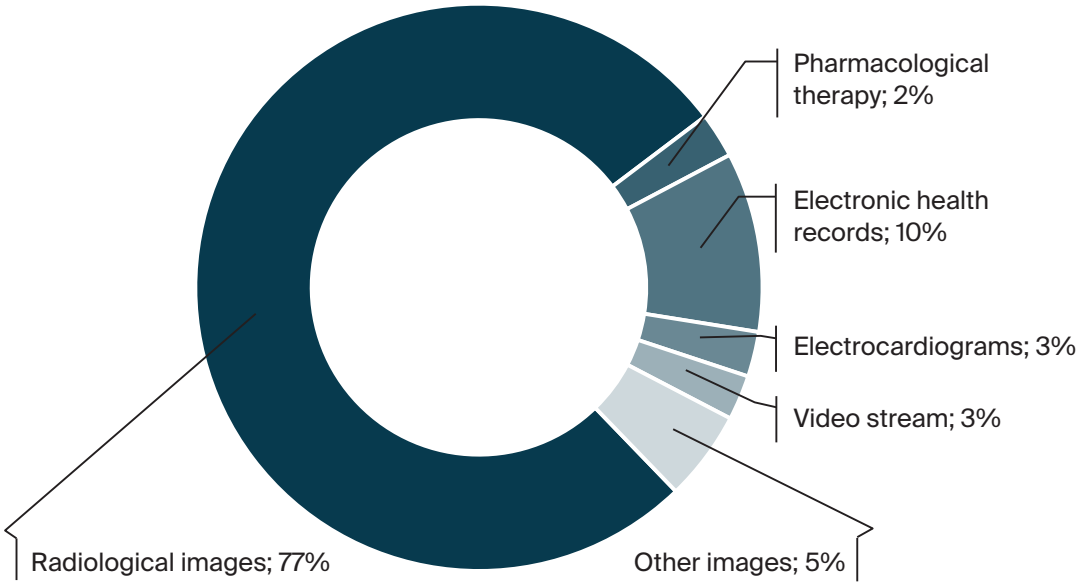
According to the 2024 results in Russia, among all registered AI MDs, 77% are in the medical image analysis segment. 10% are intended for EHR analysis, and 13% of AI MDs are intended for the analysis of other medical data (fig. 1).

A large share of registered AI MDs (34 or 87%) are domestic developments; information about these AI MDs is available in the Unified Register of Russian Software for Electronic Computers and Databases.

Support for organizations developing AI technologies

In Russia, a system of support for development companies and research teams working on the creation of applied solutions in the field of AI for healthcare has been created and is functioning effectively. In particular,

FIG. 1. Distribution of authorized medical devices with artificial intelligence technologies by types of processed data



state development institutions have created and supported several programs with targeted support measures specifically for developers of AI solutions. The leading ones are the Skolkovo Foundation, the National Technology Initiative, the Innovation Development Fund, etc. Private investors and professional investment funds also invest in the creation of relevant products.

At the request of the Ministry of Health to various state and commercial investment funds and development institutions sent in January 2025, consolidated data on investments, including various state support measures, were received and analyzed. All investments made in Russia can be divided into 3 main groups: state (development institutions), private (business angels, investment funds and commercial companies) and syndicated (rounds in which different investors participated). The distribution of all investments by investment sources is presented in fig. 2.

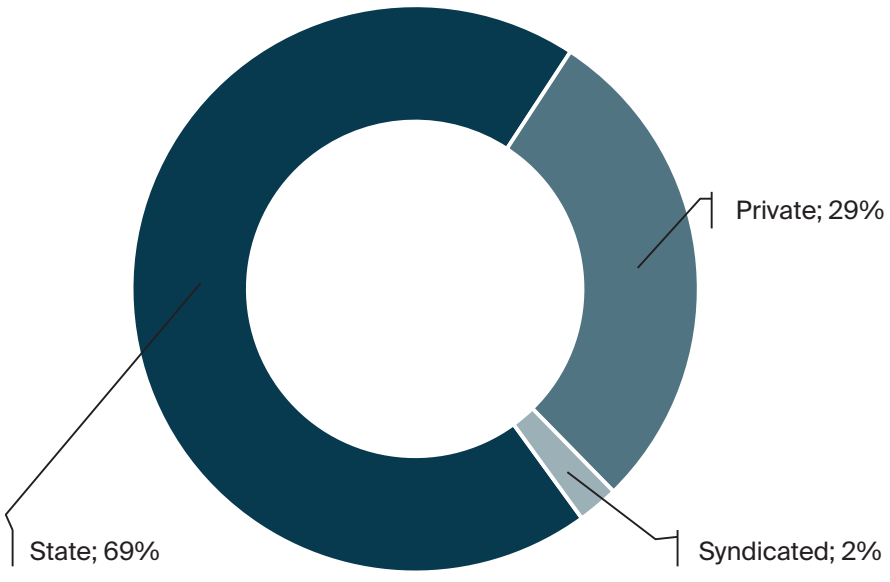
As can be seen from fig. 2, public investment in the development of AI for healthcare is the main source – it accounted for 69% of all investments. Among public investments, Moscow plays a leading role, having allocated 55.2% of public investments and 38.2% of total investments in market development as part of the Moscow Experiment on Computer Vision in 2020–2024. The second important source is the National Technology Initiative Fund – it accounted for 18.9% of public investments. The third in line is the Skolkovo Foundation, which allocated many different grants, which amounted to 12.9% of public investments.

Private investments accounted for 28.4% of all investments. In this segment, investments from various venture funds are in the lead, having allocated a total of 45.3% of the segment. In second place are private investors (business angels), having invested 33.7% of the segment. Next come commercial companies, which accounted for 21%.

Support for research and development

The Russian Ministry of Health, together with its subordinate institutions, is conducting systematic work in terms of scientific research and the creation of new developments in the most priority areas.

FIG. 2. Distribution of investments in artificial intelligence for healthcare by source



In 2024, the most in-demand clinical tasks that can be solved with the help of AI were identified. The development of over 200 new innovative domestic AI solutions, spanning various technological readiness levels, has been initiated. The majority of AI solutions for medical care stages are being developed for Diagnostics (150 AI solutions under development, addressing 54 clinical tasks). Additionally, 23 AI solutions target Prevention (13 clinical tasks), 37 AI solutions focus on Treatment (27 clinical tasks), and 9 AI solutions are designed for Rehabilitation (5 clinical tasks).

Over 190 datasets for machine learning have been prepared at the expert level, and over 100 clinical tasks have been identified. The most widely represented solutions are in the following areas: oncology, general practice, obstetrics and gynecology, radiology and radiotherapy, and endocrinology.

In 2023, as part of the implementation of the "Artificial Intelligence" federal project, the research center in the field of artificial intelligence in healthcare was created at the Federal State Budgetary Institution "N.N. Blokhin Russian Cancer Research Center" of the Russian Ministry of Health.

The research center is currently implementing projects at various stages aimed at:

- early detection of oncological diseases based on socio-demographic data, identifying people with the highest risk of developing oncological diseases and developing proposals for subsequent optimization of national screening programs;
- diagnostics and treatment of cancer patients, including the development of solutions for radiation therapy on modern linear accelerators;
- tertiary prevention and efficient use of resources in providing medical care to patients with oncological diseases.

The research center is focused on AI-based methods for creating software that can reduce the development time of personalized antitumor vaccines and research on finding tumorotropic pharmacological transport platforms for delivering therapeutic agents in radiation and nuclear medical technologies.

Development of educational programs, training courses, teaching and methodological and educational materials on AI is underway.

The Almazov National Medical Research Center of the Russian Ministry of Health, together with Sber, has created the Artificial Intelligence Center. The Center, together with industrial partners, is working on the creation of integration, platform solutions, frameworks that will allow working with an array of big data, developing predictive analytics and creating DSSs, moving from a digital clinic model to a smart clinic model. Work is underway to create digital twins of processes and digital twins of patients to conduct so-called "in silico" experiments to test innovative treatment methods and implement the concept of data-based management.

As part of the Center's program, 5 digital MDs were created, 3 of which are AI MDs (tests are being completed). The Center has been accredited under the quality management system of the site for the production of AI MDs. Together with Sber, several new AI MDs are being developed: a model for predicting inpatient risks and a model for automated calculation of the SyntaxScore for coronary studies, approbation and refinement of "CT Stroke" AI MD (SberMedAI) to improve the methodology of its implementation in Russian regions to enhance the provision of medical care to patients with cerebrovascular accident.

In 2024, significant results were achieved in training the large language model GigaChat in collaboration with Sber. The project involved over 300 employees and trainees from the Almazov National Medical

Research Centre (under the Russian Ministry of Health). A key milestone was the model's successful passing of the final certification exam in the specialty of General Medicine. The Centre continues to advance GigaChat's training and is developing a broad range of applied products for patients, healthcare professionals, and medical students. Efforts are underway to integrate the model into the healthcare information system and the remote patient monitoring system for cardiovascular care. Additionally, the application of multimodal generative models across all stages of medical care, including testing on digital twins, is one of the main priorities of the Center's future research.

The Russian Ministry of Health is developing a classification system for assessing the technological readiness levels of AI solutions. The proposed classification includes 9 levels, ranging from concept formulation to readiness for mass production of authorized medical devices.

In 2024, the Ministry issued recommendations to constituent entities of the Russian Federation to develop and publish scientific articles on the application of AI technologies in healthcare, based on the results of AI implementation in medical practice. Each constituent entity has appointed officials responsible for research activities. To date, 13 constituent entities have produced 19 publications, including 9 scientific articles.

In addition, the Russian Ministry of Health has recommended that research centers and developers of various AI solutions conduct and publish studies on the effectiveness of the created products in the scientific literature, including their impact on strategic indicators of the healthcare system, such as morbidity and mortality, as well as an assessment of the financial and economic feasibility of implementing AI technologies in practice. The first studies in this area show that the use of AI allows for a 10% increase in the detection of malignant neoplasms and a 15% reduction in the labor costs of physicians when using AI in radiation diagnostics [4]. The use of AI in preventive medicine allows for a 55% reduction in the risk of death from cardiovascular diseases, while receiving about 277 million rubles of economic effect per 1 million citizens annually due to more effective prevention of cardiovascular diseases' complications [5].

Raising the level of competence and awareness of AI technologies

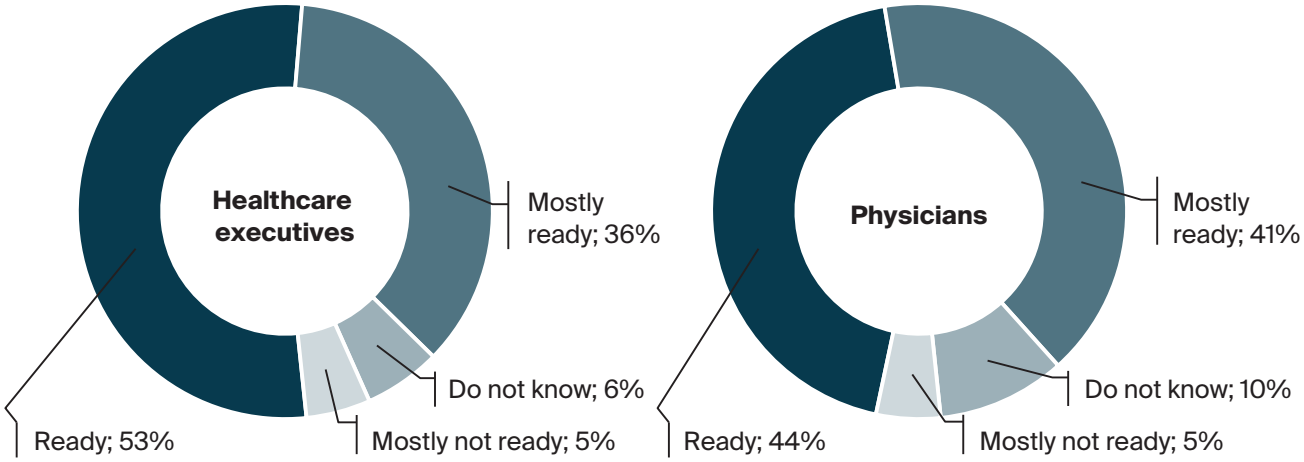
Russian healthcare executives and physicians are quite positive about the implementation of AI technologies. As can be seen from fig. 3, the relevant surveys showed that 89% of executives and 85% of physicians agree with the statement that the implementation of AI technologies will have a positive impact on work efficiency [6, 7].

According to our data [7], 63% of Russian healthcare executives consider themselves to be aware of AI, and 89% see the value of using AI technologies in healthcare, while 73% believe that in the future AI will always be used to support medical decision-making.

Targeted work is underway to create educational programs for training specialists in the field of development and application of artificial intelligence technology in the field of healthcare. Each program is designed for a specific category of listeners, including students, physicians of all specialties, medical, pharmaceutical, scientific, and pedagogical workers, as well as information technology specialists of healthcare organizations.

Research teams publish practical and methodological guidelines on the research, development, and application of AI technologies. Thus, in 2024, based on the scientific and practical results of the Moscow

FIG. 3. Results of surveys of healthcare executives and physicians regarding the prospects for the implementation of artificial intelligence technologies



Experiment on Computer Vision in Radiology, the first manual in the Russian Federation on preparing data sets for training and testing software based on artificial intelligence technology was published. This publication has been endorsed by the Coordination Council for the Educational Field of "Healthcare and Medical Sciences" as an official textbook[3].

Implementation of AI technologies in the regions of the Russian Federation

Focusing on a risk-oriented approach and the key principle of ensuring safe and controlled use of AI, the strategic direction in the field of digital transformation of healthcare, approved by the Order of the Government of the Russian Federation of 17.04.2024 No. 959-r, it was decided that the primary task for Russian healthcare is the implementation of AI MDs[4].

