Women always function as the gatekeepers to the formal/informal health sector. Despite global and regional progress in advancing women's health, the COVID-19 pandemic forced governments and development partners in the EMR and beyond to re-set their priorities. A renewed commitment to women's health is inescapable to expedite progress towards the SDGs in an integrated manner.
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Women's health in the Eastern Mediterranean Region: time for a paradigm shift

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Investing in the health of women and girls has been shown to produce good returns not only for women and girls, but also for the society as a whole (1-9). It yields high returns on investment through improved productivity, reduced absenteeism, and reduced health care costs (10-13).

Over the past decades the terms women's health and reproductive health were used interchangeably to refer to conditions related to pre-conception, pregnancy, childbirth, and postnatal care only. However, with the improvement in life expectancy, reduction in maternal mortality ratios and the constant reduction in fertility rates, women now enjoy more years and are exposed to risk factors and diseases that are not always related to the reproductive function. Women in the post-menopausal period undergo physiological and psychological changes that may cause discomfort or change their response to several risk factors, and some diseases may present differently in women than in men. With this in mind, and in an attempt to better understand and respond to women's comprehensive health needs, the WHO Office for the Eastern Mediterranean Region (WHO/EMRO) launched a programme on women's health to generate and analyze evidence related to women's overall health beyond the reproductive component and propose relevant solutions. We need to act now to ensure that health services for women are available, acceptable, and accessible, to ensure that women's health needs are well-covered in the hope of achieving Universal Health Coverage by 2030.

A proposed definition of women's health therefore should include all health conditions that affect women, especially if they are among the leading causes of death and disability for women or if they affect women and men differently. Attending to and prioritizing women's health is a strategic contributor to a healthier society because healthier women are essential gatekeepers to healthier families and healthier communities and contribute to socioeconomic development (11).

The Eastern Mediterranean Region (EMR) is home to a mix of high-, middle- and low-income countries, with resident populations ranging from around 1 million to more than 200 million. Women in the EMR, including those in fragile and emergency contexts, are not a homogeneous group, therefore, their health needs and socioeconomic circumstances vary significantly (16). The average life expectancy for women in the EMR varies widely as well (from 55 to 81 years), as do maternal mortality ratios (from 3 to 829 per 100 000 live births). Anaemia among women of reproductive age presents another stark diversity in the region, ranging from 24% to around 70% (17).

The EMR is currently experiencing a situation known as the “demographic dividend”. As the younger population cohort enters the workforce, they will age eventually and, therefore, require special attention to, and preventive investment in, their future health needs (18). Such ageing presents a phenomenal challenge for women because they comprise the greater proportion of the elderly population in the world (411 million compared to 336 million male population above 65 years of age in 2021) (19).

Women are major providers of health care; sufficiently skilled and empowered women are key to the success of the formal and informal healthcare delivery systems. The EMR is home to high-scale natural and human-made crises that jeopardize health care delivery. Adopting a women’s health lens would help minimize missed opportunities where competent workforce may play a role in addressing non-reproductive health issues such as breast cancer, which is estimated to constitute 37% of all female cancers in the region. Just as adopting an integrated model of care has the potential to reduce missed opportunities especially in emergency and low-resource settings.

UNHCR estimates that there are 16 million people in need in the EMR, of which 72% are women and children (20). It is therefore important to strike a balance between women’s health and an enabling environment, in terms of empowering laws, policies, and systems (21). Understanding and acknowledging the different roles that women play, as paid and/or unpaid caregivers, especially in emergency and fragile settings, is crucial to improving women's health in a comprehensive manner.

Women and health interact in multi-faceted pathways that contribute to healthier societies. For example, nurses and midwives in the EMR, who are mostly women, require dedicated attention by policy- and decision-
matters. Investing in nursing and midwifery workforces, which constitute up to 60% of the health workforce in some parts of the region, is vital to women’s health. They play the roles of service providers, patrons, and beneficiaries at the same time. Efficient and effective training, as well as efficient and effective recruitment and retention strategies are prerequisites to facilitating an enabling environment for healthier women and societies (Figure 1).

It is imperative for governments in the EMR to embrace a women-inclusive, whole-of-society and whole-of-government approach that involves, and builds on, the strengths of all relevant stakeholders. Investing in women’s health is a highly profitable investment for the health, wealth (economy), and wellbeing of the whole society. It is time for the United Nations with its entities such as the WHO, UNFPA, UN Women, UNICEF, UNDP, and others to partner with Member States in comprehensively addressing women’s health using the thrust created by the Sustainable Development Goals (SDGs). Healthier women contribute, not only to SDG 3 and SDG 5, but to most of the SDGs.

The momentum around the SDGs offers a unique opportunity that WHO/EMRO should capitalize on to develop an analytical framework for women’s health that will inform the development of a regional roadmap for healthier women by 2030 (22).

Figure 1: The role of women in healthcare provision

![Figure 1: The role of women in healthcare provision](image)

### References


Engagement of private healthcare sector in reproductive, maternal, newborn, child and adolescent health in selected Eastern Mediterranean countries

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Abstract

Background: The private healthcare sector in the Eastern Mediterranean Region (EMR) is active and growing, providing curative, preventive, and promotive services related to reproductive, maternal, newborn, child, and adolescent health (RMNCAH).

Aims: To understand the contribution of formal for-profit private health-care sector in delivering RMNCAH services and explore best practices for improvement.

Methods: Desk review of available literature from Saudi Arabia, Oman, Iraq, Egypt, Sudan, Yemen, Pakistan, and Islamic Republic of Iran, followed by stakeholder interviews in Iraq, Pakistan, and Oman were carried out. Directed content analysis using Maxqda 2020 was performed, and information was triangulated according to a priori themes: governance, health information systems, financing, and service delivery related to RMNCAH.

Results: Formal and informal public-private partnerships exist in RMNCAH but lack a strategic roadmap to guide collaboration. The private healthcare sector is minimally represented in the main policy stream at national and subnational levels due to resistance from the private and public sectors. They are weak in collecting, maintaining, and sharing health information. Data on abortion and postabortion complications are scarce. Various models of supply and demand financing (voucher schemes, private and social health insurance) related to antenatal care and contraception have been implemented in the EMR. Despite the higher cost of care in the private sector, limited training of providers, ill-defined service delivery packages, and lack of continuity-of-care and team-based approaches, the private sector remains the predominant sector providing RMNCAH services in the EMR.

Conclusion: Partnering with the private sector has huge untapped potential that should be harnessed by national governments for expanding RMNCAH services and progressing towards Universal Health Coverage.

Keywords: private healthcare, reproductive health, maternal health, newborn health, child and adolescent health

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Introduction

The World Health Organization (WHO) for the Eastern Mediterranean Region (EMR) comprises a diverse group of 22 countries, and presents a varied picture of reproductive, maternal, neonatal, child and adolescent health (RMNCAH). The EMR has an average maternal mortality ratio (MMR) of 164 per 100 000 and under-5 mortality rate (U5MR) of 46 per 1000 live births (second to the region of Africa) (1). The MMR improved by 50% from 1990 to 2013, and U5MR by 46% (2). Despite the downward trend, the EMR missed the United Nation’s Millennium Development Goals (2000–2015) to decrease MMR by three quarters and U5MR by two thirds (4,5). It is estimated that 26 000 maternal and 845 000 under-5 child deaths occur each year in the region (2).

The EMR countries have been implementing the Sustainable Development Goals (SDGs) and aim to reduce U5MR to < 25 per 1000 and MMR to 70 per 100 000 live births by 2030 (5). There is wide disparity in progress across the region: as of 2019, 13 countries had met the MMR target and 15 the U5MR target (6). Meeting the RMNCAH-related targets across the rest of the region remains a public health challenge. Several initiatives have been adopted to improve RMNCAH services including: The global strategy for women’s and children’s health (7); Global action plan for prevention and control of pneumonia and diarrhea (8); Every newborn action plan (9); Survive and thrive: transforming care for every small and sick newborn (10); and the Regional initiative on saving the lives of mothers and children (11).

The public sector has a mandate to provide health services and improve RMNCAH. However, with the
whole of society and whole of government approach, the vital role of the private sector is increasingly highlighted and its engagement advocated for (12). The private sector includes private healthcare providers, pharmaceutical and health technology industries, media and advertisements, information technology, private insurance, associations of private sector industries, services provided by religious institutions, trade unions and philanthropic organizations. In the context of service provision, the private healthcare sector is defined as “the individuals and organizations that are neither owned nor directly controlled by governments and are involved in provision of health services. They can be classified as for profit and not-for-profit, formal and informal, domestic and international.” (3).

The private healthcare sector is an active provider in the EMR, providing ambulatory, hospital, and medical educational services in many countries (13). It is estimated that the private healthcare sector delivers 11–81% of services to the poorest quintile and 33–86% of outpatient services, and owns more than 60% of pharmacies in the region. The WHO Regional Committee for the Eastern Mediterranean Region endorsed the Framework for Action on Effective Engagement with the Private Sector in 2018, to expand service coverage for Achieving Universal Health Coverage (UHC) (15). The private healthcare sector is now increasingly recognized as a major stakeholder in healthcare provision and is considered an untapped resource in the context of RMNCAH services and UHC. It is acknowledged that contracting with private healthcare sector providers for the delivery of essential health service packages can help countries achieve UHC (16). Engagement of the private healthcare sector to deliver agreed quality essential healthcare services for RMNCAH, using strategic purchasing and financial protection arrangements is no longer an option but a necessity (17).

There is dearth of data regarding the role, contribution and engagement of the private healthcare sector in RMNCAH services in the EMR. We designed this study to: (1) elaborate the contribution of the private healthcare sector in governance, health information systems, financing, and service delivery related to RMNCAH services at primary, secondary and tertiary care levels; (2) explore the best practices of engagement with the private healthcare sector and identify potential areas for improvement; and (3) formulate recommendations to improve and leverage private healthcare sector engagement in RMNCAH services at policy, programme and service delivery levels in the EMR.

**Methods**

The private healthcare sector includes for-profit and not-for-profit, formal and informal, domestic and international individuals and organizations that are neither owned nor directly controlled by governments and are involved in provision of health services (13). We only explored the private formal, for-profit healthcare providers in this study. An analytical framework was developed to guide the study, based on field experts’ opinions, literature review and WHO health systems framework (Table 1). The study was based on a desk review followed by stakeholder interviews and data synthesis (Figure 1).

The desk review was based on 1) systematic search using PubMed and Google Scholar; 2) solicitation of documents from WHO Regional Office for the Eastern Mediterranean; and 3) manual search for relevant reports. The countries selected for the desk review included Saudi Arabia, Oman, Iraq, Egypt, Sudan, Yemen, Pakistan and Islamic Republic of Iran. The search was carried out in August 2020 and no time filters were applied. The review helped identify gaps in evidence that were bridged through the stakeholder interviews. Based on the recommendations of the regional office, Pakistan, Iraq and Oman were selected for interviews. The WHO focal person for RMNCAH in each country served as the starting point for the interviews. Subsequently, a snowball technique was used to reach other relevant stakeholders from the public and private healthcare sectors and academia. The interviews were semistructured and based on the analytical framework and a priori themes and gaps identified by the literature review. Each key informant interview was web-based, conducted in English language and lasted for about 45–70 minutes. Verbal consent was obtained before the start of the interview, which was audio/video recorded and subsequently transcribed. An effort was made to include interviewees from the public, private and academic sectors of each country. The interviewees were key informants representing the RMNCAH section of the public sector or Ministry of Health, WHO country office, or noteworthy representatives of private healthcare organizations and academia, working directly or indirectly with the government. Gaining access to key informants was cumbersome and the maximum number of interviews from each country was conducted. Directed content analysis using Maxqda 2020 was performed, and information was triangulated with the findings of the desk review. SWOT analysis (strengths, weaknesses, opportunities, threats) based on study findings was performed to yield meaningful insights.

The Ethical Review Committee, Aga Khan University (ERC No. 2020-5383-14096) and National Bioethics Committee, Pakistan provided ethical clearance for conduct of the study.

**Results**

A total of 36 documents were eligible for inclusion in the desk review (14 peer reviewed articles, 4 dissertations, 18 reports; Figure 2) (16,18–52). Thirty-three documents addressed the EMR: 13 from Pakistan, 8 from Egypt, 6 from Iraq, 2 each from Jordan and Saudi Arabia, and 1 each from the Islamic Republic of Iran and Yemen. Sixteen stakeholder interviews were conducted from Iraq (n = 3),...
Table 1 Analytical framework for RMNCAH in the EMR

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<td>1. Availability of frameworks, national strategic plans, and technical policy documents to govern the private healthcare sector 2. Existence of platforms for effective public–private collaboration 3. Number of PPPs facilitated, strengthened, or established in RMNCAH 4. Assessing the technical supervisory role of PHS to maintain quality of RMNCAH services</td>
<td>Key Indicators: 1. Proportion of family planning demand met with modern contraception 2. Proportion of women who have received the recommended number of doses of HPV vaccine before age 15 years 3. Antenatal coverage rate (≥ 4 times during pregnancy) 4. Number of stillbirths per 1000 births 5. 3 doses of combined DTP immunization coverage (12–23 months) 6. Antibiotic treatment for suspected pneumonia</td>
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Key indicators: 1. Proportion/number of women of reproductive age who were screened for cervical cancer 2. Proportion/number of antenatal clients with haemoglobin level measured 3. Proportion/number of ANC attendees or number of facility-based deliveries 4. Proportion/number of women received postnatal care 5. Proportion/number of children with pneumonia who received amoxicillin 6. Proportion/number of antenatal clients with 4th ANC visit 7. Proportion/number of women of reproductive age who were screened for cervical cancer

RMNCAH = Reproductive, maternal, neonatal, child and adolescent health; EMR = Eastern Mediterranean Region; HPV = Human papillomavirus; THERH = Total health expenditure on reproductive health; PPP = Public–private partnership; HIS = Health information system; ANC = Antenatal care.
Pakistan (n = 7) and Oman (n = 6) (Table 2). The results of the desk review and interviews were organized according to the a priori themes of the analytical framework.

**RMNCAH governance**

The study results indicated a minimal role of the private healthcare sector in national and subnational policy-making related to RMNCAH in the EMR. Involvement of the private healthcare sector in decision-making was not well received by public sector professionals in Pakistan and Iraq. The private sector also lacked interest due to negligible incentives and high opportunity costs. On the contrary, in Oman, the private healthcare sector was represented in policy-making at the national and subnational levels. The private partners participated in the formation of strategies/policies on maternal health and infectious diseases, with the final authority resting with the government.

Public–private partnerships (PPPs) are prevalent in the EMR in the field of RMNCAH. A WHO background paper on private sector engagement for advancing UHC mentioned the dominant role of PPPs in the quality, costs and use of services (antenatal, postnatal and newborn care, and birth facilities) in Pakistan and the Islamic Republic of Iran (16,52). The national policies of Oman and Pakistan recognize the importance of PPPs for improving healthcare and achieving global targets related to RMNCAH. The not-for-profit private sector has been more active in partnerships with the government, than the for-profit sector. Apart from formal partnerships, many informal collaborations exist between the public and private sectors. However, a major gap is the lack of planning and a clear direction for rolling out PPPs. One of the academic participants in Pakistan stated: “PPPs are implemented on an ad hoc basis...and to place a burden on the private sector. They collaborate just to avoid their responsibilities. The government needs to wake up.”

The available literature reiterates regulation of the private healthcare sector as a universal challenge. There are almost 50 000 private clinics in Egypt and 75 000 private general practitioners in Pakistan that cannot be classified under any proper regulatory system (16). The Ministry of Health has a mandate and responsibility for regulation, and regulatory policies exist on paper (Iraq and Pakistan); however, there was no evidence of regulation (16,35). High-income countries such as Oman had a healthier situation: licensing of private providers and establishments was strict and inspection teams were operational to monitor quality.

**Health information systems with data on RMNCAH indicators**

The available literature indicates that the private healthcare sector is lagging in collecting, maintaining and sharing health-related data with the government across the EMR. Data regarding abortion and postabortion complications are limited in low- and middle-income countries (38,44). The interviewees from Iraq stated that secondary and tertiary care hospitals shared monthly data related to spontaneous vaginal deliveries and caesarean sections with the Ministry of Health; however, data flow from private clinics remained limited. One of the public sector respondents in Iraq stated: “The private sector information only comes indirectly via the population-based surveys.” Similarly, the private healthcare sector of Pakistan is obliged to notify about child and maternal death, but other indicators of RMNCAH are not routinely shared with the government.

Oman presented an encouraging scenario of continuous recording of number of pregnancies, maternal and child births, and deaths. The public sector offered a central health information system that kept track of patients; however, data in the public and private sectors were not comprehensive and many vital indicators of RMNCAH were missing. A public sector...
interviewee from Oman stated: “We feel our patients get lost in the private sector.” Our findings suggest that a centralized health information system was being developed in Oman through which “the public and private sectors would be able to tap into each other’s systems” (private sector interviewee).

**Financing modalities for RMNCAH**

There was a large variation in out-of-pocket payments as proportion of total health expenditure across the EMR, ranging from 10% in Oman to 70% in Yemen (53). Catastrophic payments were common for the private healthcare sector, including caesarean sections and postnatal complications (52). As a response to high out-of-pocket payments in Egypt (62%), the government rolled out a new insurance scheme to achieve UHC, based on a family physician model that separates financing from service provision; however, the impact of the model remains inconclusive (22). Private and social health insurance in Iraq was minimal. A health insurance law was drafted in 2014, but is yet to be endorsed. Public healthcare services (including RMNCAH) were free for Omani citizens and the insured population. The private sector was generally used by expatriates or people without insurance. However, there were no standard insurance packages for antenatal care.

Various models of supply- and demand-side financing have been tested in the EMR, with varied results. Financing vouchers complemented by social franchising in the form of demand-side financing have been rolled out in Pakistan for over a decade to improve family planning practices (29). Supply-side financing has been improved through social health insurance and private health insurance, which are generally available for residents of urban areas (31). Task sharing by building PPPs via the community midwives model, and community health workers connecting clients with local facilities, have been instrumental in improving family planning practices in Pakistan (31). Organizations such as Green Star, Marie Stopes, and Suruj Network have worked with mid-level private sector providers to increase the uptake of long-acting contraceptives (29). Their effectiveness is well documented in increasing family planning; however, the geographical coverage is too small to create an impact at the national or subnational levels.
In Oman, some vouchers for antenatal and postnatal care were commonly distributed during campaigns to commemorate Mother’s Day, Breast Feeding Week, Birth Spacing Week etc. Community financing was common in Najaf and Karbala (holy shrines), as stated by one of the public sector interviewees in Iraq: "Free mobile clinics are provided during holy events by the community. These services are however, not constant throughout the year”.

RMNCAH service delivery

Types and use of private healthcare sector services

The private healthcare sector remained the sector of choice for RMNCAH-related services in most of the developing countries in the EMR (31,37,38,40,45,46,49). Anecdotal evidence suggested that around 50% and 80% of RMNCAH-related healthcare services in Iraq and Pakistan were provided by the private healthcare sector (38). The role of the private healthcare sector was particularly prominent in providing postabortion care in Pakistan, given that it treated about 50% more postabortion cases (62% vs 38%) than public health facilities treated (44). The caesarean section rates tended to be higher in the private healthcare sector. In 2002, the caesarean section rate for public hospitals in Baghdad (Iraq) was 30% of all births (compared to an acceptable standard of 5–10% in most countries) and the recorded rate was much higher, at 48% in private hospitals (25). Availability of drugs such as misoprostol was better in the private healthcare sector in Pakistan (89% vs 54% in the public sector) (44). The stakeholder interviews elaborated that the service delivery packages of RMNCAH care were not well defined in the private healthcare sector. In high-income countries such as Saudi Arabia and Oman, the public sector remained the predominant provider of care (23% child health services in Saudi Arabia are provided by the private healthcare sector) (40).

Quality of services

In low- and middle-income countries of the EMR, the private healthcare sector was perceived by the public to offer higher quality of services than the public sector (45,49). However, this perception was not supported by scientific evidence. People preferred the private healthcare sector for reasons such as hospitality, short waiting time, and better laboratory and diagnostic facilities, nursing care and infrastructure. Although the communities preferred the private sector, one of the key informants from Pakistan stated: “The public and private sectors are equally incompetent.” Other concerns were raised regarding the private healthcare sector of Pakistan. Some respondents said it was a “money-making machine”, with poor quality of services. The providers were accused of using “quick relief formulas” for treating the patients. They said providers in private clinics often use steroids, antibiotics and intravenous analgesics that provided instant relief to patients. One of the academic respondents in Pakistan stated: “Everyone in the private sector gives clomid (clomiphene) for management of infertility….which can increase the risk of polycystic ovarian disease”.

In Oman, the public sector was said to be better than providers in private clinics in the provision of RMNCAH services, because of its team-based approach, skill mix and continuity of care. Public healthcare providers had better training opportunities in Oman while continuous capacity building for private providers was limited. In contrast, data from 6 private clinics in Sudan suggested that private healthcare providers had limited to no training in the diagnosis and management of sexually transmitted diseases (54). Dual practice was commonly reported in the developing countries, leaving providers with little time and interest to provide quality care for patients in the public healthcare sector.

SWOT analysis

ASWOT analysis for the engagement of private healthcare sector in RMNCAH in the EMR was conducted, based on the results of desk review and interviews. Major strengths of private healthcare sector included its vast spread, diversity of services, trust of the masses, high-quality laboratory and diagnostic support and specialized care (e.g. in vitro fertilization and neonatal care) in some countries. The sector suffered from the weaknesses of being focused on curative care for enhanced monetary benefits, uneven geographical distribution, urban bias, and poor record keeping and continuity of care. However, the sector offered opportunities such as indirect referral linkages between public and private sectors, higher technical capacity in some countries, and a drive at national and subnational levels to incorporate private healthcare sector into the mainstream. At the same time, stakeholders needed to be mindful of the accompanying threats: there was no clear roadmap for incorporating the private healthcare sector and old legislation remained incompatible with PPPs; corruption in the public sector affected regulation and accountability of the private healthcare sector; and dual practice by healthcare providers raised conflict of interest.

Discussion

Private healthcare sector is a vital stakeholder in the provision of RMNCAH care in the EMR. It has grown greatly over the past few decades and is now widespread. A general trend of a predominant private sector was reported in developing countries where the public sector was lagging, whereas its role was less prominent in high-income countries that had strong health systems, such as Oman. The international and national platforms acknowledge the need to incorporate the private healthcare sector into related activities of the public sector. Its representation, though minimal, is seen in the formation of clinical guidelines, standards and policies pertaining to RMNCAH in some countries. PPPs have been popular in the EMR, being tested for family planning, antenatal care, immunization and child nutrition, etc. However, there is lack of vision and
framework to guide the PPPs. Regulation of the private healthcare sector remains a challenge in developing countries, where corruption and lack of accountability and transparency in the public sector hamper regulation.

Private healthcare sector remains an unexplored domain due to lack of information flow to the public sector. Private tertiary care hospitals collect, maintain and share records with the public sector regarding number of deliveries and caesarean sections. The lower tiers seldom share patient records. Private healthcare sector is the preferred option due to shorter waiting time, better perceived quality, laboratory and diagnostic support, hospitality of staff and clean environment; although the technical capacity is questionable. In countries such as Pakistan and Islamic Republic of Iran, there is over-reliance on the private sector, which culminates in a potentially negative impact such as high out-of-pocket payments, caesarean section rate, and overuse and misuse of drugs. Thus, streamlining the private healthcare sector in a public-led system is critical to ensure its proper use in advancing UHC. A similar scenario of widespread private healthcare sector and limited engagement with the government has been reported across the WHO African Region (55). It is believed that the private healthcare sector can be a valuable contributor to improving population health and moving towards UHC in the WHO Region of the Americas (56). The alignment of the private healthcare sector with the public sector is similar worldwide, with limited engagement but a huge untapped potential that needs to be efficiently used by the government.

Based on our study findings, we present the following suggestions for strengthening engagement of the private healthcare sector with the public sector. We believe that a clearly stated policy needs to be formulated to engage the private healthcare sector in all health domains including RMNCAH, at the regional and national levels. The countries need to develop a guiding framework to engage the private healthcare sector in RMNCAH for all service delivery tiers of healthcare. Planning for PPPs needs improvement by building the technical capacity of the government. A separate department of private healthcare establishments (with allocated budget) should be established in the public sector for PPPs, contracting out services, ensuring accountability, licensing, regulation and accreditation of the private healthcare sector. If a separate department is not feasible, the function inside the ministry of health should be strengthened. The allocated health budget to the ministry of health should be increased, with separate allocation for PPPs. The range of services should be clearly stated with designation of responsibilities of both parties such that the collaboration is mutually beneficial. We suggest that the PPPs should typically address abortion and postabortion services, family planning, neonatal care and community awareness raising.