Under this decision, by 2030, all healthcare institutions within the state healthcare system of the Russian Federation must ensure a progressive increase in the use of AI MDs. In 2023, each constituent entity of the Russian Federation was required to implement at least 1 AI MD. In 2024, this target was raised to a minimum of 3 AI MDs. By 2030, all constituent entities must utilize at least 12 AI MDs in their operations (fig. 4).

The primary areas selected for the initial implementation of AI technologies in healthcare were medical image analysis and EHR analysis. These categories were prioritized due to the highest number of marketing authorizations of AI-based products as medical devices.

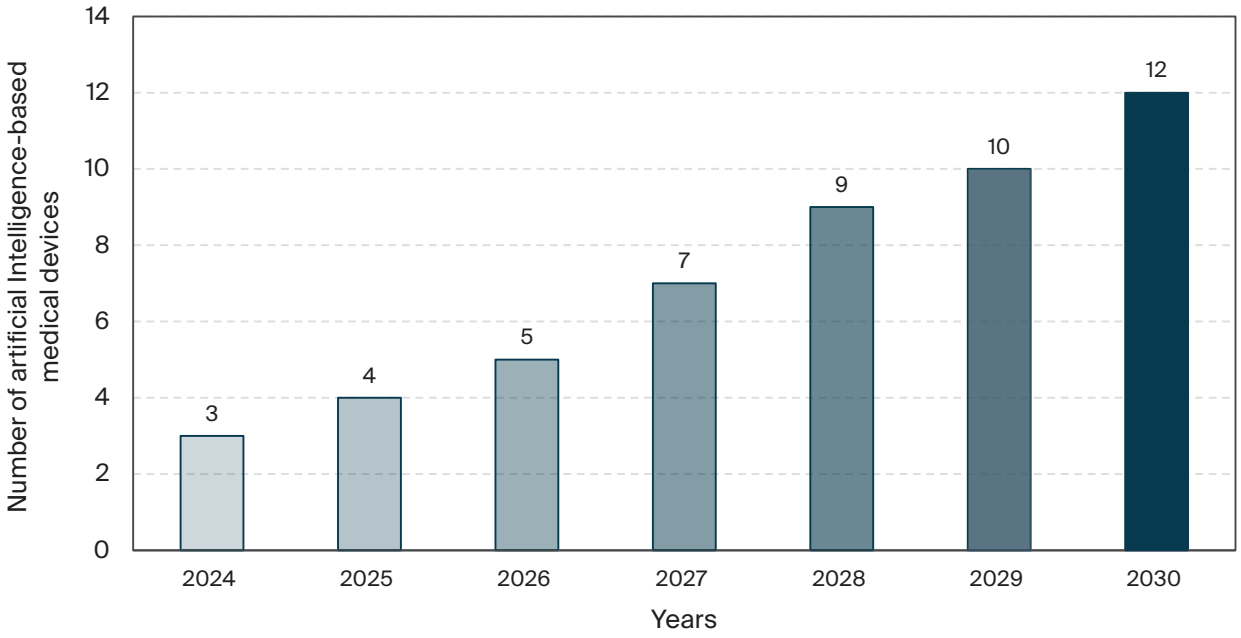
Russian regions were advised to prioritize projects aimed at reducing morbidity and preventable mortality from cardiovascular and oncological diseases, as these areas are key priorities within the framework of the "Healthcare" national project.

To support procurement and implementation of AI MDs, expert guidelines were developed with the participation of specialists from the Ministry of Health and Roszdravnadzor. These guidelines include standard requirements for AI MDs, covering product delivery

[3] Vasiliev YuA, Arzamasov KM, Vladzimirsky AV, et al. Preparing a dataset for training and testing software based on artificial intelligence technologies: a tutorial. Moscow: Izdatel'skie resheniya; 2024. 140 p. ISBN 978-5-0062-1244-2. (In Russian).

[4] Order of the Government of the Russian Federation No. 959-r of 17.04.2024. (In Russian). Accessed 01.08.2025. http://publication.pravo.gov.ru/document/0001202404190016

FIG. 4. A regulatory requirement for the number of artificial intelligence-based medical devices that must be applied on a permanent basis in the constituent entities of the Russian Federation



and deployment conditions, typical integration and application scenarios, and other relevant aspects.

In October 2024, a departmental initiative was launched to facilitate the integration of AI technologies into clinical practice. The goal of the initiative is to ensure that each constituent entity of the Russian Federation meets the target criteria for AI implementation in healthcare: at least three AI MDs must be implemented and used in routine medical care in every region.

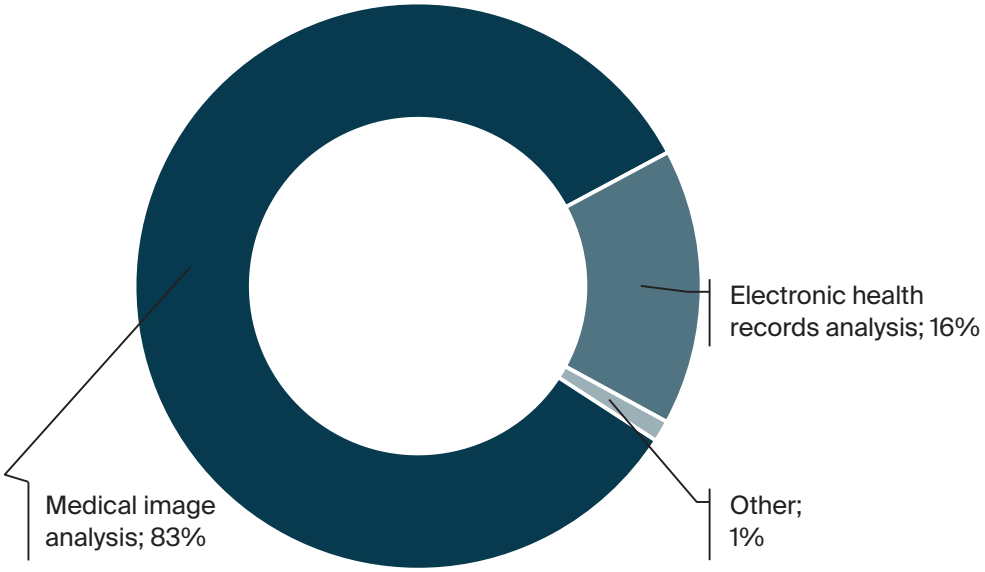
As part of this initiative, monitoring of implementation indicators was conducted in healthcare organizations, along with an analysis of regional infrastructure necessary for the operation of AI MDs and the development of recommendations for its improvement. Standard scenarios for the use of AI in clinical practice are being developed and implemented, and training programs are being created to support healthcare professionals in applying AI MDs.

Implementation of AI-based medical devices in the regions of the Russian Federation

As a result of the projects implemented in 2023 and 2024, by January 2025, the constituent entities of the Russian Federation had deployed a total of 412 authorized AI MDs of domestic origin (fig. 5). Four newly established regions were not required to implement AI MD deployment activities due to the need to first develop infrastructure and establish basic digitalization.

The majority of regions opted for a mixed implementation approach, deploying AI technologies for both medical image analysis (85 regions) and EHR analysis (58 regions), and only 5 regions implemented AI MDs intended for other purposes.

FIG. 5. Distribution of artificial intelligence-based medical devices by types of implementation



The growing prevalence in Russia of AI-enhanced medical tools utilizing computer vision to interpret and process medical imagery is fully aligned with international trends[5] [8].

Conclusion

At present, all necessary conditions have been established in the Russian healthcare system for the development and implementation of AI technologies. These include the creation of basic infrastructure, the establishment of the legal framework, the attraction of investments, the conduct of scientific research, and the development of new products.

The current key challenges are as follows:

- building trust in AI technologies among physicians and patients;
- ensuring monitoring and oversight of AI applications;
- training personnel to work with AI in healthcare;
- data management: access, protection, and confidentiality;
- further development of data processing infrastructure.

To address these challenges and mitigate associated risks, a range of initiatives is being implemented. These include the development of educational programs, the establishment of data management and data storage approaches, fine-tuning the infrastructure of centralized medical image archives, and the exchange of best practices in AI implementation. Such discussions take place at conferences, professional forums, and during regular meetings between the Ministry of Health and regional authorities as part of the federal AI implementation initiative, where reports on best practices are presented and reviewed.

The key areas for the development and application of AI technologies in 2025 include:

- continued implementation of domestic AI systems aimed at solving clinical tasks, automating routine processes, and improving healthcare management efficiency;
- increasing the number of AI MDs used within the State Healthcare Information Systems of regions;

[5] Vladzimirsky AV, Vasiliev YuA, Arzamasov KM, et al. Computer vision in radiation diagnostics: the first stage of the Moscow experiment. 2nd edition. Moscow: Izdatel'skie resheniya; 2023. 388 p; ISBN 978-5-0059-3043-9. (In Russian).

- integration of AI solutions in institutions subordinate to the Ministry of Health;
- scaling up best practices and developing standard use-case scenarios;
- regular training of healthcare professionals on the use of AI in their daily practice;
- fine-tuning infrastructure and data management to increase AI coverage and enhance the performance of AI-based medical devices;
- monitoring the effectiveness of AI technologies in healthcare delivery;
- monitoring the safety of AI usage, including adverse event reporting and usage statistics analysis;
- ensuring compliance with information security requirements.

One of the priority tasks for the future development and launch of new AI projects in healthcare is identifying existing "white spots"—clinical tasks or use cases where effective and ready-to-use AI solutions are lacking. In this regard, the Ministry of Health is exploring new AI payment models, including service-based models. This approach could attract additional investment into the industry while offering a more effective and rational method of financing such products.

Thus, the model of AI service application is shifting from direct state investment in the procurement of AI medical devices toward long-term investment through the Federal Compulsory Health Insurance Fund. This transition enables AI developers to embed AI technologies into the delivery of medical care and receive funding as part of reimbursed healthcare services involving AI. This model fosters both the advancement of AI solutions and healthy competition among developers.

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REVIEW

Advancing China's end tuberculosis strategy goals leveraged by active case finding and preventive therapy

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ABSTRACT

Tuberculosis remains a major public health issue in China, with 741,000 new cases in 2023. Despite significant strides in tuberculosis control, suboptimal case detection and low acceptance rate of tuberculosis preventive treatment hamper tuberculosis elimination. To meet the WHO's 2030 End Tuberculosis target, China's "National Tuberculosis Prevention and Control Program (2024–2030)" prioritizes active case finding and preventive treatment. Active case finding targets high-risk groups (people living with human immunodeficiency virus/acquired immunodeficiency syndrome, the elderly, individuals with diabetes and previously treated tuberculosis patients and close contacts of tuberculosis patients) using advanced screening methods. Implementation of active case finding should be performed in setting- ang region-specific manner. Tuberculosis preventive treatment focuses on latent tuberculosis infections with shorter, safer regimens. The effective implementation of tuberculosis preventive treatment requires integration into the comprehensive "Center for Disease Control and Prevention – Hospital – Primary Medical Institutions" framework. The "Zero-TB Communities" initiative integrates these strategies, aiming at fewer than 10 cases per 100,000 people. The framework of this initiative includes screening for active tuberculosis cases, drug resistant tuberculosis and latent tuberculosis infection, management

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of identified tuberculosis cases and tuberculosis preventive treatment, as long as social advocacy and mobilization. Through evidence-based interventions and multi-sector collaboration, China aims to accelerate tuberculosis control and contribute to global elimination efforts.

Key Words: tuberculosis; active case finding; preventive therapy; review

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Introduction

Tuberculosis (TB), a persistent global public health challenge, continues to pose substantial challenges particularly in China, which shoulders a significant proportion of the worldwide disease burden. According to recent World Health Organization (WHO) annually TB report, China has an estimated 741,000 new TB cases in 2023, accounting for 6.8% of global incidences and reflecting an incidence rate of 52 cases per 100,000 population[1]. This epidemiological profile is characterized by notable spatial and demographic disparities. Approximately 10% of Chinese counties (289 in total) exhibited high-incidence rates exceeding 80 cases per 100,000 population in 2023, predominantly concentrated in the western regions [1]. The disease burden disproportionately affects the elderly population compared to other age groups[2].

Despite significant strides in TB control measures in recent years, the ambitious goal of "ending the TB epidemic by 2030" set by the WHO remains elusive in the Chinese context. Key obstacles include suboptimal case detection and low uptake of TB preventive treatment (TPT). About 95% of TB patients diagnosed were identified through passive case finding [2]. This approach leaves approximately 20% of cases undiagnosed and results in significant diagnostic delays for half of the patients [2]. Additionally, the implementation of TPT remains inadequate, TPT acceptance rate is less than 60%, and the adoption of innovative diagnostic and treatment technologies is insufficient. Given the current rate of decline in TB incidence, achieving the 2030 targets seems unattainable without substantial interventions.

In response to these challenges, the National Bureau of Disease Prevention and Control, in collaboration with eight other governmental bodies, has formulated the "National TB Prevention and Control Program (2024–2030)"[3]. Central to the successful implementation of these strategies are active case finding and TPT. Active case finding, involving systematic screening of high-risk populations and quality strengthening of contact tracing and screening tests, is pivotal for early TB detection and reducing diagnostic lags. Simultaneously, TPT plays a crucial role in minimizing the risk of TB among vulnerable populations. Integrating these interventions into the Zero-TB communities initiative provides

[1] World Health Organization. Global tuberculosis report 2024. Accessed 21.07.2025. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024
[2] Ibid.
[3] National Health Commission of the People's Republic of China. National Development and Reform Commission of the People's Republic of China. Ministry of Education of the People's Republic of China. et al. National TB Prevention and Control Plan (2024–2030). Accessed 21.07.2025. https://www.gov.cn/zhengce/zhengceku/202412/content_6991217.htm (In Chinese)

a comprehensive approach that has the potential to expedite the reduction of TB incidence in China.