The private healthcare sector professionals need to be represented at the policy level for formulation of clinical standards, guidelines and strategies related to RMNCAH. The licensing of practitioners should be renewed every 5 years with strict requirements for continuous medical education to maintain standards of care. A separate directorate/commission should be established to ensure registration of all private facilities and licensing of providers. Similarly, the private facilities should be accredited and only those clearly eligible should be engaged by the public sector. Capacity building related to antenatal and postnatal care, family planning, weaning practices, integrated management of newborn and childhood illnesses guidelines, and syndromic management of sexually transmitted diseases should be offered to private healthcare providers at a minimal cost, and participation encouraged through certification and recognition. Health information systems should transit to electronic databases with standardized comprehensive data forms capturing number of antenatal visits, immunizations, postnatal and neonatal care, uptake of contraception and child mortality. The private sector should be incentivized to share data with government and such information should be incorporated in the formulation of RMNCAH-related strategic and operational plans. A legal claims department should be established in the ministries of health to address the concerns of patients, indirectly ensuring accountability of private providers. Demand-side financing in the form of voucher schemes could be implemented to improve contraceptive uptake. Regulatory mechanisms should be established to implement updated clinical guidelines and protocols related to RMNCAH in the private healthcare sector.

This study has highlighted engagement of the private healthcare sector in RMNCAH in some countries of the WHO EMR, with particular focus on Oman, Pakistan and Iraq. It captures insights of stakeholders from WHO, public and private sectors, and academia across all tiers of service delivery. The study has some limitations. Interviews were conducted in only three countries, and findings cannot be generalized to the Eastern Mediterranean Region. There was no representation from the low-income countries, which would have added robustness and balance to the results. The point of saturation for the interviews was not reached and we believe additional interviews could have helped strengthen the findings. However, this study provides a foundation for further research and identifies areas of action for engagement with the private healthcare sector.

Conclusion

The private healthcare sector offers a huge untapped potential for improving RMNCAH-related services across EMR. The public sector needs to incorporate and align services of the private sector to the national and subnational health agendas, to improve RMNCAH towards achieving UHC.

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Competing interests: None declared.
Participation du secteur privé de la santé aux soins de santé reproductive, maternelle, néonatāle, infantile et des adolescents dans la Région de la Méditerranée orientale

Résumé

Contexte : Le secteur privé des soins de santé dans la Région de la Méditerranée orientale est actif et en pleine évolution, fournissant des services curatifs, préventifs et promotionnels liés à la santé reproductive et à la santé de la mère, du nouveau-né, de l’enfant et de l’adolescent.

Objectifs : Comprendre la contribution du secteur privé des soins de santé formel à but lucratif dans la prestation des services de santé reproductive et de santé de la mère, du nouveau-né, de l’enfant et de l’adolescent ainsi qu’examiner les meilleures pratiques pour les améliorer.


Résultats : Des partenariats public-privé formels et informels existent dans le domaine de la santé reproductive et de la santé de la mère, du nouveau-né, de l’enfant et de l’adolescent, mais aucune feuille de route stratégique n’est disponible pour orienter la collaboration. La représentation du secteur privé des soins de santé dans le courant politique principal aux niveaux national et infranational est faible en raison de la résistance des secteurs privé et public. Ils sont faibles dans la collecte, la conservation et le partage des informations sanitaires. Les données sur les complications liées à l’avortement et au post-avortement sont rares. Divers modèles de financement de l’offre et de la demande (systèmes de bons, assurance-maladie privée et sociale) liés aux soins prénataux et à la contraception ont été mis en œuvre dans la Région de la Méditerranée orientale. Malgré le coût plus élevé des soins dans le secteur privé, la formation limitée des prestataires, les ensembles de prestations de services mal définis et le manque de continuité des soins et d’approches d’équipe, le secteur privé reste le secteur prédominant qui fournit des services de santé reproductive et de santé de la mère, du nouveau-né, de l’enfant et de l’adolescent dans la Région de la Méditerranée orientale.

Conclusion : Le partenariat avec le secteur privé présente un énorme potentiel inexploité dont les gouvernements nationaux devraient tirer parti pour étendre les services de santé reproductive et de santé de la mère, du nouveau-né, de l’enfant et de l’adolescent et progresser vers la couverture sanitaire universelle.
الرعاية والنُّهج القائمة على فريق، فما يزال القطاع الخاص هو المتصدر في تقديم خدمات الصحة الإنجابية وصحة الأمهات والحديثي الولادة والأطفال والطفلين في إقليم شرق المتوسط.

الاستنتاجات: هناك فوائد كبيرة لإقامة الشركات مع القطاع الخاص، وذلك ينبغي للمؤسسات ذات الصلة أن تستفيد منها لتوسيع في خدمات الصحة الإنجابية وصحة الأمهات والحديثي الولادة والأطفال والطفلين، وتحقيق تقديم خدمات باقل التكلفة الصحية الشاملة.

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Translation and cultural adaptation of the WHO generic tuberculosis patient cost survey to an Egyptian context

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Abstract

Background: Tuberculosis (TB) represents a major health problem having serious financial impact on a substantial proportion of patients. This has necessitated the development of a valid tool for measuring TB-related expenditure by patients and their households so that appropriate measures can be taken to reduce the financial burden.

Aims: To translate and culturally validate the generic WHO tuberculosis patient cost survey within the Egyptian context.

Methods: The instrument was translated and culturally adapted using forward-translation, back-translation, expert panel assessment, pretesting, cognitive interviewing, and appraisal by the developer.

Results: A final Arabic version with modifications to 35 descriptors of the original tool was produced after review by an expert committee and cognitive interviews with patients. Twelve questions were modified, 13 response options were changed, 6 questions were added, and 4 questions were removed. Pretesting of the tool ensured that the final version is culturally sensitive and fit for assessing the costs incurred by TB patients in an Egyptian context.

Conclusion: Policymakers are encouraged to use the WHO tuberculosis patient cost survey tool for assessing the expenditure of TB patients with a view to developing appropriate policies to reduce the financial burden of patients.

Keywords: Tuberculosis, Egypt, catastrophic health expenditure, WHO, cost survey, cultural adaptation.

Introduction

Tuberculosis (TB) represents a major public health problem worldwide (1). In 2019, there were an estimated 10 million new cases of TB and 1.4 million deaths and more than 90% of these cases and deaths occurred in developing countries (2). The incidence of TB in Egypt was 12 per 100 000 people according to the World Health Organization (WHO) global tuberculosis report in 2020 (1).

TB is estimated to have cost the world economy US$616 billion from 2000 to 2015 (3). A considerable proportion of the economic burden is shouldered by patients within the low-income quartiles. Three studies conducted in South Africa and Malawi stratified TB costs by income status and revealed that poorer patients incurred higher costs for treating TB than those who were richer (4–6). Accordingly, WHO set a target of zero TB-affected families facing catastrophic costs as 1 of 3 aims of the End TB Strategy (7). Catastrophic costs are defined as those that account for ≥ 20% of patients’ annual household income (including direct medical expenses, nonmedical expenses, and overall indirect costs, which include lost wages and time off work due to symptoms and treatment seeking) (8,9). In a meta-analysis of 29 studies, the aggregated proportion of catastrophic costs at a cutoff point of 20% for the 29 studies was 43% (10).

To reduce the risk of TB-related poverty, it is critical to have a valid tool to measure TB-related patient and household expenditure so that relevant policies can be implemented (11). A tool for measuring the direct and indirect costs for TB patients and their households was developed in 2015. This tool measures the proportion of patients who experience catastrophic payments due to TB. This generic tool was expanded into a handbook in 2017 after field testing in 9 countries and consultation with a WHO-led TB patient cost task force (12). By March 2020, 17 countries had completed the survey, with another 30 planning to do so by the end of 2020. According to the countries that have completed the survey evaluations, 27–83% of people with any kind of TB faced catastrophic expenditures. Those with drug-resistant TB had a substantially higher rate, ranging from 67% to 100% (13).

The tool has been cross-culturally adapted in many countries, including Indonesia (14), Ethiopia, Kazakhstan (15), South Africa, Mozambique, United Republic of Tanzania, and Gambia (11). Cross-cultural adaptation is...
a process in which a questionnaire is translated into a language other than that with which it was developed and adapted to the local context where it will be applied (16). Based on the measurements of catastrophic costs, several countries have applied TB-specific strategies such as cash transfer to TB patients in India and Nigeria, and medical insurance coverage, food support and cash transfer in Kenya (17). Other countries have applied TB-sensitive strategies such as conditional cash transfers based on income in Brazil and Universal Health Coverage (UHC) in Indonesia (18,19).

In Egypt, the national TB control programme offers free treatment; however, there is no social support to help patients cope with indirect and out-of-pocket payments. Few studies have been conducted to measure the financial burden on TB patients. In a recent study in Cairo Governorate, 33% of patients encountered catastrophic payment with the highest proportion during the prediagnostic stage (20). In Egypt a UHC law was approved in 2017 and will be applied gradually between 2018 and 2032. The law will extend insurance to 30% of the population who are not currently covered by any form of insurance (21). UHC is a social solidarity-based compulsory system that exempts individuals who cannot afford to pay contributions. In the new system, the family is the primary insurance coverage unit, as opposed to the current system, which provides separate coverage to each family member, leaving some uninsured (22). The law aims to reduce catastrophic payments due to medical care and it is considered a TB-sensitive strategy. The current study aimed to adapt the WHO cost tool to an Egyptian context. It assessed the catastrophic payments due to TB before and after applying UHC, thus enabling policymakers to determine whether this strategy is sufficient to protect TB patients against improvisation, or whether additional social protection measures are needed.

Methods

Original WHO survey
The WHO generic TB patient cost survey gathers data from patients about their current treatment and the costs incurred during the treatment phase in which they are interviewed (12).

Translation adaptation
Guidelines for translation and cross-cultural adaptation were followed (16,23). The tool was translated through the following 5 stages:

Stage 1: forward translation
Two bilingual translators whose mother tongue is Arabic translated the WHO tool. The translators were health professionals who were aware of the concepts examined by the questionnaire. The translation aimed at conceptual equivalence between the generic and translated tools rather than literal translation. The tool was translated into the written Arabic language with the goal of ensuring that the terms in the target language conveyed the same or similar meanings as the source language.

Stage 2: back translation
Two bilingual, native English-speaking translators translated the tool backwards to English. The translators were unaware of the concepts being explored in order to avoid information bias and to point out unexpected meanings of terms in the translated tool (24). Back-translation provided validity checks and uncovered inconsistencies in the translation process. Discrepancies between the original and the back-translated versions were discussed. The forward-translated tool was iterated as many times as needed by the bilingual expert panel until a satisfactory version was achieved.

Stage 3: expert committee (content validity and cross-cultural adaptation)
Content validity is defined as the extent to which the element of an assessment instrument is relevant and representative of the targeted structure for a particular assessment goal (25). Content validity was achieved in several steps. First, the content validation form was prepared to ensure that the review panel had clear expectations and understanding of the task. Second, the group responsible for reviewing the questionnaire was selected based on individual expertise on catastrophic costs incurred by TB patients. The panel consisted of 8 reviewers with specialties in tropical and infectious diseases, TB and pulmonary diseases, health economics, clinical pharmacy, and epidemiology. In a face-to-face discussion, the experts critically reviewed the field and its components before assigning a score to each. They provided verbal feedback to improve the relevance of each item to the focus area. All comments were taken into consideration to refine the domain and its items. Upon completing the review of the domain and items, the experts were requested to provide a score on each item independently based on the relevant scale (26). The conceptualized equivalence between the generic and translated tools was evaluated. The content validity index was 0.8. As recommended by the WHO task force (11), questions on income and household assets were adapted for the local context using the same wording as in the Demographic Health Survey and the Household Income and Expenditure Survey available in Egypt (27,28).

Stage 4: pretesting and cognitive interviewing
Cognitive interviewing is a research-based qualitative method for determining whether a survey question fulfils its intended purpose (29,30). The lead investigator trained a physician and a pharmacist to conduct the cognitive interview through role play. Fifteen participants were recruited for the interview (5 physicians and 10 TB patients aged > 18 years at the TB Department of El Mamora Chest Hospital, Alexandria at least 2 weeks after initiation of the intensive phase, and after signing informed consent). Recruitment of subjects for cognitive interviewing aimed to include variation of subjects rather than statistical representation. The interview was conducted in a quiet place and notes were taken
by trained cognitive interviewers. The interviewers prepared the draft form of the questionnaire together with probe questions to be asked (30).

The interviewer used concurrent probing, which is a verbal probing approach in which the interviewer asked the probe question just after the respondent had read aloud and answered each survey item (29). The following types of cognitive probes were used: (1) comprehension/interpretation: respondents were asked what they thought was meant by each questionnaire item and the chosen response; (2) paraphrasing: respondents were asked whether they could repeat the question in their own words; (3) recall: respondents were asked to explain how they came up with their answer; and (4) general: respondents were asked about any word they did not understand and any word or expression that they found unacceptable or offensive.

**Stage 5: submission of the final version to the developer for appraisal of the adaptation process**

All forms, reports and the final culturally adapted and pretested questionnaire were sent to the WHO expert panel, which audited the process of translation and adaptation and assessed whether the constructs measured the catastrophic costs.