Community and facility-based active screening for enhanced tuberculosis case detection

Early detection of TB is an indispensable cornerstone in curbing the spread of this infectious epidemic. Nevertheless, a substantial global burden persists, with approximately 20% of TB cases remaining undiagnosed or unreported each year [2]. This significant diagnostic gap not only undermines individual treatment efficacy but also exacerbates the risk of community-level transmission. In high-burden regions, the implementation of active case finding (ACF) encounters multiple challenges, primarily stemming from scarce medical resources, low public awareness of TB, and limitations in detection methodologies. Despite China achieving an 82.7% detection rate in 2023, surpassing the global average of 75.9% [2], nearly one-fifth of its TB patients still evade identification. This situation underscores the urgent need for strategic enhancements in ACF, which should involve precise targeting of high-risk populations, adoption of innovative screening methods, and optimization of screening protocols, and improvement of screening quality.

Precision targeting of high-risk populations

The pool of undetected TB cases in China predominantly comprises asymptomatic individuals, necessitating a focused approach on specific high-risk cohorts [3]. Close contacts of TB patients, people living with human immunodeficiency virus/acquired immunodeficiency syndrome (PLWHA), the elderly, individuals with diabetes and previously treated TB patients within two years completion are identified as priority populations for ACF.

Empirical evidence indicates that active screening among close contacts of smear-positive and smear-negative TB patients yields detection rates of 3.6 and 1.3%, respectively [4]. These figures are significantly higher than the baseline detection rates in the general population. Moreover, the implementation of ACF strategies has been proven to boost patient detection by 2.5-fold and reduce mortality by 40%, highlighting the effectiveness of targeted screening efforts [4].

PLWHA face an 18-fold increased risk of developing TB compared to the general population, yet a 44% detection gap persists [2]. A systematic review revealed that TB accounts for 37.2% of deaths among PLWHA [5], emphasizing the urgency of improved screening for this vulnerable group.

Previously treated TB patients exhibit a 4-fold higher risk of reinfection and a 10.2-fold elevated likelihood of developing drug-resistant TB [6].

The elderly, characterized by age-related decline in immune function and physiological deterioration, have a TB prevalence rate 2–3 times higher than other age groups [7, 8], positioning them as a critical target for screening initiatives.

Setting-specific screening strategies

Institutional ACF should be systematically implemented among PLWHA, former TB patients, the elderly, and individuals with diabetes, while community-based screening initiatives should prioritize the close contacts of TB patients. High-density settings, including schools, correctional facilities, social welfare institutions, juvenile rescue and protection agencies, psychiatric hospitals, and industrial and mining enterprises, are designated as key screening sites due to their elevated

risk of TB transmission. For example, studies have shown that the TB incidence in correctional facilities is 23 times higher than in the general place [9]. In certain industrial and mining enterprises, where miners are exposed to silica, silicosis is prevalent. Silicosis patients face a relative risk of TB ranging from 2.8 to 39 times higher than the general population, and TB patients with silicosis have a 3-fold increased mortality risk [10]. Therefore, it is strongly recommended to incorporate TB examination as a mandatory component of enrollment physical examinations in these facilities and include TB screening in annual health assessments. Regions with sufficient resources and capabilities should consider implementing comprehensive infection screening protocols. Additionally, for high-risk individuals confirmed not to have active TB, TPT should be administered to further strengthen disease prevention efforts. The successful implementation of ACF in these key settings requires seamless coordination and collaboration across multiple departments, with particular attention paid to establishing standardized protocols for class suspension, work suspension, and the resumption of normal activities.

Region-specific screening guidelines

In China, approximately 10% of counties are classified as high-prevalence areas, reporting an incidence rate exceeding 80 cases per 100,000 population [1]. In these regions, it is essential to establish evidence-based protocols regarding target populations and screening frequencies. A comprehensive evaluation should be conducted after systematic screening implementation. Once the prevalence declines to moderate levels, a transition from community-wide general population screening to facility-based screening focused on high-risk populations should be considered. In high-incidence areas with resource constraints, facility-based ACF targeting high-risk groups represents a practical and viable alternative approach.

Technological innovations in screening modalities

Current TB screening methodologies primarily include symptom-based assessment, chest imaging examinations, C-reactive protein testing, and molecular diagnostics. Symptom screening, which involves identifying long-term (chronic) cough, cough of any duration, or other TB symptoms, offers simplicity in implementation but suffers from limited sensitivity and specificity[4]. As such, it necessitates integration with complementary screening approaches for accurate diagnosis. Chest X-ray examination, the predominant technical modality for TB screening, exhibits high sensitivity. For large-scale population screening initiatives, integrating chest X-ray with computer-aided detection technology is recommended to optimize diagnostic efficiency and accuracy[5]. C-reactive protein testing, predominantly utilized in PLWHA, demonstrates superior accuracy compared to symptom screening, with optimal sensitivity achieved at a threshold of 5 mg/L. WHO advocates for the use of rapid molecular diagnostic techniques, such as the Xpert MTB/RIF® and sputum Truenat® platforms, as the initial diagnostic tools for TB. These advanced methods significantly enhance both the sensitivity and specificity of TB diagnosis, enabling the rapid detection of TB and rifampicin resistance[6].

[4] World Health Organization. WHO consolidated guidelines on tuberculosis: module 2: Screening. Systematic screening for tuberculosis disease. Geneva: World Health Organization, 2021. Accessed: 21.07.2025. https://iris.who.int/bitstream/handle/10665/340255/9789240022676-eng.pdf?sequence=1

[5] Ibid.

[6] Ibid.

Scale up tuberculosis preventive treatment through preventive treatment clinics

Latent tuberculosis infection (LTBI) is characterized by a sustained immune response to Mycobacterium tuberculosis antigens, without clinical symptoms or radiological signs of active disease. Approximately 20% of the global population are infected with Mycobacterium tuberculosis, with 5–10% of these individuals progressing to active tuberculosis during their lifetime, mostly within the first five years after infection [11]. This vast reservoir of latently infected individuals serves as a continuous source of new TB cases. TPT for high-risk LTBI populations is a crucial intervention endorsed by the WHO to achieve the strategic goal of "ending the TB epidemic". At the second United Nations High – level Meeting in 2023, a global commitment was made to administer TPT to at least 45 million individuals from 2023 to 2027[7]. Aligned with this global initiative, China's "National TB Prevention and Control Plan (2024–2030)" stipulates that the TPT coverage rate for close contacts of TB patients should reach 80% by 2030[8].

Identification of tuberculosis preventive treatment targets via tuberculosis incidence risk assessment

Although TPT is one of the cornerstones of the WHO's End TB Strategy, the efficacy of current preventive regimens varies from 60 to 90% [1]. Thus, the implementation of TPT demands a meticulous risk-benefit assessment. Defining appropriate TPT target populations requires considering multiple determinants, including the risk of disease progression in vulnerable groups, local TB epidemiology, disease burden, and available resources.

From an individual protection perspective, TPT should primarily target those at a heightened risk of progressing from LTBI to active TB. This includes individuals with recent *Mycobacterium tuberculosis* infections and those with compromised immune systems. From a community – level incidence reduction standpoint, the proportion of the target population receiving TPT is also a critical factor. In line with these principles, China has precisely defined high-risk groups for TB, which include close contacts of TB patients, people living with PLWHA, and individuals with immunosuppressive conditions, reflecting a targeted approach to disease surveillance and control. PLWHA face an 18-fold increased risk of developing TB compared to the general population. A systematic review has demonstrated that TPT reduces the overall TB risk in PLWHA by 33%, and this protective effect increases to 64% in TST positive individuals. Additionally, TPT reduces all-cause mortality by 35%, with the protective effects persisting beyond five years. Household and non-household contacts of TB patients, regardless of age, have a significantly higher risk of developing active TB than the general population, justifying TPT recommendation regardless of the local TB burden [12].

Research, development and promotion of short-course treatment regimens

Currently, the recommended TPT regimens in China mainly consist of the 6- to 9-month isoniazid monotherapy regimen (6–9H),

[7] World Health Organization. The second United Nations high-level meeting on TB: new global pledge to end the TB epidemic. Geneva: World Health Organization, 2023. Accessed 21.07.2025. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/featured-topics/un-declaration-on-tb

[8] National Health Commission of the People's Republic of China. National Development and Reform Commission of the People's Republic of China. Ministry of Education of the People's Republic of China et al. National TB Prevention and Control Plan (2024–2030). Accessed 21.07.2025. https://www.gov.cn/zhengce/zhengceku/202412/content_6991217.htm (In Chinese)

the 3-month isoniazid and rifapentine combined intermittent regimen (3HP), the 3-month isoniazid and rifampicin combined regimen (3HR), the 4-month rifampicin monotherapy regimen (4R), and the immunotherapy regimen[9]. Studies have shown that the protective efficacy of these TPT regimens ranges from approximately 60 to 90%[10].

The acceptance rate of LTBI individuals towards TPT regimens is highly correlated with treatment duration. The acceptance rates for the 3HP and 6H regimens are only 76.3 and 63.9% respectively [13], with corresponding compliance rates of 89.2 and 61.5% [14]. Notably, research has indicated that the 3HP regimen has significantly reduced hepatotoxicity [15], suggesting that the continued promotion of short-course regimens should be a priority to improve acceptance and compliance among LTBI patients. Although randomized trials have confirmed the effectiveness and safety of the 1HP regimen compared to the 9H regimen, it has not been included in national guidelines due to insufficient research evidence in the Chinese context[11]. Currently, several Chinese researchers are conducting relevant investigations in this area.

Standardized establishment of tuberculosis preventive treatment clinics

The "National TB Prevention and Control Plan (2024–2030)" recommends that local regions establish TPT clinics based on their specific conditions and available resources[12]. From a systems-based perspective, the effective implementation of TPT requires integration into the comprehensive "Center for Disease Control and Prevention – Hospital – Primary Medical Institutions" TB prevention and control service framework.

Through optimized resource allocation and enhanced information-sharing mechanisms, both active case-finding and TPT initiatives can be strengthened. Within this framework, TPT clinics enable Centers for Disease Control and Prevention to perform their core functions of providing technical guidance, quality control, and outcome evaluation. At the same time, the role of primary medical institutions in TB infection screening and TPT supervision should be clearly defined and supported. TPT should be incorporated into health management projects within the basic public health services framework, establishing a precision – intervention model based on risk stratification using comprehensive health records. This approach should be integrated into the pilot deployment for public health practicing physicians, leveraging their expertise to identify TPT candidates, enhance diagnostic and treatment competencies, and implement standardized management protocols.

The construction of "Zero-tuberculosis communities initiative": integrating tuberculosis case management, active case finding and preventive treatment

The construction of "Zero-TB Communities" initiative stands as an exemplary practice that effectively integrates TB case management, active case finding and preventive treatment strategies, serving as a cornerstone for TB control and elimination efforts. In accordance with

[9] Guidelines for preventive treatment of tuberculosis in China [M]. Beijing, China, Chinese Center for Disease Control and Prevention, 2021. Accessed 21.07.2025.

[10] World Health Organization. Appendix to the guidelines on the management of latent tuberculosis infection. Evidence to decision framework. Accessed 21.07.2025. https://iris.who.int/bitstream/handle/10665/158915/WHO_HTM_TB_2015.01_eng.pdf;sequence=1

[11] Guidelines for preventive treatment of tuberculosis in China [M]. Beijing, China, Chinese Center for Disease Control and Prevention, 2021. Accessed 21.07.2025.

[12] National Health Commission of the People's Republic of China. National Development and Reform Commission of the People's Republic of China. Ministry of Education of the People's Republic of China et al. National TB Prevention and Control Plan (2024–2030). Accessed 21.07.2025. https://www.gov.cn/zhengce/zhengceku/202412/content_6991217.htm (In Chinese)

the WHO's pre-elimination threshold criteria applicable to China, Zero-TB Communities are defined as specific geographical or institutional entities—including townships, streets, educational institutions, military units, long-term care facilities, large-scale enterprises, and public institutions—characterized by an annual TB incidence rate among permanent residents of less than 10 cases per 100,000 population. This initiative encapsulates a comprehensive, multi-faceted public health approach designed to substantially mitigate TB transmission dynamics and reduce disease incidence at the community level.

The operational framework of Zero-TB Communities is systematically structured around the principle of "three screenings (screening for active TB cases, drug resistance TB cases, LTBI), two managements (manage for TB cases and TPT cases), and one mobilization (social advocacy and mobilization)", which collectively form an integrated and synergistic system for TB control [1].

Three screenings

1. Active case finding: Systematically implement screening programs in high TB-incidence regions and among high-risk groups (e.g., close contacts of TB patients, PLWHA, the elderly, and immunocompromised individuals). Targeted screening enhances early TB detection, enabling timely intervention and preventing progression.
2. Comprehensive TB infection testing: Conduct systematic testing for LTBI in high-risk individuals [16]. Early LTBI identification is critical for initiating preventive treatment to block progression to active TB.
3. Enhanced drug-resistant TB screening: To address the threat of drug-resistant TB, specialized protocols should be implemented to rapidly identify multidrug-resistant TB. Timely detection of resistant cases is critical for initiating tailored treatment, minimizing community transmission of resistant strains.

Two managements

1. Standardized treatment management: For individuals diagnosed with active TB, including those with drug-resistant forms of the disease, immediate access to standardized anti-TB treatment protocols is ensured, complemented by comprehensive case management [17]. This approach rigorously monitors treatment adherence, minimizes treatment interruptions, and shortens the infectious period of patients, thereby effectively curbing the onward transmission of the TB pathogen.
2. Preventive treatment management: Individuals identified with LTBI are enrolled in carefully monitored TPT programs [16]. Rigorous surveillance of TPT ensures treatment completion, which is crucial for preventing the development of active TB, particularly among vulnerable and high-risk populations.

One mobilization

1. Governmental advocacy and public health education: This component focuses on engaging all levels of government to prioritize TB control and allocate adequate resources specifically for developing and implementing Zero-TB Community programs. Concurrently, comprehensive public health education campaigns are launched to enhance community-wide awareness regarding TB prevention

strategies, the significance of early detection, and the importance of treatment compliance. Cultivating a health-conscious society, these initiatives mobilize individual responsibility and community engagement to accelerate TB elimination.