**Analysis**

The raw data were coded and entered using Microsoft Excel software and the data were described using frequency distribution tables. Qualitative data were described using number and percentage and the variable “age” was described using arithmetic mean and standard deviation. Analysis of the cognitive interviews was based on text summarization (30); the interviewers’ written notes were summarized and the consistent themes were identified, and the questions modified based on results of the analysis.

**Results**

A total of 35 modifications were made to the original WHO cost survey. Twelve questions were modified, 13 response options were changed, 6 questions were added and 4 questions were removed. Examples of the changes in questions were replacing “patient registration number” with “patient ID number” and “province” with “governorate” (Table 1). Thirteen sociodemographic questions had their response options altered, including education, employment and occupation, so that the answers represented the local categories. Other examples of alterations were questions on health insurance and social protection schemes, to reflect the schemes in Egypt (e.g. government insurance, private insurance and donors), and types of facilities for diagnosis and treatment, to reflect the health facilities in Egypt (e.g. chest hospital and chest clinics) (Table 2). Six questions were added, including questions about savings in the cost of TB treatment; cost of accommodation because sometimes patients received treatment in remote facilities that required an overnight stay in a governorate other than their home governorate; and nonessential jobs in the informal sector for additional income (Table 3). Four questions were removed, such as “Was a fee paid to pick up medications?” TB medications are subsidized by the National Tuberculosis Control Program and dispensed free to patients. Questions on vouchers were

<table>
<thead>
<tr>
<th>Original item</th>
<th>Item after adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient registration number in the TB register</td>
<td>Patient ID number</td>
</tr>
<tr>
<td>2. Name of province</td>
<td>Name of governorate</td>
</tr>
<tr>
<td>3. Name of district</td>
<td>Name of administrative region</td>
</tr>
<tr>
<td>4. Supplements during healthcare visit or hospital stay</td>
<td>Divided into separate questions for nutritional supplements, vitamins and food</td>
</tr>
<tr>
<td>5. Cost of travel (total for the stay)</td>
<td>Total cost of transportation for patient and relatives throughout the stay in addition to ambulance costs</td>
</tr>
<tr>
<td>6. Cost of food (total for the stay)</td>
<td>Cost of food during stay and travel for patient and relatives</td>
</tr>
<tr>
<td>7. Other (payment for furniture, soap and other administrative and services)</td>
<td>Other costs (payment for furniture, soap, cloths and other administrative and services and personal supplies for patients and relatives)</td>
</tr>
<tr>
<td>8. (total for the stay)</td>
<td>Did you pay for medications?</td>
</tr>
<tr>
<td>9. Are fees charged to obtain drugs?</td>
<td>What fees did you pay during your last outpatient follow-up visit for X-rays and other imaging scans?</td>
</tr>
<tr>
<td>10. What fees did you pay during your last outpatient follow-up visit for X-rays and other imaging scans?</td>
<td>What is your job after getting TB? (the choices are the same as the question “what is your main job?”)</td>
</tr>
<tr>
<td>11. What is your primary job, regular work, or other regular major activity now?</td>
<td>How many rooms are in the house except the bathroom and kitchen?</td>
</tr>
<tr>
<td>12. How many rooms are in the house except the bathroom?</td>
<td>What is your household’s weekly expenditure in the following items? transportation?</td>
</tr>
<tr>
<td>13. What is your household’s weekly expenditure in the following items?</td>
<td>- Oil?</td>
</tr>
</tbody>
</table>

TB = tuberculosis.
Table 2: World Health Organization TB patient cost survey questions and their adaptation to the Egyptian context

<table>
<thead>
<tr>
<th>Questions</th>
<th>Original options</th>
<th>Options after adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Type of health facility</td>
<td>- Primary health care facility</td>
<td>- Chest hospital</td>
</tr>
<tr>
<td>2. Diagnostic place</td>
<td>- Public hospital</td>
<td>- Chest clinic</td>
</tr>
<tr>
<td></td>
<td>- Nongovernmental organization / health centre or charitable hospital</td>
<td>- Other</td>
</tr>
<tr>
<td></td>
<td>- Hospital or private clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other</td>
<td></td>
</tr>
<tr>
<td>3. Type of TB</td>
<td>- Pulmonary, bacteriologically confirmed</td>
<td>- Lung, confirmed by bacteriological analysis</td>
</tr>
<tr>
<td></td>
<td>- Pulmonary, bacteriologically unconfirmed</td>
<td>- Lung, not confirmed by bacteriological analysis</td>
</tr>
<tr>
<td></td>
<td>- Extrapulmonary</td>
<td>- Outside the lung</td>
</tr>
<tr>
<td>4. Is the patient currently in the stage of intensive or complementary treatment?</td>
<td>- Intensive treatment stage, ----- weeks completed</td>
<td>- Intensive treatment stage, ----- weeks completed</td>
</tr>
<tr>
<td></td>
<td>- Complementary treatment phase, ----- weeks completed</td>
<td>- Continuation treatment phase, ----- weeks completed</td>
</tr>
<tr>
<td>5. Before your TB treatment began in this facility, from which of the following facilities did you seek care or advice for symptoms of current illness (including hospitalization; several types of facilities can be mentioned)?</td>
<td>- Dispensary</td>
<td>- Family health centre</td>
</tr>
<tr>
<td></td>
<td>- Health centre</td>
<td>- Central / public hospitals</td>
</tr>
<tr>
<td></td>
<td>- Public hospital</td>
<td>- Private clinic / hospital</td>
</tr>
<tr>
<td></td>
<td>- Pharmacy</td>
<td>- District health department</td>
</tr>
<tr>
<td></td>
<td>- Herbalist/traditional practitioner</td>
<td>- Chest clinic</td>
</tr>
<tr>
<td></td>
<td>- Private clinic</td>
<td>- Primary health centre</td>
</tr>
<tr>
<td></td>
<td>- Private hospital</td>
<td>- Health insurance hospital / clinic</td>
</tr>
<tr>
<td></td>
<td>- Community health worker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other facility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Point</td>
<td>- Point</td>
</tr>
<tr>
<td></td>
<td>- DOT intensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- DOT continuation</td>
<td></td>
</tr>
<tr>
<td>7. On a daily basis, are you currently taking your medications on your own without supervision or support [self-administered or do you have a supervising or supportive therapy (DOT)]?</td>
<td>- Dispensary</td>
<td>- Chest hospital</td>
</tr>
<tr>
<td></td>
<td>- Health centre</td>
<td>- Chest clinic</td>
</tr>
<tr>
<td></td>
<td>- Public hospital</td>
<td>- Health insurance</td>
</tr>
<tr>
<td></td>
<td>- Pharmacy</td>
<td>- Others, specify</td>
</tr>
<tr>
<td></td>
<td>- Herbalist/traditional practitioner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Private clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Private hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Community health worker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other facility</td>
<td></td>
</tr>
<tr>
<td>8. Did you take your medications in the intensive phase on your own without supervision or support (self-administering) or did you have a supervising or supportive therapy (DOT)?</td>
<td>- Payment scheme</td>
<td>- Government insurance</td>
</tr>
<tr>
<td></td>
<td>- Medical allowance</td>
<td>- Private insurance</td>
</tr>
<tr>
<td></td>
<td>- Health insurance from NGOs in the form of donations</td>
<td>- Donors (e.g., charities)</td>
</tr>
<tr>
<td></td>
<td>- Family / community fund</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Private health insurance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other</td>
<td></td>
</tr>
<tr>
<td>9. Where do you or a family member get your TB medicines?</td>
<td>- Dispensary</td>
<td>- Chest hospital</td>
</tr>
<tr>
<td></td>
<td>- Health centre</td>
<td>- Cold hospital</td>
</tr>
<tr>
<td></td>
<td>- Public hospital</td>
<td>- Other</td>
</tr>
<tr>
<td></td>
<td>- Pharmacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Herbalist/traditional practitioner</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Private clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Private hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Community health worker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other facility</td>
<td></td>
</tr>
<tr>
<td>10. Do you have any of the following types of health insurance? (Multiple answers)</td>
<td>- Payment scheme</td>
<td>- Government insurance</td>
</tr>
<tr>
<td></td>
<td>- Medical allowance</td>
<td>- Private insurance</td>
</tr>
<tr>
<td></td>
<td>- Health insurance from NGOs in the form of donations</td>
<td>- Donors (e.g., charities)</td>
</tr>
<tr>
<td></td>
<td>- Family / community fund</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Private health insurance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other</td>
<td></td>
</tr>
<tr>
<td>11. What is your level of education (for the patient)?</td>
<td>- No education</td>
<td>- Below education age</td>
</tr>
<tr>
<td></td>
<td>- Elementary education (up to grade 3)</td>
<td>- Illiterate does not read or write</td>
</tr>
<tr>
<td></td>
<td>- Incomplete high school (up to grade 9)</td>
<td>- Read and write</td>
</tr>
<tr>
<td></td>
<td>- Completion of high school (up to grade 12)</td>
<td>- Elementary</td>
</tr>
<tr>
<td></td>
<td>- Professional</td>
<td>- Preparatory</td>
</tr>
<tr>
<td></td>
<td>- Vocational high school</td>
<td>- Secondary</td>
</tr>
<tr>
<td></td>
<td>- Higher education (university)</td>
<td>- Higher education (university)</td>
</tr>
<tr>
<td>12. What is your main job?</td>
<td>- School student</td>
<td>- Student</td>
</tr>
<tr>
<td></td>
<td>- Technical</td>
<td>- Employee</td>
</tr>
<tr>
<td></td>
<td>- Service</td>
<td>- Professional</td>
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<tr>
<td></td>
<td>- Factory worker</td>
<td>- Manual worker</td>
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<td></td>
<td>- Farmer</td>
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<tr>
<td></td>
<td>- Government employee</td>
<td>- Housewife</td>
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<tr>
<td></td>
<td>- Teacher</td>
<td>- Not working</td>
</tr>
<tr>
<td></td>
<td>- Retired</td>
<td>- Retired</td>
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<td></td>
<td>- Housewife</td>
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<td></td>
<td>- Unemployed</td>
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<tr>
<td></td>
<td>- Other</td>
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</tr>
<tr>
<td>13. Who did you borrow / receive from?</td>
<td>- the last option “other”</td>
<td>- the respondent was asked to specify “others”</td>
</tr>
</tbody>
</table>

DOT = directly observed therapy; TB = tuberculosis.
removed because such a system does not exist in Egypt (Table 4).

For cognitive interviews, 10 patients and 5 physicians were interviewed [10 male, 5 female, mean age 34.56 (12.32) years]. All patients were living in Alexandria and recruited from Mamora Chest Hospital. All patients were drug sensitive, and 8 of them were in the continuation phase (Table 5). After the interviews, subjects declared that questions were clear and understandable and suggested minor changes. The date of presentation of symptoms and initiation of treatment could not be recalled precisely, especially for patients in the continuation phase. One of the confusing items was the cost of drugs other than anti-TB treatment (nutritional supplementation and vitamins) because these 2 items were inseparable in the prescription. Therefore, a question was added about the total cost of other medication if the patient could not report the cost of each item; patients usually receive a hospital bill with the total cost of hospitalization without itemization. Thus, we added an item that reported the total cost of hospitalization if the patient did not know the cost of each subcategory.

Some words were confusing, such as ambulatory treatment, consultation fee, and biopsy. These words were adapted to suit the local context; for example, energy drinks were replaced with milk and consultation fee with examination fee. We added a question that asked for other national forms of transportation, such as toktok (in Egypt, a 2-wheeled pulled rickshaw with a seat for 1 or 2 people). A question was added about household monthly expenditure on rent. We also asked about the cost of utilities, the estimated monthly net income from work-related activities, the methods of rubbish and municipal waste disposal, and other fixed sources of income.

**Discussion**

A final Arabic version of the original WHO tuberculosis patient cost survey was developed with modifications to 35 descriptors. Twelve questions were modified, 13 response options were changed, 6 questions were added and 4 questions were removed. We encountered some challenges during translation. First, the Arabic language has a rich vocabulary, with many terms used to convey the same meaning. One description in English may have a rich vocabulary, with many terms used to convey the same meaning. Thus, a decision was taken to translate the tool into written Arabic. This resulted in a translated version that could be valid for use in all Arab-speaking countries with some cultural adaptation.

The research team made the following changes to adapt the generic WHO survey to the Egyptian context: changing wording of the questions, changing the response options, and adding and omitting questions. For example, we omitted questions about transportation or accommodation vouchers for TB patients because the voucher system does not exist in Egypt. Similarly, we omitted a question about fees paid to collect TB medications because patients receive TB medications at no charge under the National Tuberculosis Control Program. We added 6 questions. For example, the accommodation costs for the patients and their caregivers because some patients receive treatment in a governorate other than the one they resided. We added a question about nonessential jobs because it is common for Egyptians to take up informal private employment in addition to their main employment as a means to increase their income (32). We changed questions about type of healthcare facilities, education, employment, facilities for dispensing TB medications...etc. to make them appropriate for the Egyptian context.