Conclusion

In summary, the rollout of the "National TB Prevention and Control Program (2024–2030)" inaugurates a transformative phase in China's TB control paradigm. Building on the empirically validated success of initiatives such as Zero-TB Communities, this Plan serves as a strategic roadmap, guiding local authorities to leverage technological innovation, ground their practices in scientific evidence, and optimize TB prevention strategies. By continuously refining intervention methodologies, implementing holistic control measures, and enhancing service delivery across the care spectrum, China strengthens its multi-pronged defense against TB. The integrated strategies of targeted case finding, comprehensive preventive treatment, and community-based interventions – central to the Plan – have already demonstrated significant efficacy in curbing TB incidence. As these evidence-based approaches are further bolstered, China is set to accelerate the decline of the TB epidemic, enhance population health, and contribute substantially to the "Healthy China" initiative. This comprehensive approach not only aligns with global efforts to end TB strategy goals but also underscores China's commitment to sustainable, high-quality development for public health advancement.

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ORIGINAL ARTICLE

Development of approaches for evaluating the pharmacokinetics of meropenem during endolymphatic antibiotic treatment in critically ill patients

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ABSTRACT

Introduction: The use of conventional methods of drug administration during antibiotic therapy of critically ill patients may be insufficient since the minimum inhibitory concentration required for effective therapy may not be maintained for the required amount of time due to the peculiarities of the patients' pharmacokinetics. Endolymphatic therapy has been proposed as an alternative approach.

Aim: The evaluation of meropenem pharmacokinetics during endolymphatic antibiotic therapy and its comparison to intravenous administration route.

Materials and methods: The blood samples from patients treated with meropenem endolymphatically (n = 1) and intravenously (n = 1) were analyzed using high-performance liquid chromatography with diode-array detection and high-performance liquid chromatography with electrospray ionization tandem mass-spectrometry.

Results: In intravenous and endolymphatic administration of meropenem minimum plasma concentration at steady state was 10 μg/ml and 16.39 μg/ml, maximum plasma concentration at steady state – 42.41 μg/ml and 42.57 μg/ml, area under the curve at steady state – 363.997 μg·h·ml^{-1} and 521.86 μg·h·ml^{-1}, mean residence time – 8.446 and 11.365 hours.

Conclusion: Our results demonstrate longer persistence of meropenem in circulation after endolymphatic administration thus indicating preferable pharmacokinetics. Additionally, minimum plasma concentration at steady state after endolymphatic treatment remained at a high level, exceeding minimum inhibitory concentration. However, further studies in larger cohorts are required for obtaining reliable confirmations of endolymphatic administration route benefits.

Key Words: carbapenems; sepsis; endolymphatic administration; HPLC-DAD; HPLC-ESI-MS/MS; therapeutic monitoring; comparative pharmacokinetics

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Introduction

Carbapenems belong to the class of β-lactam broad-spectrum antibiotics, structurally similar to penicillin, where the sulfur atom is replaced by a carbon atom [1]. All else being equal, among all carbapenems, meropenem is currently preferred because of the greater activity against gram-negative bacteria, which is increased by the possibility of higher doses due to less neurotoxicity [2]. Meropenem is actively used in modern clinical practice in the Russian Federation and a number of other countries. In the Russian Federation, it is included in a number of existing clinical recommendations of the Ministry of Health of the Russian Federation, for example, a drug of choice for patients with severe community-acquired pneumonia and risk factors for infection with P. aeruginosa and enterobacteria[1,2,3].

The most important pharmacokinetic/pharmacodynamic parameter of carbapenems is the ratio of the time when the concentration of the free drug exceeds the minimum inhibitory concentration (MIC) to the time between injections of the drug. This is expressed as a percentage time above MIC and requires 20% to achieve bacteriostatic effect of carbapenems and 40% to achieve maximum bactericidal effect. The MIC value depends on a specific microorganism and ranges from 0.03 to 8 μg/ml, reaching in some cases up to 32 μg/ml for resistant pathogens. It is worth noting that the value of this indicator required to achieve a certain effect is different for different groups of beta-lactams [3, 4]. Patients with severe infectious diseases are at risk of reaching only subtherapeutic concentrations (insufficient percentage time above MIC) due to pathophysiological changes affecting the pharmacokinetics of the drug, for example, renal and hepatic dysfunction, increased renal clearance, increased apparent volume of distribution [5]. Plasma concentrations of carbapenems may be insufficient with recommended dosages for severely ill patients with increased volume of distribution or for dialysis patients [2].

The use of intravenous or intramuscular routes of administration in antibiotic therapy of severe infectious diseases is not enough to achieve the necessary therapeutic effectiveness and eliminate pathogens. As an alternative approach, the use of endolymphatic therapy has shown its effectiveness in military field surgery, oncology, urology, gynecology, traumatology, phthisiology, as well as in the treatment of acute surgical diseases of the abdominal cavity [6]. Endolymphatic administration allows

[1] Community-acquired pneumonia in adults: clinical guidelines. Ministry of Health of the Russian Federation. 2024. (In Russian). Accessed 22.08.2025. https://cr.minzdrav.gov.ru/preview-cr/654_2

[2] Urinary tract infection: clinical guidelines. Ministry of Health of the Russian Federation. 2024. (In Russian). Accessed 22.08.2025. https://cr.minzdrav.gov.ru/view-cr/281_3

[3] Meningococcal Infection in Children: clinical guidelines. Ministry of Health of the Russian Federation. 2023. (In Russian). Accessed 22.08.2025. https://cr.minzdrav.gov.ru/view-cr/58_2

you to increase the flow of the drug into the pathological site (inflammation, wound, degenerative tissues, etc.) due to transport mediated by immunocompetent cells [7]. With endolymphatic administration, antibiotics are delayed in the lymphatic system for up to 24–48 hours, creating a depot of the drug in the body, followed by a slow dosage of them into the blood. When in lymph, it is expected that up to 50% of the dose of the administered antibiotic is adsorbed on the surface of lymphocytes, in addition, unstable coupling of drugs with immunoglobulins occurs, which ensures the entry of antibiotics into the site of inflammation together with immunocompetent cells and immunoglobulins [8]. Endolymphatic administration involves direct administration of the drug into the lymph in the following ways: catheterization of the peripheral lymphatic vessel (antegrade method) or superficial lymph node (intranodular method), through the thoracic lymphatic duct (retrograde method). A number of authors note the advantage of endolymphatic methods of administering drugs compared to traditional ones: faster recovery and recovery of patients, shorter length of hospital stay, reduced number of complications, reduced side effects of drugs [9].

Since meropenem refers to time-dependent antibiotics, that is, the effectiveness of treatment depends on the time of retention of the antibiotic concentration in the site of infection above the MIC for this pathogen, an important factor ensuring the effectiveness of therapy is therapeutic monitoring of the antibiotic concentration in order to adjust the dose in case of insufficiency of the percentage time above MIC indicator, which requires a sensitive, specific and suitable for routine analysis method for the quantitative determination of antibiotic in biosamples. The high-performance liquid chromatography (HPLC) with diode-array detection (HPLC-DAD) method was developed and validated to monitor the concentration of meropenem in blood plasma, and HPLC with electrospray ionization tandem mass-spectrometry (HPLC-ESI-MS/MS) to assess the concentration in white blood cells. The aim of this study was the evaluation of meropenem pharmacokinetics during endolymphatic antibiotic therapy and its comparison to intravenous administration route using HPLC-DAD and HPLC-ESI-MS/MS methods.

Materials and methods

Selection of biosamples

Two critically ill patients aged 36 (patient 1) and 45 (patient 2) with sepsis, hospitalized in April 2023, received 1 g of meropenem twice a day participated in the study, the first received meropenem intravenously, the second endolymphatically. Blood plasma was selected as possible biosamples for analysis to study the pharmacokinetics of meropenem during endolymphatic administration and further therapeutic monitoring. Based on the literature data on meropenem plasma concentration levels, HPLC-DAD was selected as the assay method.

Also, to evaluate the hypothesis of the delivery of antibiotics by immunocompetent cells to the site of inflammation, it was proposed to analyze lysates of leukocytes previously isolated from whole blood. Given the lower expected concentrations than plasma, HPLC-ESI-MS/MS was selected as the assay method.

Blood sample preparation

To obtain plasma, whole blood was centrifuged at 2500 revolutions per minute (RPM) for 15 minutes, and the supernatant was transferred to an individual tube.

300 µL of plasma was transferred to a 1.5 mL microtube, 600 µL of acetonitrile was added, and centrifuged at 13000 RPM for 10 minutes to precipitate proteins. The supernatant was transferred to an individual vial and the samples were stored at -70 °C until analysis.

Sample preparation of peripheral blood mononuclear cells

To obtain leukocyte lysates, the peripheral blood mononuclear cells (PBMCs) isolation method followed by lysis was used. A whole blood sample (5 mL) was transferred to saline tube 1 (5 mL). Ficoll solution (3 mL) was then added to tube 2 (15 mL). Ficoll solution has a specific density of 1.077 g/ml, which ensures the correct separation of blood layers. After neatly layering the blood (from tube 1) onto the gradient (tube 2), centrifugation was performed at 400 *g* (20 min). The principle of the gradient separation method is based on the separation of blood cell elements by size when centrifuged in a Ficoll gradient with a specific density of 1.077 g/ml.

After centrifugation, various layers of whole blood were visible. The main cellular component of blood is red blood cells, which make up 45% of the total blood volume. The remaining 55% is plasma. The PBMCs fraction lies just below the plasma layer. It includes lymphocytes (T- and B-cells), naive cells, monocytes, dendritic cells, stem cells. Granulocytes, which are heavier than PBMCs, are located between their layers and the erythrocyte layer.

Next, 3 mL of the formed PBMCs ring was sampled over the entire cross-sectional area of the tube by pipetting through the plasma fraction. The PBMCs fraction was transferred to another tube with 10 mL saline. The contents of the tube were centrifuged at 400 *g* (7 min). As a result, PBMCs settled at the bottom of the tube, 500 µl of guanidine lysis solution was added to PBMCs to disrupt the leukocyte membrane. The last stage of sample preparation is protein precipitation by adding 400 µl of acetonitrile to 200 µl of PBMCs lysate and centrifuged at 13000 RPM for 10 minutes. The supernatant was transferred to an individual vial and the samples were stored at -70 °C until analysis.

High-performance liquid chromatography with diode-array detection development

A system consisting of an Agilent Infinity II 1260 high-performance liquid chromatograph equipped with a gradient pump, column thermostat, degasser, manual input and diode-array detector was used for chromatographic separation and detection of meropenem in plasma samples.

The following reagents and materials were used: acetonitrile (HPLC grade ≥99.9%), ammonium acetate (≥98%), acetic acid (≥99%), concentrated ammonia solution, purified water (Milli-Q) for HPLC, meropenem trihydrate drug substances (series: 110522; manufacturer: Sintez OJSC), intact plasma samples.

To prepare mobile phase (MP) A, 1.925 g of ammonium acetate was placed in a 1000 mL resistant glass bottle and dissolved in 1000 mL of water, 1.925 mL of acetic acid was added, mixed, and the pH of the solution was adjusted to 6.0 ± 0.1 with concentrated ammonia solution. The resulting solution was filtered through a 0.45 µm membrane filter and degassed. To prepare MP B, 1000 mL of acetonitrile was placed in a 1000 mL refractory glass bottle.

To validate the method and further quantify, model reference standards prepared by mixing 500 µL of the corresponding working solution with 500 µL of intact plasma were used, after which sample preparation was carried out as described above. The concentrations of the obtained

standard calibration solutions corresponded to the following concentration range: 5, 10, 25, 50, 100, 250, 500, 1000 μg/mL.

Development of high-performance liquid chromatography with electrospray ionization tandem mass-spectrometry procedure

A system consisting of an Agilent Infinity II 1290 high-performance liquid chromatograph equipped with a gradient pump, column thermostat, thermostatic multisampler, degasser and ESI-MS/MS detector was used for chromatographic separation and detection of meropenem in leukocyte lysates.

The following reagents and materials were used: acetonitrile (HPLC grade ≥99.9%), formic acid (≥99%), purified water (Milli-Q) for HPLC, meropenem trihydrate drug substances (batch: 110522; manufacturer: Sintez OJSC), intact plasma samples.

To prepare MP A, 1000 mL of water and 1000 mL of formic acid were added and mixed in a 1.0 mL refractory glass bottle. To prepare MP B, 1000 mL of acetonitrile was placed in a 1000 mL resistant glass bottle and 1.0 mL of formic acid was added and mixed.

To validate the method and further quantify, model reference standards prepared by mixing 500 μL of the corresponding working solution with 500 μL of intact plasma were used, after which sample preparation was carried out as described above. The concentrations of the obtained standard calibration solutions corresponded to the following concentration range: 0.01, 0.05, 0.25, 0.5, 1, 2.5, 5, 7.5 and 10 μg/mL.

Validation of bioanalytical methods

The methods were validated in accordance with the rules for conducting bioequivalence studies of drugs within the Eurasian Economic Union (approved by decision No. 85 of the Council of the Eurasian Economic Commission of 03.11.2016) for the following validation parameters: specificity, limit of quantification, linearity, analytical range, precision (repeatability), accuracy, transfer effect, matrix effect, stability. All obtained values complied with the regulatory documentation requirements.

Results

High-performance liquid chromatography with diode-array detection

To develop the HPLC-DAD method, a chromatographic column was selected: Agilent Eclipse Plus C8, 4.5 × 150 mm in size, octasilane (C8) sorbent, 5 microns. An Eclipse Plus C18 2.1 × 12.5 mm, 5 μm protective column was used to protect the main column from biological sample related substances. The MP composition was optimized as follows: MP A 25 Mm ammonium acetate buffer pH 6.0 ± 0.1, MP B acetonitrile in a ratio of 89:11, the elution mode is isocratic. Oven temperature 30 °C, injection volume 20 μL. To select the wavelength of detection, the ultraviolet spectrum of the meropenem substance solution was recorded (Fig. 1), the obtained maximum absorption corresponded to the literature data and amounted to 298 nm. The retention time of the meropenem peak was about 3 minutes.