The WHO patient cost survey adapted in our study has a cross-sectional design in which the patient is interviewed only once. Expenditure incurred after treatment completion is not included, and costs cannot be linked to treatment outcomes, which are sometimes unavailable at the time of the survey. This is likely to underestimate the economic impact of TB because costs incurred after treatment for TB sequelae or loss of job or income due to disability would be overlooked (11). Accordingly, several TB cost studies have drawn attention to the necessity for longitudinal studies, including the costs incurred by patients after recovery, including economic recovery (e.g. ability to repay debts or regain production), and the ability to build resilience against future shocks after completion of TB treatment (11). In one study, the WHO generic cost survey was adapted for longitudinal use in African countries: at enrolment

<table>
<thead>
<tr>
<th>Table 3 Questions added to the World Health Organization TB patient cost survey after adaptation to the Egyptian context</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost of dietary supplements</strong></td>
</tr>
<tr>
<td>1. What is the accommodation cost for you and the accompanying person during direct observation?</td>
</tr>
<tr>
<td>2. How many TB follow-up visits have you had so far during this phase of treatment (to see a doctor or nurse, have follow-up checks, etc.)?</td>
</tr>
<tr>
<td>3. How much did you spend on food and drinks on the last follow-up visit (on the road, while waiting, lunch, etc.), in total, for you and any accompanying person?</td>
</tr>
<tr>
<td>4. What is your non-essential job? (the choice options are the same as the question &quot;What is your main job?&quot;)</td>
</tr>
<tr>
<td>5. How much savings did you spend?</td>
</tr>
</tbody>
</table>

TB = tuberculosis.
(start of TB therapy at day 0), and at 2, 6, 12 and 24 months after enrolment. The periods were designed to determine expenditure for diagnosis, treatment and long-term follow-up once treatment was concluded. Repeated measurements allowed for comparison of costs over time, measuring the economic impact after concluding TB treatment, and linking the cost survey to treatment outcomes. Thus, further studies adapting the current tool for use in longitudinal studies is recommended.

The income provided by patients in the generic WHO survey is self-reported income. This can be challenging in an informal economy setting (4,33). For example, it would not be possible to measure lost income due to illness for patients who report a zero income (11). A report by the World Bank estimated that income from informal private employment accounted for 62% of the overall income (32). In the current study, questions about the monetary value of all items consumed by households were added, using the Demographic Health Survey and the Household Income and Expenditure Survey available in Egypt (27,28). Estimating the income based on possession of assets, such as televisions, refrigerators and mobile phones, is more accurate than self-reported income. This was illustrated in a study in South Africa that used 6 different approaches for estimating catastrophic expenditure. Depending on the estimation method, the total proportion of households experiencing catastrophic costs ranged from 0% to 36%, with the self-reported income significantly lower than the estimated income based on asset linking (34). The South African study highlighted the difficulty of accurate assessment of income when estimating disease-specific catastrophic costs. A consumer expenditure questionnaire is the gold standard for estimating permanent income.

The current study had some limitations. The Demographic Health Survey and Household Income and Expenditure Survey provided accurate estimates of the respondents' income. However, these surveys are specific to the Egyptian context and will be difficult to use in other countries. If the survey is to be replicated in an Arab country, the local context should be taken into consideration when estimating income. Another limitation was that the tool did not account for expenditure incurred after treatment completion. Further adaptation of the tool for use in longitudinal studies is recommended.

**Conclusion**

This study has resulted in the availability of an Arabic version of the WHO TB patient cost survey that could be used to estimate the catastrophic health expenditure among TB patients in Arab countries. With the use of the adapted tool, focused interventions could be applied to reduce the financial burden on TB patients.

**Acknowledgement**

We are grateful for the assistance with the cognitive interviewing provided by Dr. Nesma Abbas Mohamed, Clinical Pharmacist at the Egyptian Ministry of Health, and Dr. Heba Hassan, National Institute of Chest Diseases, Imbaba.

**Funding:** None

**Competing interests:** None declared.
Traduction et adaptation culturelle de l’enquête générique de l’OMS sur les coûts de la tuberculose pour les patients dans un contexte égyptien

Résumé

Contexte : La tuberculose représente un problème de santé majeur qui a de graves répercussions financières sur une proportion importante des patients. Il a donc été nécessaire de mettre au point un outil valable pour mesurer les dépenses liées à la tuberculose par les patients et les membres de leur foyer afin de prendre les mesures appropriées pour réduire la charge financière.

Objectifs : Traduire et valider culturellement l’enquête générique de l’OMS sur les coûts de la tuberculose pour les patients dans le contexte égyptien.

Méthodes : L’instrument a été traduit et adapté culturellement à l’aide de la traduction initiale, de la rétrotraduction, de l’évaluation par un groupe d’experts, du prétest, de l’entretien cognitif et de l’évaluation par le développeur.

Résultats : Après avoir été examinée par un comité d’experts et après des entretiens cognitifs avec les patients, une version finale en arabe a été produite avec des modifications apportées à 35 descripteurs de l’outil original. Douze questions ont été modifiées, 13 options de réponse ont été changées, six questions ont été ajoutées et quatre questions ont été supprimées. Le prétest de l’outil a permis de s’assurer que la version finale tient compte des différences culturelles et qu’elle est adaptée pour l’évaluation des coûts supportés par les patients tuberculeux dans un contexte égyptien.

Conclusion : Les responsables politiques sont incités à utiliser l’outil d’enquête de l’OMS sur les coûts de la tuberculose pour les patients afin d’évaluer les dépenses de ces derniers en vue d’élaborer des politiques appropriées pour réduire leur charge financière.

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Pilot study of safety and efficacy of topical liposomal amphotericin B for cutaneous leishmaniasis caused by Leishmania major in Islamic Republic of Iran

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Abstract

Background: Topical nanoliposomes containing 0.4% amphotericin B (Lip-AmB 0.4%) have shown promising safety results in preclinical and phase 1 clinical trials in healthy volunteers.

Aims: To evaluate safety and efficacy of Lip-AmB 0.4% in cutaneous leishmaniasis patients.

Methods: Fourteen patients with a total of 84 lesions received national standard treatment of weekly intralesional meglumine antimoniate with biweekly cryotherapy, or daily intramuscular meglumine antimoniate (20 mg/kg/day for 14 days), and topical Lip-AmB 0.4% twice daily for 28 days. Twenty-two patients with a total of 46 lesions (7 at most) were treated with topical Lip-AmB 0.4% alone twice daily for 28 days. Thirty patients with a total of 68 lesions received national standard treatment of weekly intraleSIONal meglumine antimoniate (to blanch around the lesion) and biweekly cryotherapy.

Results: Sixty-six patients with cutaneous leishmaniasis lesions completed the study. In the safety evaluation, 2 of the 36 patients evaluated reported a tolerable burning sensation and they preferred to continue treatment. Twelve (92%) of 14 patients with 84 lesions who received national standard treatment combined with Lip-AmB 0.4% completed the study with complete cure. In 1 of the patients with 4 lesions, 1 lesion showed complete cure and 3 showed partial cure. Among 22 patients with 46 lesions who received only topical Lip-AmB 0.4%, 10 completed the study and 18 showed complete cure (95% efficacy). In the 30 patients who received national standard treatment alone, 33 lesions in 15 patients showed complete cure (48.5%) on day 42 follow-up.

Conclusion: Lip-AmB 0.4% alone or in combination with national standard treatment is safe with high-efficacy rate and warrants further investigation during phase 3 clinical trials.

Keywords: nano, liposomal, amphotericin B, cutaneous, leishmaniasis, Ghacantime, Iran

Citation: Khamesipour A; Mohammadi A; Jaafari M; Eskandari S; Tasbihi M; Javadi A; et al. Pilot study of safety and efficacy of topical liposomal amphotericin B for cutaneous leishmaniasis caused by Leishmania major in Islamic Republic of Iran. East Mediterr Health J. 2022;28(9):658–663.

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Introduction

Cutaneous leishmaniasis is the most common form of leishmaniasis and it is endemic in about 90 countries, with 600,000 to 1 million new cases annually. According to the World Health Organization (WHO), more than 90% of cutaneous leishmaniasis cases reported in 2019 were from Afghanistan, Algeria, Brazil, Colombia, Islamic Republic of Iran, Iraq, Libya, Morocco, Pakistan, Peru, Syrian Arab Republic and Tunisia (1). Cutaneous leishmaniasis is a vector-borne parasitic disease caused by different Leishmania species and transmitted through sand fly bites, specifically in uncovered parts of the body. The most common species of the parasite include Leishmania major, Leishmania tropica, Leishmania infantum and Leishmania donovani, which are found in many geographical areas such as North Africa, Mediterranean, Middle East, Indian Subcontinent and Central Asia (1,2).

Cutaneous leishmaniasis causes skin lesions with various clinical features from slow-healing lesions to permanent scars (3), resulting in social stigma and psychological disorders that negatively affect the quality of life (4). Standard treatment for cutaneous leishmaniasis currently depends on multiple injections of antimoniate derivatives. However, several alternative therapies are under investigation because of the challenges of antimoniate derivatives, including injection site pain, high cost, severe adverse effects, variable efficacy and drug resistance. Oral treatments such as azole antifungal drugs, dapsone, azithromycin, miltefosine and zinc sulfate have been evaluated for treatment of cutaneous leishmaniasis but are associated with adverse effects and
variable efficacy (2–7). Topical formulations have been developed against cutaneous leishmaniasis and tested in clinical trials but they are not yet available in the market (8–10). Amphotericin B (AmB) is a polyene antifungal agent that kills pathogens by binding to ergosterol and causing subsequent pore formation in the cell membrane and oxidative damage. Despite the effectiveness of AmB against fungal infections and visceral leishmaniasis, its use is limited because of the significant toxicity, especially nephrotoxicity and infusion-related reactions (11). To reduce the adverse effects and increase tolerance to AmB, 3 lipid-based formulations have been developed (Amphotec, Abelcet and AmBisome) to treat visceral leishmaniasis but their efficacy for cutaneous leishmaniasis is not high (11–13). Therefore, novel formulations with optimal skin penetration are needed to improve cutaneous leishmaniasis treatment.

Liposomes are spherical biodegradable vesicles that are extensively used because of their safety and improved delivery. Numerous studies have revealed that topical liposomal formulations reduce adverse effects and improve skin penetration and on-site drug accumulation (13,14). Nanoliposomes containing 0.4% amphotericin B (Lip-AmB 0.4%) have been developed under good manufacturing practice guidelines using phosphatidylcholine and cholesteryl for treatment of cutaneous leishmaniasis. The formulation demonstrated promising results against *L. tropica* and *L. major in vitro* and *L. major in vivo* (15) and shown to be safe in animal models (16). The safety of Lip-AmB 0.4% has been evaluated in healthy volunteers in a phase I clinical trial. The skin before and after topical application of Lip-AmB 0.4% twice daily showed no significant difference in hydration, transepidermal water loss, melanin, erythema, temperature, sebum and pH (17). Another clinical study showed no significant difference in the safety and efficacy of Lip-AmB 0.4% compared to intralesional injection of meglumine antimonate in cutaneous leishmaniasis patients (18). In the current study, we compared the safety and efficacy of topical Lip-AmB 0.4% alone, topical Lip-AmB 0.4% combined with meglumine antimonate, and meglumine antimonate plus cryotherapy for treatment of cutaneous leishmaniasis lesions.

**Methods**

**Study design**

This was an open, pilot clinical trial, registered at the Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), conducted in accordance with guidelines for good clinical practice. Ethical approval was obtained from the institutional ethics committees at CRTSDL, and informed consent was obtained from all candidates before enrolment. The study objectives and procedures were explained to the patients and the treatment option was selected based on the patient’s wishes and physician’s decision. The study evaluated the safety and efficacy of the following treatments for cutaneous leishmaniasis lesions caused by *L. major*: topical Lip-AmB 0.4% alone, topical Lip-AmB 0.4% combined with meglumine antimonate, and meglumine antimonate plus cryotherapy.

**Study patients**

The inclusion criteria were: (1) age 14–60 years; (2) parasitologically confirmed cutaneous leishmaniasis lesions caused by *L. major* using direct smear, culture and polymerase chain reaction (PCR); and (3) clinical diagnosis of up to 5 cutaneous leishmaniasis lesions with a diameter < 5 cm. Patients who were eligible to receive national standard treatment and willing to apply Lip-AmB 0.4% were included and received both treatments. Patients who were not willing or eligible to receive meglumine antimonate but were willing to receive Lip-AmB 0.4% were treated with Lip-AmB 0.4% alone.