Typical chromatograms of the blank, the lowest concentration standard calibration solution (5 μg/mL) and the patient's plasma sample with maximum concentration are presented in Fig. 2. The developed method was used to analyze the blood plasma of two seriously ill patients receiving 1 g of meropenem twice a day, at 9 am and 5 pm intravenously

FIG. 1. The ultraviolet spectrum of the meropenem substance solution

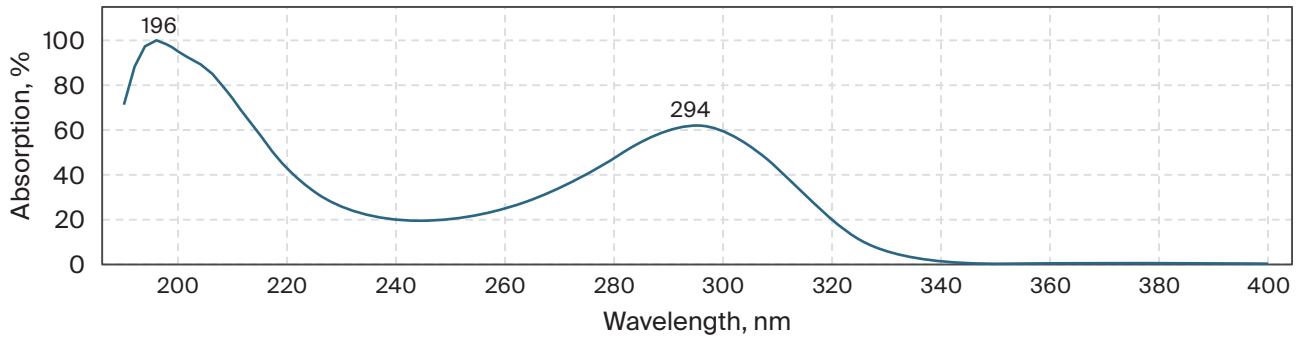
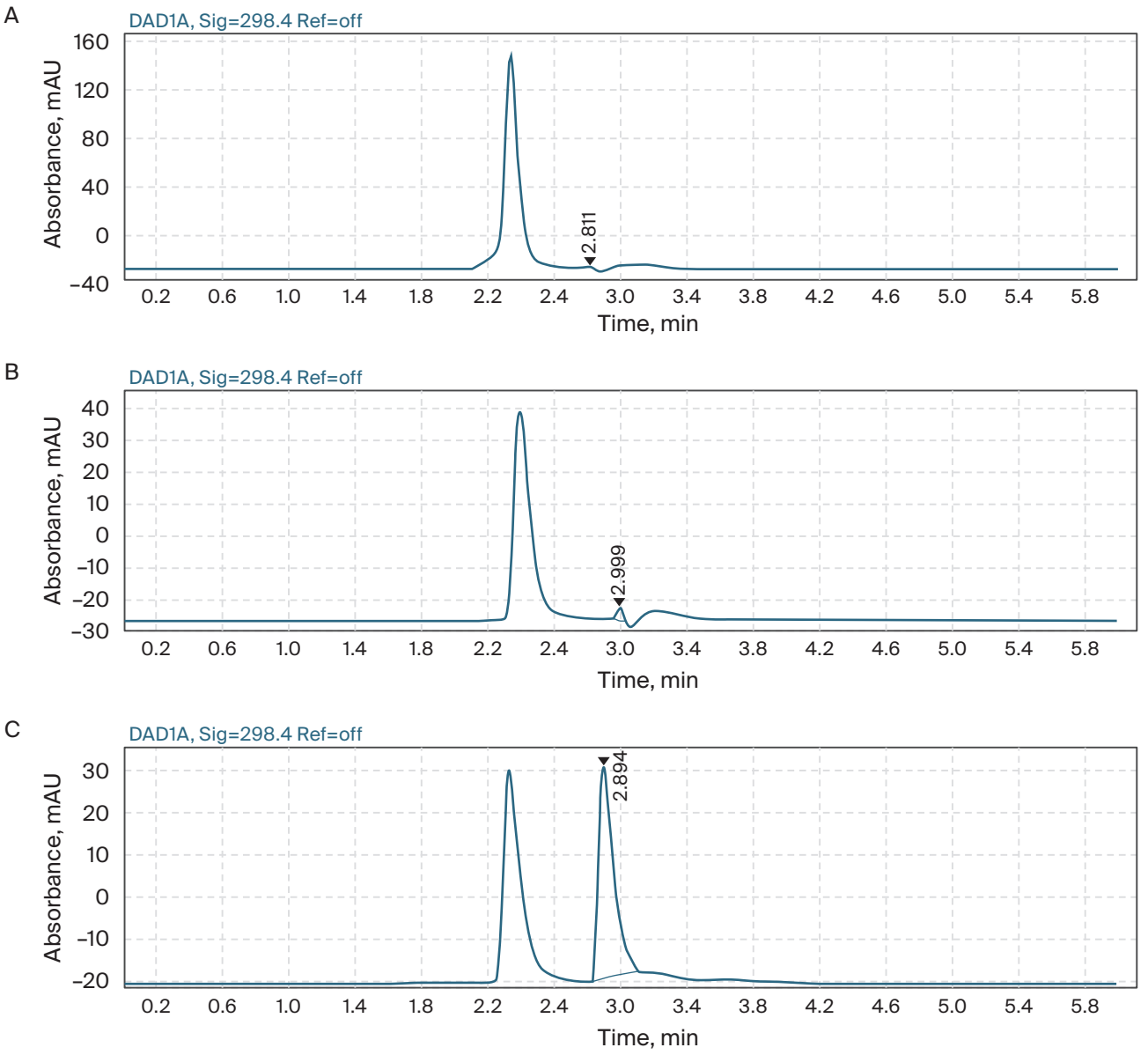


FIG. 2. Typical high-performance liquid chromatography with diode-array detection chromatograms of blank (A), lowest concentration standard calibration solution (B), patient's plasma sample with maximum concentration (C)



Note: mAU-mili-absorbance units

Table. Comparative pharmacokinetic parameters for intravenous and endolymphatic routes of administration

Route of administration	Minimum plasma concentration at steady state, μg/ml	Maximum plasma concentration at steady state, μg/ml	Area under the curve at steady state, μg·h·ml^{-1}	Mean residence time, h
Intravenous	10	42.41	363.997	8.446
Endolymphatic	16.39	42.57	521.86	11.365

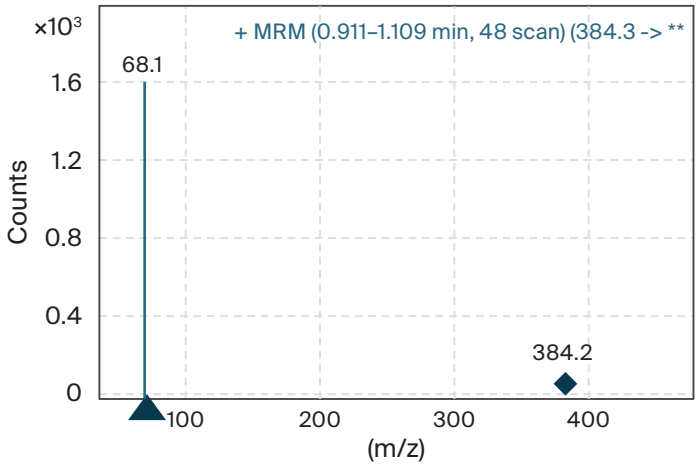
and endolymphaticaly, respectively. Blood was collected at 0, 0.083, 1, 2, 3, 4, 5, 6, 8, 12, 24, 27 and 28 hours. Comparative pharmacokinetic parameters (Table) were calculated from the concentrations found.

From the obtained pharmacokinetic parameters, it can be seen that, despite comparable maximum plasma concentration at steady state with intravenous and endolymphatic routes of administration, in the second case, the drug remains in the body for a longer time, which demonstrates the mean residence time indicator. Also, with endolymphatic administration, minimum plasma concentration at steady state remains at a fairly high level, exceeding MIC = 12 μg/ml, which is critical for achieving a therapeutic effect during antibiotic therapy.

High performance liquid chromatography with electrospray ionization tandem mass-spectrometry

The HPLC-ESI-MS/MS method was developed on a chromatographic column for ultra HPLC “Zorbax Eclipse C18”, C18, 50 × 2.1 mm, 1.7 μm. An Eclipse Plus C18 2.1 × 12.5 mm, 5 μm protective column was used to protect the main column from biological sample related substances. The MP composition was selected as follows to obtain a positively charged parent ion of meropenem: MP A 0.1% formic acid in purified water, MP B 0.1% formic acid in acetonitrile, elution mode isocratic, solvent ratio 95:5%. Oven temperature 30 °C, injection volume 5 μL. To select the multiple reaction monitoring transition for meropenem detection, the mass spectrum was recorded and the most intense product ion 68.1 was selected (Fig. 3). ESI-MS/MS parameters were optimized to achieve the highest sensitivity of the method: precursor ion 384.2; product ion 68,1; gas temp 350 °C; gas flow 9 l/min; sheath gas flow 9 l/min; ion spray voltage 5500; collision energy 51.

FIG. 3. Multiple reaction monitoring transition of meropenem

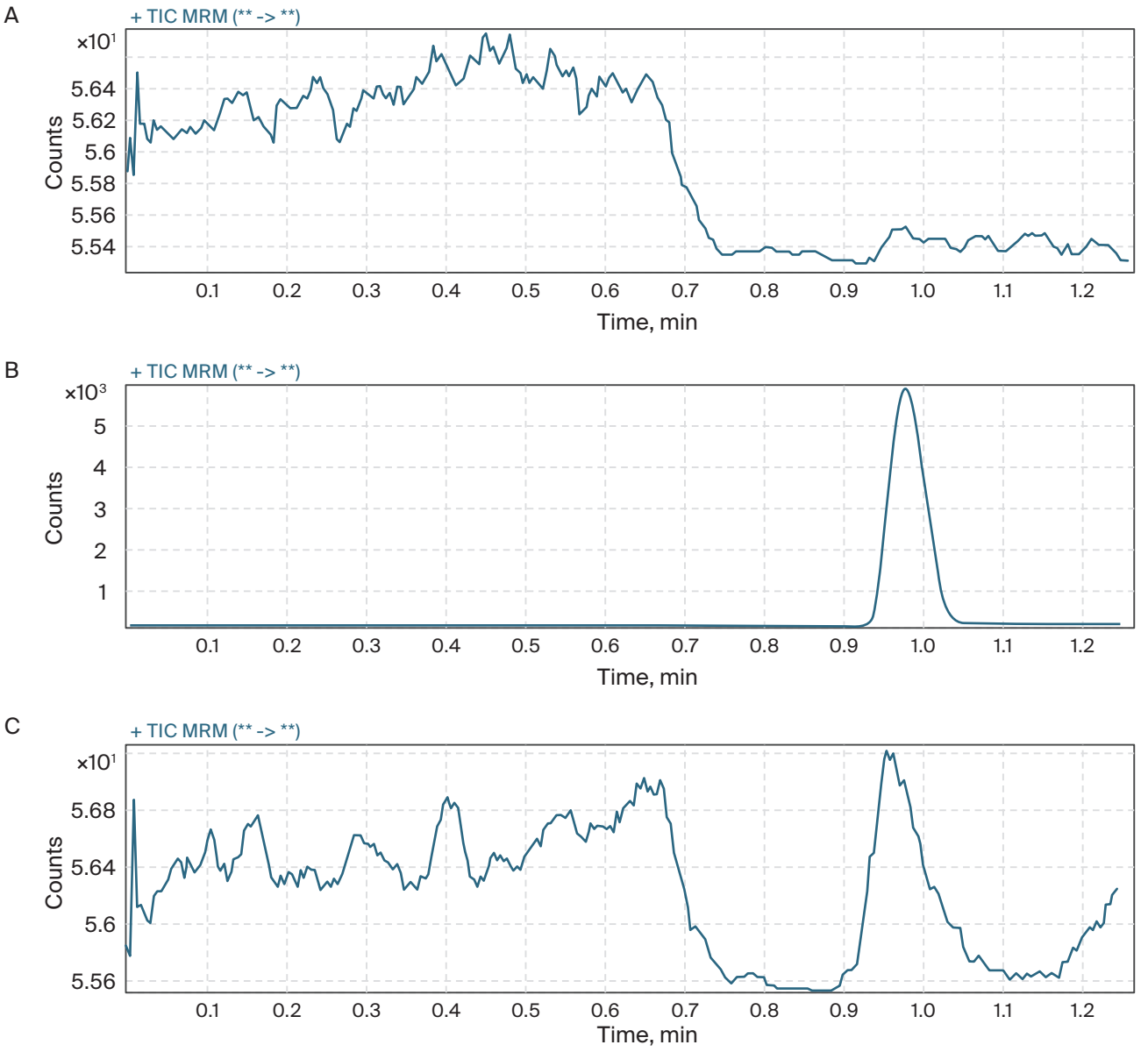


The retention time of meropenem was approximately one minute, typical chromatograms of blank, blood plasma and leukocyte lysate are shown in Fig. 4. These data demonstrate the concentrations of meropenem in leukocyte lysates at intravenous administration route at the limit of determination level. In the endolymphatic route of administration, concentrations of meropenem in lysate ranged from low limit of quantification to 30 ng/mL, which is associated with a high antibiotic content in the lymphatic system when directly injected into lymph.

Discussion

Meropenem demonstrates significant pharmacokinetic variability across different patient populations, underscoring the need for

FIG. 4. Typical high performance liquid chromatography with electrospray ionization tandem mass-spectrometry chromatograms of blank (A), blood plasma (B) and leukocyte lysate (C)



individualized dosing strategies. To achieve the necessary therapeutic effect, various dosage regimens can be considered, including changing the duration of the infusion and the dose administered as well as the use of alternative routes of administration [10, 11]. Despite the lower bioavailability of meropenem for routes of administration other than intravenously, the time when the concentration of the free drug exceeds MIC increases [12, 13]. Considering the data obtained on the steady-state concentrations in this study, this information confirms the above statement – minimum plasma concentration at steady state for intravenous route of administration was 10 μg/ml, for endolymphatic was 16.39 μg/ml, which leads to an increase in the time when the concentration of the free drug exceeds required MIC. It is necessary to optimize the dosage regimen to achieve the required MIC for patients with pathophysiological changes, for example, kidney function or in patients with severe burns, amputated limbs, because these changes affect the pharmacokinetics of the antibiotic [14–16]. The use of therapeutic drug monitoring is an effective approach to optimize dosing, ensuring improved therapeutic outcomes while reducing the risk of toxicity and reducing the development of antibiotic-resistant bacteria [17, 18].

A study of the inflammatory exudate of patients receiving meropenem intravenously shows high concentrations of meropenem almost comparable to plasma concentrations [19]. Administration of the antibiotic directly into the lymphatic system will theoretically increase the concentration of meropenem in exudate, what can be mediated by the delivery of meropenem to the inflammatory site by immunocompetent cells, which requires further research. According to our data, the concentrations of meropenem detected in PBMCs lysate were below 30 ng/ml for the endolymphatic route of administration, and no clear signal was obtained for the intravenous route. This shows a higher content of meropenem in PBMC with the endolymphatic route of administration than with the intravenous route. In vitro experiments demonstrated elevated IL-1β secretion in infected macrophages after incubation with meropenem concentrations above 5 μg/ml, indicating activation of host innate immune response by pathogen-associated molecular patterns as a result of the release of damage-associated molecular patterns [20]. Apparently, an increase in the concentration of meropenem in the site of inflammation will lead to a more active death of bacterial cells, which in turn will stimulate the immune response more strongly.

Conclusion

The developed methods for the quantitative determination of meropenem in biological samples of seriously ill patients were validated in accordance with the current regulatory documents in the field of bioanalytical studies and tested on real samples taken from seriously ill patients. In the future, these methods are planned to be used both for further studies of the comparative pharmacokinetics of meropenem in various routes of administration, and for therapeutic monitoring of the concentration of meropenem at the time of antibiotic therapy using the HPLC-DAD method.

The calculated pharmacokinetic parameters from the results obtained using the HPLC-DAD method demonstrate the advantages of endolymphatic administration route over intravenous at the pharmacokinetic level, however, in order to reach more reliable conclusions, it is necessary to analyze a larger sample of patients, and extending the study period to observe steady-state concentrations

for several days and then comparing groups intravenous and endolymphatic administration routes for statistically significantly different results. It is also advisable to continue the study of meropenem in PBMCs using the developed and validated HPLC-ESI-MS/MS method to better understand the pharmacokinetic features of endolymphatic administration and the causes of their occurrence.

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REVIEW

The population growth in Egypt: from health perspective challenges to comprehensive solutions

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ABSTRACT

Egypt faces a major challenge due to its rapid population growth. The growth rate of 2.56% from 2006 to 2017 far exceeds the economic growth needed to support it. Even though life expectancy has improved and mortality rates have decreased, high birth rates remain a significant obstacle. The country's large youth population could offer a demographic advantage. Several health-related challenges are currently faced by the country, including high out-of-pocket spending, uneven distribution of health services, and the growing burden of non-communicable diseases. Despite the challenges, the government successfully maintained several ongoing health programs, initiated multiple national projects, and achieved

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significant international recognition for the milestones it reached. The country also successfully implemented universal health coverage in six governorates by 2025, out of 27 Egyptian governorates. Additionally, Egypt hosted multiple international conferences that contributed to the design and implementation of global, regional, and national population and health strategies. Recently, Egypt launched its National Population Strategy (2023–2030) and National Health Strategy (2024–2030), which outline plans to mitigate the risks of overpopulation and focus on improving health and well-being. These efforts are aligned with the initiation of several public health interventions that have successfully alleviated suffering from various endemic diseases. All these initiatives are crowned by the national project for human development, paving the way for healthy, efficient, and culturally rich generations. Although fertility rates have decreased significantly, Egypt continues to aim for these reductions to align with improvements in the Human Development Index and longer life expectancy.

Key Words: demographics; healthcare system; fertility rate; non-communicable diseases; public health initiatives; universal health coverage; human development; national population strategy

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Introduction

Egypt ranks fourteenth globally in terms of population size, ranking as the largest among Arab nations and the third-largest among African countries, after Nigeria and Ethiopia. Egypt's population constitutes approximately 1.3% of the world's population. The population growth rate increased from 2.05% between the 1996 and 2006 censuses to 2.56% between the 2006 and 2017 censuses, surpassing the annual growth rate of the global population and many developing nations[1].

According to the United Nations estimates, the world's population increased at an average annual rate of 1.23% from 2000 to 2010. India, the second most populous country, experienced a yearly growth rate of 1.64% during the same period, while China, the most populous country, had an annual growth rate of 0.5% from 2000 to 2010[2].

Egypt's population grew by about 24.7 million people (roughly 30% increase) from 2010 to early 2023. This illustrates the scale of population growth during this period and its impact on health, the economy, and other areas. Additionally, there is an imbalance between population growth and economic growth in Egypt[3].

Numerous research studies have emphasized that economic growth should be three times the rate of population growth to create enough jobs for the new generation. This means that Egypt's population growth rate, which was 2.56% between 2006 and 2017, requires an economic

[1] UNFPA Egypt. The National Strategy for Population and Development. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/national-strategy-population-and-development

[2] UNFPA Egypt. Population Situation Analysis Egypt 2016 Report. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/population-situation-analysis-egypt-2016-report

[3] UNFPA Egypt. The National Strategy for Population and Development. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/national-strategy-population-and-development

growth rate exceeding 7.5% annually for citizens to truly benefit from development [1].

Population demographics

The demographic trends in Egypt over the past few decades have shown significant progress. There has been a notable improvement in healthcare, evidenced by lower mortality rates and higher life expectancy at birth. Since the 1960s, Egypt has experienced a substantial decline in death rates. The crude death rate fell from 16.9 per 1000 people in 1960 to 7.3 in 2021, and infant and child mortality rates have also decreased rapidly[4].

The infant mortality rate dropped from 141 per 1,000 live births during 1965–1969 to 25 per 1,000 live births in 2017–2021; additionally, under-five child mortality decreased from 243 per 1,000 live births to 28 per 1,000 live births in 2021[5]. The maternal mortality rates also dropped from 174 deaths per 100,000 live births during 1992–1993 to 49 deaths in 2021. Due to these improvements in death rates, life expectancy in Egypt reached 74.1 years for females and 69.7 years for males in 2022[6].

The fertility rates have also declined, with the number of births dropping from 2.7 million in 2014 to 2.183 million in 2022; the total fertility rate decreased from 3.5 children per woman in 2014 to 2.85 in 2021, and further to 2.76 in 2022; family planning coverage increased to 66.4% in 2021, up from about 58.5% in the 2014 survey; if current fertility rates of 2.76 children per woman continue, Egypt's population is projected to reach 117 million by 2030 and 157 million by 2050[7].

Egypt experienced a significant drop in birth rates over the past years, from 30.3 live births per 1000 people in 2013 to 21.1 in 2022. Despite this decline, the current birth rates, which exceed two million births annually, still present a major challenge across various economic, social, environmental, and health sectors[8].

Migration

The number of migrants from Egypt was estimated at around 1.4 million according to the 1976 population census, representing 3.6% of the total population; the 2006 census reported that international migration from Egypt had reached 3.9 million migrants, making up 5.4% of the population; by the 2017 census, there was a significant increase in the number of migrants abroad, reaching 9.5 million, which accounts for 10% of the population; estimates indicate that the highest migration flows from Egypt are directed to the Gulf countries compared to other Arab nationalities; however, Egyptian labor in the Gulf countries faces fierce competition in the job market with the Asian labor, and these countries are also tending to replace foreign labor with domestic workforce[9].

Egypt has also become an attractive destination for certain nationalities. According to a report by the International Organization for Migration (IOM), the number of residents in Egypt has reached

[4] The DHS Program – Egypt DHS 2014 – 25 Government Fact Sheets. Accessed 23.06.2025. https://dhsprogram.com/publications/publication-OF30-Other-Fact-Sheets.cfm?cssearch=1818059_1

[5] Egypt Family Health Survey EFHS 2021. (In Arabic). Accessed 23.06.2025. https://www.capmas.gov.eg/Pages/Publications.aspx?page_id=5109&Year=23639

[6] The World Health Organization. Health data overview for the Arab Republic of Egypt. Accessed 23.06.2025. https://data.who.int/countries/818

[7] UNFPA Egypt. Trends of Fertility Levels in Egypt in Recent Years. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/trends-fertility-levels-egypt-recent-years

[8] UNFPA Egypt. The National Strategy for Population and Development. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/national-strategy-population-and-development

[9] Ibid.

9 million migrants and refugees, equivalent to 8.7% of the Egyptian population[10].

Most Egyptian migrants are concentrated in Arab countries, where their number reached 7 million in 2017, making up 68.4% of all Egyptian expatriates. However, due to current issues in Arab nations caused by security instability in Libya, Iraq, and the war in Yemen, along with falling global oil prices, the number of Egyptians abroad has dropped to 4.9 million, representing 54.6% of the total Egyptian expatriates[11] [2].

Population characteristics

Both the dependency ratio for the young (the population under 15 years old divided by the population aged 15–64) and the dependency ratio for the elderly (the population 65 years and older divided by the population aged 15–64) have increased from about 51 and 6%, respectively, in 2011 to 55 and 8% in 2021, the overall dependency ratio (the combined population under 15 years old and 65 years and older divided by the population aged 15–64) rose to approximately 61.6% by 2022. This increase is due to higher birth rates and a growing elderly population caused by longer average lifespans; to fully benefit from the demographic dividend, the dependency rate needs to decrease, which can be achieved by lowering overall birth rates[12].

Egypt has a large youth population that tapers at the top, as of July 1, 2021, approximately 34.3% of the population is under 15 years old, and youth aged 15 to 29 make up 25% of the total population, offering Egypt an opportunity to benefit from the potential demographic dividend. The percentage of people aged 60 and over increased from 6.9% in 2011 to 8.2% in 2021, and this group is expected to grow to 10.6% by 2030 (Fig. 1). This shift indicates changes in the population structure, which can lead to various health and social challenges. The rise in the percentage of those over sixty means greater health and social needs for this group, resulting in higher healthcare and pension costs. This, in turn, requires additional investments in health infrastructure[13].

Health-related challenges

As of 2025, Egypt's Central Agency for Public Mobilization and Statistics (CAPMAS) announced that the Egyptian population had exceeded 107 million[14], and was classified by the World Bank as a lower-middle-income country with a Gross National Income per Capita reaching $3,000 in 2020. Although the country has experienced economic growth, especially in the manufacturing sector, it still faces challenges such as high public debt, sluggish exports, and the impact of regional conflicts and political unrest[15]. These factors were augmented by the population growth and negatively influence healthcare delivery, infrastructure setup, and future planning, leading to significant challenges such as:

[10] IOM Egypt estimates the current number of international migrants. IOM Egypt. Accessed 23.06.2025. https://egypt.iom.int/news/iom-egypt-estimates-current-number-international-migrants-living-egypt-9-million-people-originating-133-countries

[11] UNFPA Egypt. The National Strategy for Population and Development. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/national-strategy-population-and-development

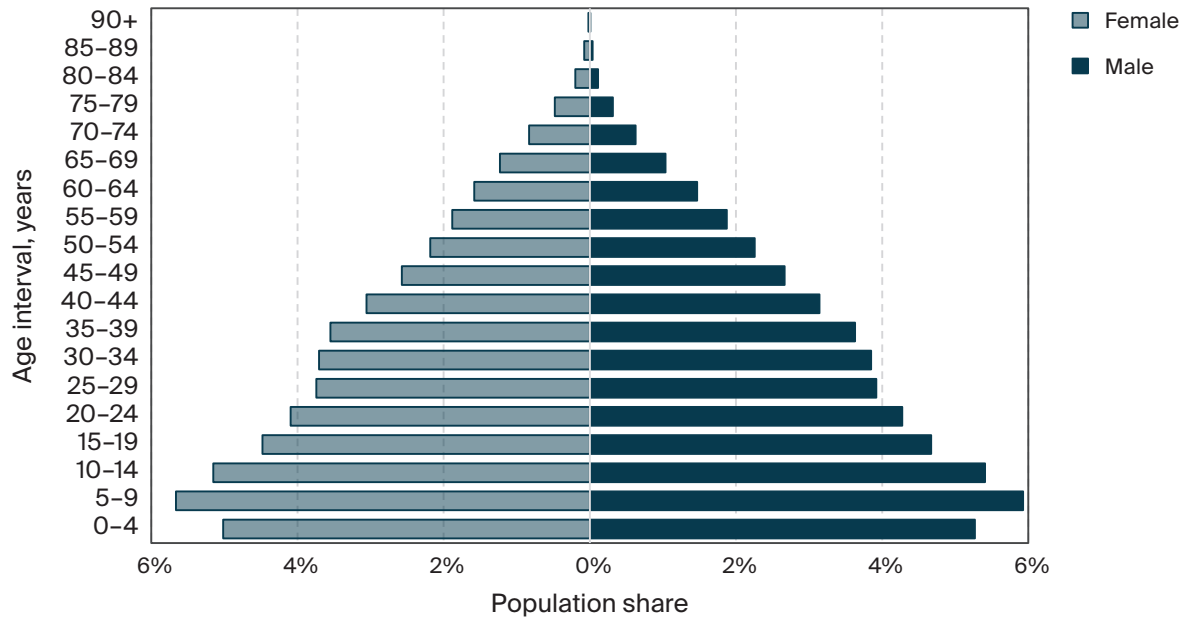
[12] UNFPA Egypt. Egypt's Demographic Opportunity (Preliminary Assessment based on 2017 Census). Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/egypts-demographic-opportunity-preliminary-assessment-based-2017-census

[13] UNFPA Egypt. Building a Future Powered by Egypt's People: Navigating the Demographic Trends. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/building-future-powered-egypts-people-navigating-demographic-trends

[14] CAPMAS. Accessed 23.06.2025. https://www.capmas.gov.eg/

[15] World Bank. Egypt Overview: Development news, research, data. Accessed 23.06.2025. https://www.worldbank.org/en/country/egypt/overview

FIG. 1. Egypt population pyramid 2023



- Health system financing: According to the Egyptian Constitution of 2014, the government's health expenditure should be at least 3% of the gross domestic product (GDP). Egypt's healthcare system heavily relies on out-of-pocket payments, accounting for 62% of total health expenditure, compared to 39% in other lower-middle-income countries. Government health spending accounts for approximately one-third of the total health spending. The Universal Health Insurance System (UHIS), introduced in 2018, aims to expand coverage and reduce both out-of-pocket and catastrophic health expenditures; however, it has only reached six governorates out of the 27 Egyptian governorates by 2025, covering approximately 3.1 million people. Although the national health budget has increased nearly 10-fold since the fiscal year 2014/2015, this increase has been absorbed by several challenges, such as the repeated devaluation of the Egyptian Pound, the dedication of resources to set up the new UHIS kick-off, and the progressive population growth[16].
- Access to healthcare services: The healthcare system in Egypt includes multiple providers of health services, with evident disparities between governorates. The average national bed capacity is 11.09 per 10,000 people, which is significantly lower than the international standard of 30 per 10,000 people; Only nine governorates exceed the national average, and just two are close to the global standard. The health workforce is also impacted similarly; over the last decade, the number of physicians has decreased from 11.3 per 10,000 people in 2011 to 9.3 per 10,000 people in 2022, and the number of nursing staff has declined from 21.3 per 10,000 people to 19.9 per 10,000 in 2022[17]. The defective health services in some areas usually encourage people to self-medicate due to the presence of a high number of community pharmacies [3].