Exclusion criteria were: (1) pregnancy or patients not willing or unable to use contraceptives during and 3 months after the end of therapy; (2) lactation; and (3) using any other treatment for cutaneous leishmaniasis. Initially 46 patients were enrolled to receive Lip-AmB 0.4% based on the inclusion/exclusion criteria. Ten patients were excluded for the following reasons: (1) 2 patients’ lesions were not confirmed parasitologically using direct smear, culture and PCR; (2) lesions in 6 patients were caused by *L. tropica*; and (3) 2 patients developed sporotrichoid lesions. Thirty-six patients completed the study.

**Drug administration**

Lip-AmB 0.4% was produced under good manufacturing practice conditions at Razaak Arak Pharmaceutical Company (Tehran, Islamic Republic of Iran). The production was supported by DNDi (Geneva, Switzerland). Glucantime (meglumine antimonate) was produced by Sanofi Aventis (France). Fourteen patients with a total of 84 lesions received national standard treatment of weekly intralesional meglumine antimonate (7 IL injections) plus biweekly cryotherapy (3 or 4 sessions), or daily intramuscular meglumine antimonate (20 mg/kg) per day for 14 days plus topical Lip-AmB 0.4% twice daily for 28 days. Twenty-two patients with a total of 46 lesions (7 each at most) were treated with topical Lip-AmB 0.4% alone twice daily for 28 days. Thirty patients aged 14–60 years with a total of 68 lesions received national standard treatment of weekly intralesional meglumine antimonate (7 IL injections) plus biweekly cryotherapy (3 or 4 sessions).

**Study procedures**

At baseline before treatment initiation and at each of the weekly visits up to day 28 of follow-up, patients were given a written instruction to rub each of their lesions with Lip-AmB 0.4%, twice daily in the morning and at night. During each weekly visit, the Lip-AmB 0.4% tubes were replaced with new ones and the old ones were collected and kept till the end of the study.
Measurement of lesions

At baseline, each patient was interviewed for demographic and health backgrounds. The number, location and type of each lesion were recorded and the lesions were measured in 2 dimensions using a digital calliper. The details were entered into a computer and after double entry, the data were cleaned and analysed by the data management team. The lesion specifications were recorded during each visit and a standardized digital photograph was taken.

Results

Treatment safety

Safety evaluation in 36 patients, aged 19–60 years (20 female and 16 male) showed no adverse events such as itching, burning, inflammation, or pain at the lesion site. In 2 other patients with lesions > 15 cm, topical treatment with Lip-AmB 0.4% induced a burning sensation that was tolerable and the patients preferred to continue treatment.

Treatment efficacy

Fourteen patients, aged 24–51 years (8 female and 6 male) with 84 lesions received national standard treatment (weekly intralesional meglumine antimonate and biweekly cryotherapy, or daily intramuscular meglumine antimonate plus topical Lip-AmB 0.4% twice daily for 4 weeks). Follow-up was conducted on 12 of the patients, and on day 42 after treatment initiation, 11 showed complete cure (91.7% efficacy). In 1 of the patients with 4 lesions, 1 lesion showed complete cure and 3 showed partial cure at 42 days after initiation of treatment. Twenty-two patients, aged 28–51 years (13 female and 9 male) with 46 lesions (7 lesions each at most) were treated with topical Lip-AmB 0.4% alone twice daily for 4 weeks. One patient did not take the treatment and 2 were not available for follow-up visits. Thus, 19 patients completed the study according to the protocol. On day 42 after treatment initiation, 18 patients with 36 lesions showed complete cure (94.7% efficacy). Among the 30 patients who received standard treatment alone, 15 (50% efficacy) showed complete cure on day 42 after treatment initiation. On day 42, in the patients who received standard treatment plus Lip-AmB 0.4%, 70 of 77 lesions showed complete cure (90.9% efficacy). In the patients who received Lip-AmB 0.4% alone, 36 of 39 lesions showed complete cure (92.3% efficacy). In the patients who received standard treatment alone, 33 of 68 lesions showed complete cure (48.5% efficacy).

Discussion

The current study was completed during the period that antimoniate derivatives (Glucantime/Pentostam) were not easily available in the Islamic Republic of Iran, partly due to the economic sanctions. Generous support from DNDi enabled formulation and production of Lip-AmB under good manufacturing practice conditions, and the topical formulation was tested first in animal models and then its safety was checked in healthy volunteers (15–17). The results of current study showed an acceptable efficacy and tolerable safety profile for Lip-AmB 0.4% alone and in combination with meglumine antimonate for treatment of cutaneous leishmaniasis lesions caused by L. major.

Cutaneous leishmaniasis is a major public health threat in some endemic areas, with 600 000 to 1 million new cases worldwide annually (1, 2). Various treatments have been used for cutaneous leishmaniasis. Antimoniate derivatives, the costly WHO-recommended treatment for cutaneous leishmaniasis, require multiple long-term injections, are accompanied by adverse effects and are not always effective, making treatment of cutaneous leishmaniasis a challenge in developing and developed regions (5, 6, 19, 23). Accordingly, alternative treatments, especially topical formulations, are desired by patients, physicians and governments. Different topical formulations, mainly paromomycin formulations, have shown promising results in preclinical and clinical studies and are marketed (21–24).

Amphotericin B is an antifungal agent and second-line treatment for cutaneous leishmaniasis, visceral leishmaniasis and mucocutaneous leishmaniasis, but is associated with severe toxicity (25). Although Lip-AmB (Ambisome) has limited toxicity and has improved the efficacy of amphotericin B for treatment of visceral leishmaniasis, its application in treatment of cutaneous leishmaniasis is limited due to variable efficacy in different geographical areas, high cost and limited access (26–28). Conventional topical formulations of amphotericin did not show acceptable efficacy, mainly due to the high molecular weight and amphipathic nature of amphotericin, which limits skin penetration (29, 30). The epidermis is the outer layer of the skin and the main barrier to cutaneous absorption of drugs (31, 32). An ideal topical drug delivery system for the treatment of cutaneous leishmaniasis should have enough penetration to reach the dermis, where Leishmania parasites reside (33). The advantages of nanocarriers for cutaneous drug delivery are under investigation (34). The advantages of using liposomes as nanodelivery systems include greater skin penetration, controlled drug release, drug deposition and targeting in skin layers, lower systemic absorption, and limited adverse effects in transdermal delivery (35).

Previously, the same group have developed several topical liposomal drugs, including amphotericin B. The characteristics of these topical liposomal formulations, including stability, diffusion and efficacy have been investigated in vitro and in vivo. Different concentrations of topical Lip-AmB (0.1, 0.2 and 0.4%) were checked in vitro and in vivo against a few Leishmania species in comparison with Fungizone (micellar formulation) in vitro [5]. Accordingly, it seems that Lip-AmB 0.4% is a promising formulation for treatment of cutaneous leishmaniasis. Lip-AmB 0.4%, with a size ~100 nm, has
received a US patent and is produced according to good manufacturing practice guidelines. An irritancy potential test (Draize test) revealed that Lip-AmB 0.4% is safe in animal models (16). In a double-blind, randomized, phase 1 clinical trial, the safety of Lip-AmB 0.4% and its vehicle was evaluated in 27 healthy human volunteers. The healthy volunteers applied Lip-AmB 0.4% and its vehicle twice a day for 1 week or 3 times a day for 2 weeks. In 7 of the volunteers, no skin reactions (including pruritus, burning, skin redness, oedema and scaling) were seen and no significant differences in biophysical characteristics of the skin were observed between Lip-AmB 0.4% and its vehicle. Local skin reactions were observed in some of the remaining 20 volunteers that resulted in withdrawal of 2 of the volunteers (17).

**Conclusion**

Lip-AmB 0.4% alone or combination with national standard treatment showed acceptable efficacy and safety for treatment of cutaneous leishmaniasis lesions caused by *L. major* and warrants further investigation in phase 3 clinical trials.

**Finding:** None.

**Competing interests:** None declared.

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**Étude pilote sur l’innocuité et l’efficacité de l’amphotéricine B liposomale topique pour le traitement de la leishmaniose cutanée causée par *Leishmania major* en République islamique d’Iran**

**Résumé**

**Contexte :** Les nanoliposomes topiques contenant 0,4 % d’amphotéricine B ont montré des résultats prometteurs en termes d’innocuité lors d’essais précliniques et cliniques de phase 1 chez des volontaires en bonne santé.

**Objectifs :** Évaluer l’innocuité et l’efficacité de l’amphotéricine B à 0,4 % chez les patients atteints de leishmaniose cutanée.

**Méthodes :** Quatorze patients présentant un total de 84 lésions se sont vu administrer le traitement standard national constitué d’injections intralésionnelles d’antimoniate de méglumine hebdomadaire avec cryothérapie bihébdomadaire, ou d’antimoniate de méglumine intramusculaire de manière quotidienne (20 mg/kg/jour pendant 14 jours), et d’amphotéricine B topique à 0,4 % deux fois par jour pendant 28 jours. Vingt-deux patients présentant un total de 46 lésions (sept au maximum) ont été traités seulement par amphotéricine B topique à 0,4 % deux fois par jour pendant 28 jours. Trente patients présentant au total 68 lésions ont reçu le traitement standard national d’antimoniate de méglumine intralésionnel chaque semaine (pour blanchir le pourtour de la lésion) et de cryothérapie bihébdomadaire.

**Résultats :** Soixante-six patients présentant des lésions de leishmaniose cutanée ont terminé l’étude. Dans l’évaluation de l’innocuité, deux des 36 patients évalués ont signalé une sensation de brûlure tolérable et ont préféré poursuivre le traitement. Douze (92 %) des 14 patients présentant 84 lésions qui ont reçu le traitement standard national associé à l’amphotéricine B à 0,4 % ont terminé l’étude avec une guérison complète. Chez l’un des patients présentant quatre lésions, on a observé une guérison complète pour une lésion et une guérison partielle pour trois lésions. Parmi les 22 patients présentant 46 lésions qui ont reçu uniquement de l’amphotéricine B topique à 0,4 %, 19 ont terminé l’étude et 18 ont montré une guérison complète (efficacité à 95 %). Chez les 30 patients ayant reçu le traitement standard national seul, 33 lésions chez 15 patients ont présenté une guérison complète (48,5 %) au 42ème jour de suivi.

**Conclusion :** L’amphotéricine B à 0,4 % seule ou en association avec le traitement standard national est sans risque et présente un taux d’efficacité élevé. Elle mérite donc d’être étudiée de manière plus approfondie lors des essais cliniques de phase 3.
الاستنتاجات:

تلقى أربعة عشر مريضًا يعانون إجمالًا من 84 آفة، شفاء تامًّا من آفة واحدة بترکيز مع العلاج بالتبريد مرتين أسبوعيًّا، وشفاء جزئيًّا من ثلاث آفات. ومن بين المرضى الذين تلقوا العلاج الوطني القياسي، بالإضافة إلى نانو ليبوسومال الذي يحتوي على الأمفوتريس، تلقى 0.4% مريضًا بين 0 و14 آفة يعانون من آفة موضعيًّا، وحققتهم الشفاء تامًا. ووجدهم أن 68 مريضًا شملوا العلاج الوطني القياسي، بالإضافة إلى نانو ليبوسومال الذي يحتوي على الأمفوتريس، تلقى 0.4% مريضًا من 36 مريضًا يعانون من آفة، أتم المشاركتين في الدراسة، وشُفيت من آفة واحدة ومريض واحد من آفة موضعيًّا. وقد تحقق لهم الشفاء تامًا.

تلقى 28 مريضًا يوميًّا لمدة 28 يومًا. وتشمل تأثيرات المريضين، إجمالًا إجمالًا من 88 آفة العلاج المعياري، وللعلاج النانو ليبوسومال الذي يحتوي على الأمفوتريس. ووجدهم أن 46 مريضًا، 0.4% من 68 مريضًا من 36 مريضًا، أتم المشاركتين في الدراسة، وشُفيت من آفة واحدة ومريض واحد من آفة موضعيًّا. وقد تحقق لهم الشفاء تامًا. ووجدهم أن 68 مريضًا، 0.4% من 36 مريضًا، أتم المشاركتين في الدراسة، وشُفيت من آفة واحدة ومريض واحد من آفة موضعيًّا. أما المرضى الذين تلقوا العلاج الوطني القياسي فقط وعددهم 30، فقد شفيت 33 مريضًا منهم، 11 مريضًا منهم شفاء شافٍ. ووجدهم أن 82 مريضًا، 0.4% من 36 مريضًا، أتم المشاركتين في الدراسة، وشُفيت من آفة واحدة ومريض واحد من آفة موضعيًّا.

استنتاجات: استخدام نانو ليبوسومال الذي يحتوي على الأمفوتريس، وحيدة، مع العلاج القياسي الوطني من الوجهين، يمكن لتعزيز فعالية العلاج، ويستحق إجراء مزيد من الدراسة، في التجارب السريرية من المرحلة الثانية.

References


Could self-reported symptoms be predictors of RT-PCR positivity in suspected COVID-19 cases? The Libya experience

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Abstract

Background: COVID-19 has symptoms similar to several other respiratory and non-respiratory diseases, which makes differentiating them a challenging task and could lead to unnecessary use of realtime reverse transcriptase polymerase chain reaction (RT-PCR) resources.

Aims: The study aimed to assess self-reported symptoms as predictors for RT-PCR positivity in suspected COVID-19 cases.

Methods: This was a cross-sectional study. We retrospectively reviewed the database of COVID-19 care centres in the eastern district of Tripoli, Libya, from May to December 2020. Presenting symptoms and RT-PCR test data were extracted.

Results: Of the 4593 subjects, 923 (20.1%) had positive RT-PCR result. Sensitivity for COVID-19 disease diagnosis was very low (≤ 18.2%) for all symptoms, except for myalgia (82.1%). Specificity was high for all symptoms (907–99.8%), except for myalgia (11.0%). Loss of taste and smell had the highest positive likelihood ratio (LR) for RT-PCR positivity (LR+ = 3.59, 95% CI: 2.95–4.37). In the multiple logistic regression, three symptoms maintained significant contribution to RT-PCR positivity: these were loss of taste and smell (odds ratio (OR) = 3.90, 95% CI: 3.04–4.99), sore throat (OR = 1.50, 95% CI: 1.02–2.19), and myalgia (OR = 0.65, 95% CI: 0.49–0.85). Other significant predictors were history of contact with a COVID-19 case (OR = 0.50, 95% CI: 0.39–0.62), and being female (OR = 1.33, 95% CI: 1.15–1.55).

Conclusion: The findings of this study do not support the use of self-reported symptoms for the confirmation of COVID-19 disease in suspected cases because of their poor diagnostic properties.

Keywords: COVID-19, self-reported symptoms, predictors, sensitivity, specificity, respiratory disease, PCR

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Introduction

COVID-19 emerged at the end of 2019 in China, and by 7 January 2020, a novel type of coronavirus was identified (1,2). The disease then spread to other countries, and was declared a Global Health Emergency of International Concern on 30 January 2020 (2), and declared a pandemic on 11 March 2020 (3). The first case in Tripoli, Libya, where this study was conducted, was confirmed on 25 March 2020 (4). The pandemic has had adverse impacts on health (5,6), education and the economy (7,8), and constituted a major challenge to health care systems (9).

Early and accurate diagnosis of COVID-19 is important for disease management and control. The most accurate diagnostic test for the disease is the real-time reverse transcriptase-polymerase chain reaction (RT-PCR), which is based on the detection of the genetic material of the virus (10). However, the high global demand, and the shipment issues affected supplies to many countries. The shortage of RT-PCR resources is prominent in some developing countries, such as Libya, and has affected the early detection of COVID-19 cases. Besides RT-PCR, there are other tests with variable accuracy and complexity including antigen and antibody detection tests. Antigen rapid diagnostic tests are quick but less accurate than RT-PCR (11). They are more accurate in the first week of the development of symptoms (12), particularly in cases with high viral load (13). Antibody detection tests have limited value in the first week of the infection because of their low sensitivity (10,14).

Researchers have evaluated the usefulness of symptoms in the identification of COVID-19 cases (15–21). Generally, the use of presenting symptoms in the prediction of a disease has been examined before, especially in respiratory diseases (22,23) or in diseases that have the same symptoms with respiratory diseases (24). In the context of epidemic infectious diseases, some studies have investigated the accuracy of symptoms for the diagnosis of severe acute respiratory syndrome (SARS) (25), and Ebola (26).

COVID-19 has the same symptoms with several respiratory infections like the common cold and influenza, and may present with nonrespiratory symptoms. This makes differentiation a challenging task, and can lead to unnecessary use of RT-PCR resources. Symptoms could be of value in guiding the decision about who is likely to have a positive RT-PCR, especially in settings where resources are limited, as in Libya, besides reducing the demand for RT-PCR.
Evidence from previous research on the accuracy of symptoms in distinguishing COVID-19 cases is inconsistent (27). Several studies were undertaken in hospitals (16,17) rather than in primary care settings, or among specific groups like health care workers (15,20,21) rather than in general public cohorts. Therefore, there is a need for further evaluation of the usefulness of symptoms for the diagnosis of COVID-19 (27).

In this study we examined self-reported symptoms as predictors of RT-PCR positivity in suspected COVID-19 cases.

Methods

Study design and settings

A cross-sectional study was conducted using the database of COVID-19 rapid response team at the COVID-19 care centres in the eastern district of Tripoli, Libya. The database was retrospectively reviewed from 1 May 2020 to 31 December 2020. The total number of recorded attendees with complete data was 4708. Of this total, 115 subjects were excluded based on the eligibility criteria of this study.

Study variables

The outcome variable, RT-PCR test status, was defined as a binary variable (positive, negative). It was based on the examination of nasopharyngeal swab specimens using RT-PCR. In addition to the presenting symptoms, data on age, sex, nationality and contact history were extracted. Both the sociodemographic data and the symptoms were self-reported.

Eligibility criteria

Based on literature relevant to children’s survey methods (28–30), only the data for cases aged 8 years and older were included. Subjects with inconclusive RT-PCR results, which were coded as “repeat” in the database, were excluded.

Ethical considerations

Permission was obtained from the National Center of Disease Control (NCDC), Tripoli, Libya. Confidentiality was maintained as the data were anonymously coded.

Statistical analysis

We used SPSS, version 26, for statistical analysis. Frequency, percentage, mean and standard deviation were used to summarize the characteristics of the participants. The bivariate association between study variables and RT-PCR test status were assessed using the chi-squared test, Fisher’s exact test and the independent t-test. Sensitivity, specificity, positive and negative predictive values and likelihood ratios were estimated to evaluate the diagnostic properties of each symptom. Variables that showed significant ($P < 0.05$), or nearly significant ($P < 0.25$) crude association with the RT-PCR test status in the bivariate analysis were considered in a multiple logistic regression analysis for the predictors of positive PCR test.

Results

Sociodemographic characteristics and distribution of symptoms

Data for 4593 subjects with suspected COVID-19 were considered in the analysis (Table 1). Mean age was 38.2 (standard deviation 16.7) years, and males represented 54.7% of the sample. Overall, 94.9% were symptomatic and most presented with more than one symptom. The most frequently reported symptom was myalgia (88.0%); this was followed by fatigue, fever, cough and loss of taste and smell, but these were reported less frequently (Figure 1). A total of 16.2% reported other symptoms less frequently: headache (4.9%), dyspnoea (4.0%), sore throat (3.4%), runny nose (3.1%) and vomiting and diarrhea (0.8%).

Unadjusted association between symptoms and RT-PCR positivity

Around 20.1% of the respondents suspected of having COVID-19 were confirmed positive with the RT-PCR (Table 2). A significantly greater proportion of females than males showed positivity ($P < 0.001$). Positivity was greater among subjects who had no history of contact with a COVID-19 patient than among those who reported a history of contact and in those who reported having no myalgia than in those who reported having myalgia ($P < 0.001$ for both). The symptoms that showed statistically significant associations with RT-PCR status were loss of taste and smell, headache, sore throat, fever, fatigue, Table 1 Demographic characteristics of study subjects ($n = 4593$), Tripoli, Libya, 2020

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
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<td></td>
<td></td>
</tr>
<tr>
<td>Children (8–18)</td>
<td>491</td>
<td>10.7</td>
</tr>
<tr>
<td>Young adults (8–18)</td>
<td>2189</td>
<td>47.7</td>
</tr>
<tr>
<td>Adults (41–65)</td>
<td>1617</td>
<td>35.2</td>
</tr>
<tr>
<td>Elderly (≥ 66)</td>
<td>296</td>
<td>6.4</td>
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<tr>
<td><strong>Sex</strong></td>
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<td></td>
</tr>
<tr>
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<td>2081</td>
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</tr>
<tr>
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<td>4584</td>
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<td>9</td>
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<td>Yes</td>
<td>4159</td>
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<tr>
<td>No</td>
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<td>9.4</td>
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<tr>
<td><strong>Presentation</strong></td>
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<tr>
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<td>4360</td>
<td>94.9</td>
</tr>
<tr>
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<td>233</td>
<td>5.1</td>
</tr>
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</table>
myalgia and cough ($P < 0.001$ for all except cough $P = 0.002$).

**Validation of individual symptoms**

Table 3 shows the diagnostic properties of each symptom. Sensitivity was very low for all symptoms ($\leq 18.2\%$) except for myalgia ($82.1\%$). However, specificity was high for all symptoms ($90.7\%–99.8\%$) except for myalgia ($10.5\%$). All symptoms had a low positive predictive value (PPV) ($\leq 47.4\%$), and the PPV of some symptoms like abdominal pain had wide $95\%$ confidence interval (CI) indicating uncertainty. Loss of taste and smell had the highest positive likelihood ratio for RT-PCR positivity and thus for COVID-19 diagnosis ($3.59, 95\%CI: 2.95–4.37$). All symptoms had negative likelihood ratio of $1$ or close to $1$.

**Multivariate logistic regression analysis for RT-PCR positivity predictors**

In the multivariate logistic regression analysis for the predictors of positive PCR test, $3$ symptoms maintained significant contribution to PCR positivity in the controlled analysis (Table 4). These were loss of taste and smell, sore throat and myalgia. Other significant factors were sex and history of contact with a COVID-19 case.

Subjects who lost taste and smell were almost 4 times more likely to have a positive PCR than those who had not lost those senses [odds ratio (OR) = 3.90, 95\% CI:3.04–4.99]. Subjects who reported having sore throat had 1.5 times greater odds of having a positive PCR than those who did not (OR = 1.50, 95\% CI:1.02–2.19). Females were slightly more likely to have a positive test than males (OR = 1.33, 95\% CI: 1.15–1.55).

Myalgia and history of contact with a COVID-19 case were negative predictors. Subjects who complained of myalgia had lower odds of having a positive test result than those who did not present with it (OR = 0.65, 95\% CI: 0.49–0.85). Subjects who reported a history of contact had lower odds of RT-PCR positivity than those who had no contact history (OR = 0.50, 95\% CI: 0.39–0.62).

This logistic regression model had very poor properties. Based on Nagelkerke's $R^2$, it explains only $72\%$ of the variation in having the PCR test positive. The overall accuracy is $79.9\%$, but it displayed a very low sensitivity ($6.0\%$). The logistic regression model had a high specificity ($98.4\%$), a low positive predictive value (PPV) ($49.5\%$) and a moderate negative predictive value (NPV) ($80.6\%$).

$$Z = -0.700 + 1.362 \times \text{Loss of taste and smell (Yes)} + 0.694 \times \text{Contact history (No)} + 0.290 \times \text{gender (Female)} - 0.424 \times \text{Myalgia (Yes)} + 0.406 \times \text{Sore throat (Yes)}$$

Probability (positive PCR) = $1/1 + e^Z$

**Discussion**

A substantial proportion of the suspected cases were symptomatic, but the majority had presented with myalgia more often than with any other symptoms. Fatigue, fever, cough and loss of taste and smell were much less commonly presented. This symptom pattern differs in terms of frequency of symptoms and order of commonness from that reported in some other settings ($18,20,21$).

Initially, in the unadjusted analysis, $7$ symptoms showed statistically significant association with RT-PCR status. Loss of taste and smell had the highest crude odds of RT-PCR positivity, with a $4$-fold increase in the likelihood of the test being positive. As in our study, loss of taste showed the highest unadjusted odds of RT-PCR positivity among all studied symptoms in several other studies ($20,21$). We found that fever, cough and fatigue were associated with increased crude odds of test positivity, and this is consistent with other research ($20$). Sore throat was associated with an almost $2$ times increase in the likelihood of having the infection. However, previous research findings on sore throat have been mixed; while some studies reported lower odds of having the disease in those who had a sore throat ($20$), others reported no difference unless the sore throat was combined with nasal symptoms ($15$), or even higher odds.
Table 2: Distribution of real-time polymerase chain reaction status and bivariate associations using data from the database of the COVID-19 pandemic rapid response team (n = 4593), Tripoli, Libya, 2020

<table>
<thead>
<tr>
<th>Attribute</th>
<th>RT-PCR status</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td></td>
<td>+ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
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<tr>
<td><strong>All</strong></td>
<td>923</td>
<td>3670</td>
<td>20.1</td>
<td>79.9</td>
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<td><strong>Sex</strong></td>
<td></td>
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<tr>
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<td>472</td>
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<tr>
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<td>451</td>
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<td>79.9</td>
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<td><strong>Contact history</strong></td>
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<tr>
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<td>794</td>
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<tr>
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<td>758</td>
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<td>388</td>
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<td>135</td>
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<td>186</td>
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<td>3561</td>
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<td>Mean</td>
<td>SD</td>
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<td>16.9</td>
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<td>16.7</td>
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</table>

*Independent t-test.