[16] Egypt National Health Accounts establishing an expenditure baseline to support Egypt's health care reform 2019/2020. Accessed 23.06.2025. https://iris.who.int/handle/10665/375668
Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/
[17] Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/

- Disease threats: The past decade has shown a rise in the incidence and prevalence of non-communicable diseases (NCDs). 29.5% of people have high blood pressure, 15.5% have high blood glucose levels, 35.7% are obese, and 22.7% are tobacco smokers. Eighty-six percent of deaths are due to NCDs with cardiovascular diseases being the leading cause, accounting for 43.9%, followed by cancers, which represent 14.8% of deaths. Breast and liver cancers are the highest incident cancers (48.7 and 22.7/100,000 population). Despite national efforts, school children (6–12 years) still suffer from anemia, obesity, and stunting, reaching 9.4, 8.7, and 3.8% respectively[18].

The path to comprehensive solutions

According to Article 41 of the Egyptian Constitution, which states that the government is committed to implementing a population program aimed at balancing population growth with available resources, maximizing investment in human development, and improving people's characteristics within the framework of sustainable development, and in light of emerging and ongoing demographic changes and shifts, despite these challenges related to population growth, the Egyptian government has taken several actions to curb the rise in birth rates and has implemented measures to lessen the impact of population growth on different sectors, particularly the health sector, through various initiatives.

- Global leadership in Policies and Strategies: Cairo hosted the first International Conference on Population and Development (ICPD) in 1994. During the conference, 179 governments agreed that the goal of any population policy should be to ensure reproductive rights and choices for people, rather than focusing solely on demographic targets. They also adopted a Program of Action aimed at empowering women and girls for their own benefit, as well as for the benefit of their families, communities, and nations[19]. In 2023, after three decades, President El-Sisi directed the Egyptian Ministry of Health and Population (MoHP) to organize the Global Congress on Population, Health and Development (PHDC) on an annual basis, which represents a significant opportunity and an essential platform for researchers, policymakers, and decision-makers from around the globe to address the population dilemma[20].
- National Strategies: The National Population and Development Strategy (2015–2030) was launched in November 2014 with the goal of improving citizens' quality of life by balancing population growth and economic development. It also aims to enhance population characteristics, reshape Egypt's population distribution, and achieve social justice and harmony by reducing developmental gaps between regions. The strategy includes four pillars: increasing access to family planning and reproductive health, promoting youth and adolescents' health and civic engagement, advancing women's economic empowerment, strengthening girls' education, and finally, media. During the PHDC 2023 conference, the MoHP launched the National Population Strategy (2023–2030), which highlights the state's latest efforts to address the overpopulation crisis. This strategy has been developed in light of the Sustainable Development Goals (SDGs), Egypt's Vision 2030,

[18] Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/
WHO. Egypt Steps Survey 2017. Accessed 23.06.2025. https://cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/data-reporting/egpyt/steps/egypt-steps-survey-2017-facts-and-figures.pdf?sfvrsn=f4dd4788_2

[19] Programme of Action. Adopted at the International Conference on Population and Development, Cairo, 5–13 September 1994. Accessed 23.06.2025. https://www.unfpa.org/sites/default/files/event-pdf/PoA_en.pdf

[20] Global Congress on Population, Health and Human Development (PHDC 2023). Accessed 23.06.2025. https://www.globalphdc.com/

the Egyptian Constitution, the National Strategy for Population and Development, and the National Project for Family Development. The strategy is built around seven pillars: ensuring reproductive rights, investing in human capital, empowering women, promoting education and learning, leveraging communication and media for development, addressing climate change and population dynamics, and governance of the population sector. It focuses on key areas such as economic empowerment, service provision, cultural and educational awareness campaigns, and digital transformation[21].

- National Projects: In 2019, Egyptian President Abdel Fattah El Sisi launched the Descent Life initiative, also known as the National Project for the Development of the Egyptian Countryside, called "Haya Karima" or "Decent Life". It mainly aims to address the social determinants of health and improve the living conditions and daily lives of people in thousands of villages and rural areas by promoting cooperation and unity among government institutions, private sector entities, civil society, and development partners in Egypt. Additionally, it enhances medical services, expands educational opportunities, and creates job opportunities[22].

In 2022, the government established the National Project for Development of Egyptian Family (NPDEF), as a comprehensive development initiative that extends beyond family planning and healthcare. It covers five areas, including promoting the economic independence of women. Furthermore, the NPDEF's efforts align with Article 41 of Egypt's 2014 constitution, which mandates the implementation of a population program aimed at balancing demographic growth with available resources and maximizing investments in human resources[23].

- Universal Health Coverage Expansion: In 2018, Egypt achieved a significant milestone in healthcare reform with the introduction of the Universal Health Insurance Law, aimed at revolutionizing the nation's health system and advancing Universal Health Coverage (UHC). This law designates families as the primary unit for enrollment and establishes family health units and centers as the initial point of service for insured individuals. Aligned with the SDGs principle of inclusivity, Egypt's UHC reform seeks to ensure equitable access to high-quality healthcare for all citizens, addressing critical health priorities and promoting health equity. The reform's overarching goal is to break the cycle of poor health and poverty at both individual and societal levels by providing accessible, quality healthcare services, thereby improving health outcomes and alleviating the financial burden of medical costs on households. This, in turn, supports poverty reduction and fosters economic growth. The Universal Health Insurance (UHI) system aims to secure sustainable funding for healthcare while reducing out-of-pocket expenses through a comprehensive overhaul of the health financing system. Implementation is planned across six phases, targeting all Egyptian governorates with a comprehensive package of quality health services and financial protection by 2032, with strategies to expedite the rollout within a decade. The UHI law introduces a purchaser-provider split, supported by the establishment of three independent organizations in mid-2019: the Universal Health Insurance Authority (UHIA) to procure services, the Egypt Healthcare Authority (EHA) to deliver services, and the General Authority for Healthcare

[21] UNFPA Egypt. The National Strategy for Population and Development. Accessed 23.06.2025. https://egypt.unfpa.org/en/publications/national-strategy-population-and-development

[22] Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/

[23] National Project for Development of the Egyptian Family-SIS. Accessed 23.06.2025. https://www.sis.gov.eg/Story/164868/National-Project-for-Development-of-the-Egyptian-Family?lang=en-us

Accreditation and Regulation (GAHAR) to oversee accreditation and regulation[24].

- Public Health Initiatives: For several decades, the Egyptian people suffered the double burden of both communicable and NCDs. Since 2018, the government has launched a series of innovative public health interventions aimed at eliminating several infectious diseases and reducing the impact of multiple NCDs. Through these initiatives, Egypt has been recognized by the World Health Organization (WHO) as the first country to achieve the gold tier certificate on the path to eliminating hepatitis C virus (HCV) [4] together with elimination of Measles and Rubella in 2023 [5], followed by the certificate to achieve hepatitis B control targets in 2024[25] and the elimination of malaria in 2025[26]. In addition, the MoHP is driving robust early detection programs for six cancers, including breast, liver, prostate, colorectal, lung, and cervical cancer. Parallelly, screening for NCDs such as diabetes mellitus and hypertension, along with their risk factors like dyslipidemia and sequelae such as renal impairment, is also ongoing. On the other hand, several screening programs are ongoing to detect rare diseases early and the leading causes of disabilities[27]. Special focus on improving nutritional indicators for school children has been ongoing since 2019, with annual screening for anemia, obesity, and stunting leading to remarkable improvements: anemia decreased from 42.3% in 2019 to 9.4% in 2024, obesity from 12.7% in 2019 to 8.7% in 2024, and stunting from 6.9% in 2019 to 3.8% in 2024. At the forefront of this effort is the 1000 Golden Days program, which started in 2017 and aims to improve the health indicators of pregnant women and newborns, address the high fertility rate through indirect interventions, encourage families to have better pregnancy spacing, promote breastfeeding, reduce malnutrition among newborns and children, and support overall mental health. In 2023, the program was upgraded to a national presidential initiative with comprehensive national plans and indicators aligned with the NPDEF[28].

The national project for human development

In July 2024, the Egyptian Prime Minister appointed the Minister of Health and Population as his deputy for human development for the first time ever. This decision truly demonstrates the national commitment to human capital. The government announced the launch of the national project for human development under the slogan “Bedaya” or “A New Beginning for Human Development.” The goal of that ambitious Presidential Initiative is to create a pathway for the Egyptian people toward self-development, health, education, sports, culture, and behavior, in order to nurture a healthy, educated, empowered, capable, aware, cultured, and ethical citizen for society. The project supports Egypt’s Vision 2030 and the United Nations (UN) SDGs by addressing poverty, gender equality, and economic growth, it complements initiatives like Haya Karima, which target rural development and financial inclusion, especially for women-led businesses; the WHO’s Director-General, Tedros Adhanom Ghebreyesus,

[24] Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/
[25] WHO EMRO. Egypt becomes the first country in the Region to achieve hepatitis B control status. Accessed 23.06.2025. https://www.emro.who.int/egy/egypt-news/egypt-becomes-the-first-country-in-the-region-to-achieve-hepatitis-b-control-status.html
[26] Egypt is certified malaria-free by WHO. Accessed 23.06.2025. https://www.who.int/news/item/20-10-2024-egypt-is-certified-malaria-free-by-who
[27] Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/
[28] Egypt National Health Strategy 2024-2030. Accessed 23.06.2025. https://www.100millionseha.eg/
Egypt to launch “1000 Golden Days” initiative to develop Egyptian family-SIS. Accessed 23.06.2025. https://sis.gov.eg/Story/183913/Egypt-to-launch-‘1000-Golden-Days’-initiative-to-develop-Egyptian-family?lang=en-us

praised Bedaya for its comprehensive vision, especially its focus on cross-sectoral collaboration and women/youth empowerment[29].

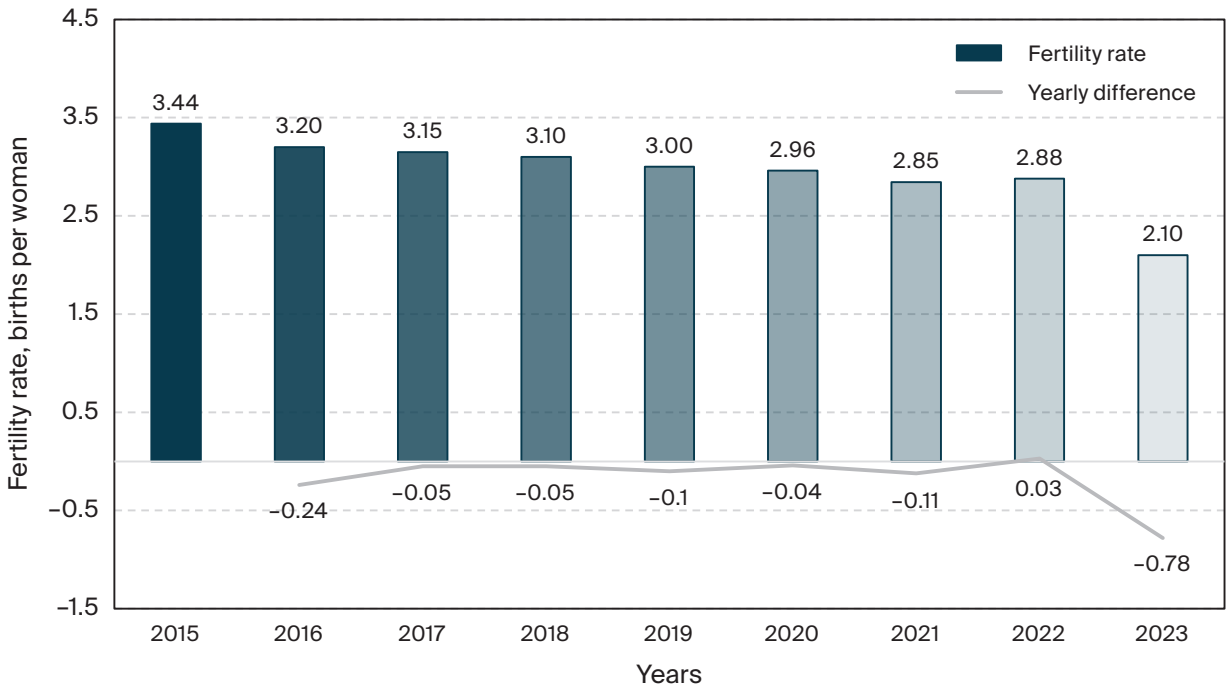
Achieved targets

The exerted national efforts during the past decade have led to significant changes in several indicators, which are paving the way toward a better containment of population growth in line with the improvement of people's social and health characteristics. The total fertility rate in 2021 was 2.85 births per woman, and it declined to 2.1 births per woman in 2023 (Fig. 2). Meanwhile, the usage of family planning methods increased from 66.4 percent in 2021 to 75 percent in 2023, the illiteracy rate among people aged 10 and above decreased from 25.8 percent in 2021 to 12.6 percent in 2023, educational enrollment rose from 94 percent in 2021 to 98 percent in 2023, the youth unemployment rate dropped from 16.5 percent in 2021 to 12 percent in 2023, the percentage of children in the labor market declined from 4.9 percent in 2021 to 2 percent in 2023, the percentage of child marriages decreased from 15.8 percent in 2021 to 8 percent in 2023[30].

Conclusion and way forward

Despite the challenges posed by population growth and its impact on health, which hinder progress in improving access to high-quality health services, impede the expansion of the UHC program,

FIG. 2. Egypt fertility rate and yearly change



[29] Home – Bedaya. (In Arabic). Accessed 23.06.2025. https://bedayaforegypt.org/
WHO Director commends President Abdel Fattah el-Sisi for leading Egypt's national development through "Bedaya". Accessed 23.06.2025. https://www.zawya.com/en/press-release/companies-news/who-director-commends-president-abdel-fattah-el-sisi-for-leading-egypts-national-development-through-bedaya-lxlk4oot

[30] Egypt launches national strategy to curb overpopulation-SIS. Accessed 23.06.2025. https://sis.gov.eg/Story/185585/Egypt-launches-national-strategy-to-curb-overpopulation?lang=

and significantly affect morbidity and mortality rates in Egypt, national efforts succeeded in mitigating these effects and made significant advancements in many health indicators. The national health strategy 2024–2030 has set several ambitious targets, including increasing life expectancy to 75 years by 2030 and reducing maternal mortality, neonatal mortality, and mortality rates below five years old. Achieving those targets will complement the national goal to reduce the fertility rate to 1.6 births per woman by 2030, aligned with increasing the human development index to be among the top 30 countries by 2030. Achieving these targets requires extensive parallel work on the subnational levels to strengthen the role of governorates in implementing population strategies and human development plans, mobilize religious and community leaders to support behavioral change and positive social transformation related to population and development, increase access to all health services, especially reproductive health services for girls and adolescents, particularly in underserved areas.

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BRIEF REPORT

Gastrointestinal symptoms and RT-PCR in adults with COVID-19: a post-hoc analysis

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ABSTRACT

Background: Reverse transcription polymerase chain reaction (RT-PCR) using lower gastrointestinal (GI) specimens can detect SARS-CoV-2 RNA in patients with gastrointestinal symptoms. However, the association between cycle threshold (Ct) values from such specimens and the presence of GI manifestations remains unclear.

Materials and methods: An analytical cross-sectional study was conducted using secondary, de-identified hospital records from three Indonesian medical centers (July–November 2020). Adult patients with positive lower GI RT-PCR results and available Ct values were included. Ct values were dichotomized as low (<25) or high (≥25). GI symptoms assessed included nausea, vomiting, abdominal pain, diarrhea, and constipation. The primary outcome was the association between Ct category and the presence of any GI symptom, analyzed using Fisher's exact test. Results are presented as prevalence ratios (PRs) with 95% confidence intervals (CIs).

Results: A total of 37 patients met the inclusion criteria (43.2% male; mean age 44.8 ± 13.2 years). Only one patient (2.7%) exhibited a low Ct value, while 36 (97.3%) had high Ct values. Overall, 22 patients (59.5%) reported at least one GI symptom. The most frequently reported symptom was nausea (54.1%), followed by vomiting (18.9%), abdominal pain (16.2%), and diarrhea (13.5%); constipation was not observed. No significant association was found between Ct category and the presence of GI symptoms (p = 0.595; PR 1.048, 95% CI 0.956–1.148).

Conclusion: Among adults with SARS-CoV-2 detected via RT-PCR from lower GI specimens, Ct value category was not significantly associated with GI symptom presence. These findings underscore the limited prognostic value of Ct values from lower GI sampling and emphasize the need for larger, prospectively designed studies with standardized protocols.

Key Words: SARS-CoV-2; RT-PCR; anal swab; cycle threshold; gastrointestinal symptoms

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Introduction

Coronavirus disease (COVID-19) is caused by SARS-CoV-2 and has spread globally since December 2019 [1]. To date, over 6.8 million COVID-19 cases have been reported in Indonesia, with an estimated 162,063 associated deaths[1]. COVID-19 manifests with respiratory symptoms (e.g., dyspnea) and gastrointestinal (GI) symptoms such as nausea, abdominal pain, and diarrhea [2, 3]. The diagnostic gold standard is reverse transcription polymerase chain reaction (RT-PCR) from respiratory specimens – typically nasopharyngeal swabs – but alternative specimens can be informative [2, 3]. Wang et al. reported SARS-CoV-2 positivity in fecal specimens of up to 53.4%, and a higher specificity for gastrointestinal symptoms when using lower GI specimens (anal swabs) at approximately 67.5%, compared to nasopharyngeal swabs [4]. Additional studies show high positivity and viral loads in lower

[1] Worldometer. COVID Live – Coronavirus Statistics. Accessed 01.08.2025. https://www.worldometers.info/coronavirus/

GI specimens, detection among asymptomatic cases, and potential reduction in false negatives; anal swabbing may also limit exposure risk for examiners and help pediatric sampling [5, 6]. One analytic parameter, the cycle threshold (Ct), inversely reflects viral load and is often used to contextualize RT-PCR results [5, 7].

Materials and methods

A secondary analysis was conducted using de-identified records from three Indonesian hospitals (RSCM, Mitra Keluarga Depok, and Mitra Keluarga Kelapa Gading) collected between July and November 2020, originally included in Abdullah et al. [3]. Among 136 screened cases, 45 had positive RT-PCR results from lower GI specimens (anal swabs). After excluding 8 records with missing Ct values, 37 participants with complete data were included in the final analysis. This dataset represents all eligible positive cases with Ct information from the three participating centers in the Jakarta region.

GI symptoms captured included diarrhea, constipation, nausea, vomiting, and abdominal pain. Ct values were dichotomized: low <25 vs high ≥25. Categorical variables are presented as the number of patients (n) and the corresponding percentage (%). Age is presented both as a mean with standard deviation and as categorical age groups. Association between Ct category and GI symptom presence was assessed with Fisher's exact test; effect size is presented as prevalence ratio (PR) with 95% confidence interval (CI). Analyses used SPSS v26. (IBM, the USA).

Table 1. Demographic characteristics of participants

Characteristic	Patients, *n*	Patients, %
Sex		
Male	16	43.2
Female	21	56.8
Age (years), mean ± standard deviation	44.8 ± 13.2	
< 40	14	37.8
40–60	19	51.4
> 60	4	10.8
Comorbidities		
None	25	67.6
< 2	9	24.3
≥ 2	3	8.1
Physical activity		
Low	18	48.6
Rarely (<3/week, <30 min/session)	19	51.4
Smoking status		
Never	28	75.7
Current	6	16.2
Former	3	8.1
Body mass index (kg/m^2)		
18.5–24.9	25	67.6
≥ 25	12	32.4

Results

Participant characteristics (Table 1) showed a near-even sex distribution (43.2% male; 56.8% female) with the majority aged 40–60 years (51.4%), followed by <40 years (37.8%) and >60 years (10.8%). Most patients had no recorded comorbidity (67.6%), while 24.3% had fewer than two and 8.1% had two or more. Obesity (body mass index ≥25[2]) was present in 32.4%. Lifestyle factors included current smoking in 16.2% and former smoking in 8.1%; almost half reported low physical activity and 51.4% reported rarely exercising.

Ct values were predominantly high: 36/37 (97.3%) fell in the high (≥25) category and only 1/37 (2.7%) in the low (<25) category.

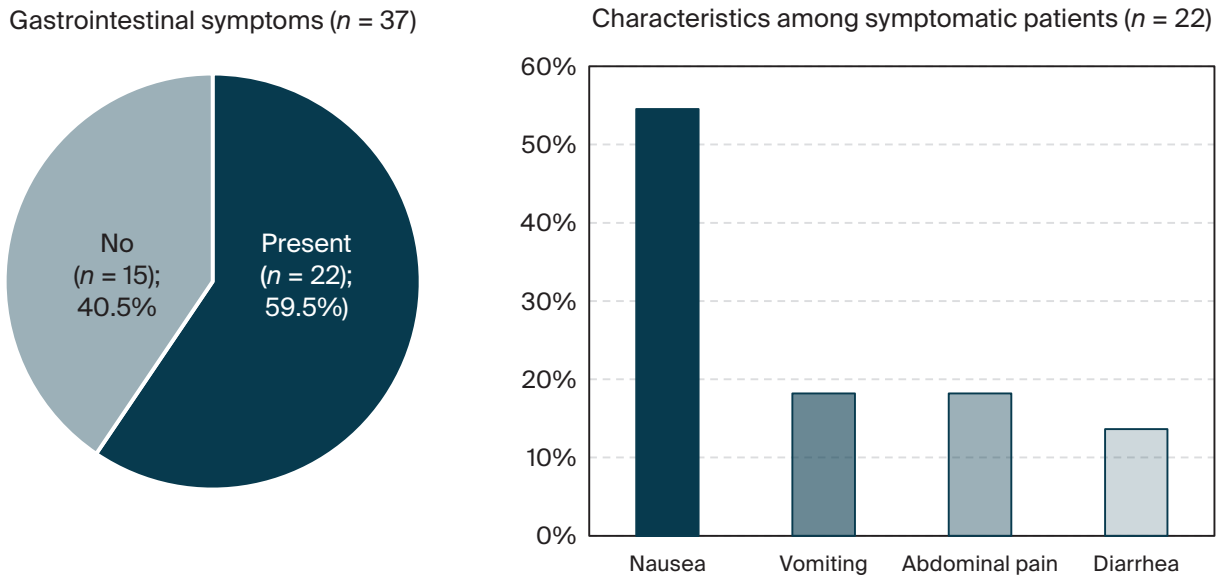
GI symptom prevalence was 59.5% (22/37), with 40.5% (15/37) reporting none (Fig). Among symptomatic patients, nausea was most common (12/22), followed by vomiting (4/22), abdominal pain (4/22), and diarrhea (3/22); constipation was not recorded.

In the primary analysis, the association between Ct category and the presence of any gastrointestinal symptom was evaluated. Due to sparse expected counts, Fisher's exact test was applied and revealed no statistically significant association (p = 0.595). The prevalence ratio (PR) comparing high versus low Ct values was 1.048 (95% CI: 0.956–1.148), consistent with a null effect estimate (Table 2).

Discussion

Testing of lower GI specimens serves as a practical complement to nasopharyngeal sampling and has demonstrated higher detection rates in patients with gastrointestinal manifestations, consistent with previous findings from both Indonesian and international studies [3–5, 8, 9]. Our

FIG. Prevalence and characteristics of gastrointestinal symptoms



[2] The Asia-Pacific perspective: Redefining obesity and its treatment World Health Organization. Western Pacific Region IASO international association for the study of obesity Accessed 01.08.2025. https://iris.who.int/bitstream/handle/10665/206936/0957708211_eng.pdf?utm_source=chatgpt.com

Table 2. Association between cycle threshold category and gastrointestinal symptoms

Gastrointestinal symptoms	Low cycle threshold (*n* = 1)	High cycle threshold (*n* = 36)	*p*-value (Fisher's exact)	Prevalence ratio (95% confidence interval)
Present	0 (0%)	15 (41.7%)	0.595	1.048 (0.956–1.148)
No	1 (100%)	21 (58.3%)		

descriptive data similarly show that GI symptoms were common among adults with positive lower GI specimens RT-PCR.

Despite biologic plausibility that lower Ct (higher viral load) might align with symptomatology, we did not find an association between Ct category and GI symptoms. Ct values are influenced by numerous pre-analytical and analytical factors – including sampling technique, timing relative to illness, transport/storage, and assay efficiency – so crude categorization may obscure clinically meaningful relationships [5, 7]. The very low number of low-Ct observations (*n* = 1) further limits power to detect differences.

Observed heterogeneity in comorbidities and lifestyle risks such as obesity and smoking could also confound relationships between Ct and symptoms, as these factors are associated with COVID-19 outcomes and severity [10]. Future studies should incorporate multivariable adjustments and standardized collection protocols to reduce noise from these sources.

Comparative evidence suggests average Ct values around the high-20s among patients with GI involvement and variable links to severity, yet these patterns originate largely from nasopharyngeal or fecal sampling rather than lower GI specimens [7, 9, 11]. Standardized, prospective designs that analyze Ct as a continuous measure and align sampling with symptom timing are likely needed to clarify any true association.

Conclusion

In this secondary analysis of 37 adults with positive RT-PCR results from lower GI specimens at three Indonesian hospitals, GI symptoms were common; however, the Ct category (low <25 vs high ≥25) showed no statistically significant association with the presence of GI symptoms (Fisher's exact $p = 0.595$; PR 1.048, 95% CI 0.956–1.148). Given substantial pre-analytical variability and potential confounding by comorbidities and lifestyle factors, Ct values from lower GI specimens should be interpreted cautiously for symptom prognostication. Larger, prospective studies with standardized protocols are warranted.

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