Fisher’s exact test.

OR = odds ratio.

CI = confidence interval.
Table 3

<table>
<thead>
<tr>
<th>Symptom</th>
<th>PPV 95%CI</th>
<th>NPV 95%CI</th>
<th>Sensitivity 95%CI</th>
<th>Specificity 95%CI</th>
<th>Likelihood ratio 95%CI</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Fever</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Cough</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Loss of taste &amp; smell</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Headache</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.89–0.97</td>
<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Diarrhoea</td>
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<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
<tr>
<td>Abdominal pain</td>
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<td>0.97–1.00</td>
<td>98.1–98.8</td>
<td>96.3–97.5</td>
<td>2.95–4.37</td>
</tr>
</tbody>
</table>

Of PCR positivity in those who did not have sore throat (21). In our study, myalgia was associated with lower crude odds of test positivity, which is not consistent with the findings in some other studies (20,21).

With the exception of myalgia, all symptoms had very low sensitivity, but high specificity for detecting PCR positivity, and thus, for COVID-19 infection diagnosis. The high specificity of the symptom indicates that it correctly identifies subjects who do not have COVID-19 infection. That means those who do not have that symptom, generally do not have the infection. However, the very low sensitivity implies that sole reliance on any symptom for the diagnosis of COVID-19 would be associated with a high false-negative rate. In other words, many of the suspected subjects who actually have COVID-19 infection would not be identified. Consistent with our findings, a review of similar studies concluded that individual COVID-19 symptoms have very low sensitivity and moderate to high specificity (27). However, one study reported a relatively better sensitivity and a lower specificity for certain symptoms like loss of taste, sore throat and fever (19).

Subjects who had lost taste and smell were almost 4 times more likely to test positive than those who had not lost those senses. Several studies have reported loss of taste as one of the strongest predictors of PCR positivity (15,17–21). Sore throat showed a 1.5 times increase in the odds of having a positive RT-PCR, and this was in contrast to some studies (19,21).

Interestingly, myalgia maintained its contribution as a negative predictor in the controlled analysis, suspected cases who reported myalgia had lower odds of having a positive test result than those who did not report it. Myalgia is a subjective symptom, especially if measured via self-reporting, and this may partially explain this finding. The study did not control for comorbidity and a proportion of the reported myalgia may have been related to morbidities other than COVID-19. In contrast to our finding, some studies reported myalgia among the predictors of positive RT-PCR (15,19,21). As the respondents in those studies were either health care workers (15,21), or included a health care workers group (19), reporting of myalgia may have been more accurate than in our study.

History of contact with a COVID-19 case contributed significantly to the PCR test result as a protective factor, those who reported contact were less likely to be positive. In contrast to our findings, and in line with the theoretical expectations, a Hong Kong study found that contact history increased the likelihood of PCR positivity 10-fold (16). The reported protective contribution in our study may have been driven by some factors that were not controlled. Considering the Health Belief Model (31,32), we suggest that being aware of a positive contact nearby may increase the self-susceptibility perception and adherence to COVID-19 preventative behaviours. This could be one reason for the reported protective contribution. Another possible
explanation is that the “no contact history” group may have included a proportion of subjects with “unknown positive contacts”. A proportion of those with “contact history” may have falsely tested negative as they presented early when they realized they had contacted a positive case, and thus were counted within the negative group.

This multiple regression model has a very low sensitivity, but a high specificity for diagnosis of COVID-19 infection. Although this regression model may be good at excluding those who do not have COVID-19 infection because of the high specificity, many of the subjects who have the infection will be missed if it is used. As in our study, some research has questioned the use of such models for the diagnosis of COVID-19 infection for their low sensitivity (23).

Several limitations should be considered in the interpretation of our findings. Most of these limitations are related to the nature of retrospective data collection. The subjective nature of self-reporting of symptoms, especially general nonrespiratory ones like myalgia and fatigue, may have affected measurement accuracy. Another weakness of the study is that it did not control for co-morbidity due to the considerable amount of missing data on this variable in the database. Our study did not account for the time between the appearance of symptoms and performing the RT-PCR tests because this information was not available in the database. Thus, cases who had the RT-PCR test when they had just observed the symptoms may have been falsely included in the negative group due to the relatively higher false negativity of the test in the early stages of COVID-19.

However, the study does have its strengths. While several previous studies were undertaken in hospitals, or among specific groups like health care workers, which limits their external validity, this study used data from a relatively large cohort of the general public presenting in COVID-19 care centres, which is deemed to enhance the generalizability of its results.

**Conclusions**

Our findings agree with previous research on the importance of loss of taste and smell as a predictor of RT-PCR positivity. However, we do not support relying on symptoms alone for COVID-19 disease diagnosis in practice because of their overall poor diagnostic properties. Further research is recommended to assess the use of symptoms as predictors of RT-PCR positivity and to address our study limitations. In particular, we recommend considering a fixed time from the appearance of symptoms to taking the RT-PCR test for all subjects, which was not feasible in our study due to the limited availability of data and its retrospective nature. The current study was conducted when the original strain of SARS-COV-2 was dominant in Libya. Thus, further research is needed because the symptom pattern and the order in which symptoms appear vary between the original SARS-CoV-2 virus strain and other variants.

**Acknowledgement**

We would like to thank the rapid response team in the COVID-19 care centres in the study district and the National Center of Diseases Control in Libya for supporting this study.

**Funding:** None

**Competing interests:** None declared.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>B</th>
<th>Wald</th>
<th>P</th>
<th>Adj OR (95% CI)</th>
</tr>
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<tbody>
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<td>Female vs male</td>
<td>0.290</td>
<td>14.548</td>
<td>&lt; 0.001</td>
<td>1.33 (1.15–1.55)</td>
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<tr>
<td>Contact vs no contact</td>
<td>−0.694</td>
<td>35.607</td>
<td>&lt; 0.001</td>
<td>0.50 (0.39–0.62)</td>
</tr>
<tr>
<td>Fever vs no fever</td>
<td>0.230</td>
<td>2.979</td>
<td>0.084</td>
<td>1.25 (0.96–1.63)</td>
</tr>
<tr>
<td>Cough vs no cough</td>
<td>−0.073</td>
<td>0.230</td>
<td>0.631</td>
<td>0.93 (0.69–1.25)</td>
</tr>
<tr>
<td>Dyspnoea vs no dyspnoea</td>
<td>−0.043</td>
<td>0.044</td>
<td>0.833</td>
<td>0.66 (0.37–1.19)</td>
</tr>
<tr>
<td>Sore throat vs no sore throat</td>
<td>0.406</td>
<td>4.445</td>
<td>0.035</td>
<td>1.50 (1.02–2.21)</td>
</tr>
<tr>
<td>Fatigue vs no fatigue</td>
<td>0.009</td>
<td>0.004</td>
<td>0.950</td>
<td>1.00 (0.77–1.32)</td>
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<tr>
<td>Loss of taste and smell vs no loss</td>
<td>1.362</td>
<td>116.699</td>
<td>&lt; 0.001</td>
<td>3.90 (3.04–4.99)</td>
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<tr>
<td>Myalgia vs no myalgia</td>
<td>−0.424</td>
<td>9.327</td>
<td>0.002</td>
<td>0.65 (0.49–0.85)</td>
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<tr>
<td>Headache vs no headache</td>
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<td>0.371</td>
<td>0.83 (0.55–1.24)</td>
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<tr>
<td>Diarrhoea vs no diarrhoea</td>
<td>−0.038</td>
<td>0.006</td>
<td>0.937</td>
<td>0.96 (0.37–2.48)</td>
</tr>
</tbody>
</table>
| Constant                      | −0.700| 19.140| < 0.001| ADJ OR = adjusted odds ratio.
| CI = confidence interval.    |       |       |        |
الأعراض التي يبلغ عنها المريض ينسبة: هل يمكن أن تستخدم للتنبؤ بالنتيجة الإيجابية لتحليل التنسخ العكسي لتفاعل البوليميراز المتسلسل في حالات كوفيد-19؟

الة البيئية

الخليفة: مرض فيروس كورونا-2019 (كوفيد-19) أعراضًا مشابهة مع العديد من الأمراض الأخرى التنفسية وغير التنفسية، وهو ما يمثل تحديًا في التمييز بين تلك الأمراض. وقد يؤدي ذلك إلى استنفاد الموارد المخصصة لاختبارات التنسخ العكسي لتفاعل البوليميراز المتسلسل. 

لا يوجد

التالي: من بين من شملت الدراسة بياناتهم، الذين بلغ عددهم 4593 شخصًا، كانت نتيجة اختبار "تفاعل البوليميراز التنسيجي العكسي المتسلسل" إيجابية لدى 923 شخصًا (19.62%)، وكانت حساسية جميع الأعراض تشخيص مرض كوفيد-19 منخفضة جداً (%18.2). وتأتي هذه النتائج في عام 2020، ما عدا الأعراض القلبية (11.0%) والتهاب القصبات (30.7%). وهذا الأعراض هي في حالة مساهمة مرض كوفيد-19 في النتائج الإيجابية لتفاعل البوليميراز التنسيجي العكسي المتسلسل. 

الاستنتاجات: توليد هذه الأعراض لا تؤثر استخدام الأعراض التي يبلغ عنها المريض لتأكيد الإصابة بمرض كوفيد-19 في الحالات المشتبه فيها، وذلك بسبب ضعف ارتباطها بالتشخيص.
References


Evaluation and comparison of vitamin A supplementation with standard therapies in the treatment of patients with COVID-19

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Abstract

Background: Incomplete data are often presented for determining the role of vitamin A supplement therapy for improving treatment outcomes in patients with COVID-19.

Aims: We compared treatment effects between a group that received vitamin A added to the standard COVID-19 treatment and another group that received the standard drug treatment alone.

Methods: Participants in this triple-blind controlled trial comprised 182 COVID-19 outpatients in Saveh City, Markazi Province, Islamic Republic of Iran, in 2020. Patients were randomly divided into experimental (n = 91) and control (n = 91) groups. Patients in the control group received the national standard treatment for COVID-19 (hydroxychloroquine), and those in the intervention group received 25 000 IU/d oral vitamin A for 10 days in addition to the standard treatment recommended by the national protocol. We evaluated the clinical symptoms, paraclinical criteria, and hospitalization status before and after 10 days of interventions.

Results: The treatment groups did not differ significantly in clinical and paraclinical symptoms before the intervention. However, clinical symptoms such as fever, body ache, weakness and fatigue, paraclinical symptoms, white blood cell count, and C-reactive protein showed significantly greater decreases in the experimental group 10 days post-intervention compared with the standard treatment alone (P < 0.05).

Conclusion: Vitamin A supplementation demonstrated efficacy in improving some clinical and paraclinical symptoms in patients with COVID-19. Future studies should evaluate vitamin A supplementation with a larger sample size and compare different dosages, especially in hospitalized patients.

Keywords: COVID-19, vitamin A, treatment, hydroxychloroquine

Introduction

In December 2019, an epidemic emerged in Wuhan, China, and drew the attention of the world (1). The virus rapidly spread to other countries and soon became a pandemic (2). On 30 January 2020, the World Health Organization declared the disease a public health emergency of international concern that threatened not only China, but also all countries (3,4). The evolutionary analyses based on genes indicated that the virus belongs to the family of beta-coronaviruses (5).

Beta-coronaviruses cause a wide range of viral diseases, including more severe illnesses such as the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) (6,7). In the novel coronavirus (nCoV-2019) COVID-19, the incubation period lasts about 7 days when the antibodies are not yet developed. The asymptomatic period is from the time of infection until the fifth day; and the period of onset of clinical symptoms is from the fifth to the eighth day (8,9). The most common clinical symptoms of infection are fever (87.9%), cough (67.6%), fatigue (38.1%), diarrhoea (3.7%), and vomiting (5%), and therefore COVID-19 is similar to other coronaviruses.

Vitamin A is an essential nutrient for bodily processes, especially immune system functioning. It is an anti-inflammatory substance (10) and plays a considerable role in immunity against infectious diseases (11); its deficiency causes numerous injuries that disrupt the response to infection (12). Recent clinical trials have indicated that vitamin A reduces complications and mortality in various infectious diseases such as measles, diarrhoea, measles-related pneumonia, and human immunodeficiency virus infection (11). Its deficiency is associated with higher susceptibility, severity and duration of infection (13).
Vitamin A is necessary for consistent immunity and plays a role in the growth of T cells, T helper cells (Th cells), and B cells. In particular, vitamin A deficiency decreases the antibody-mediated responses by Th2 cells. Its deficiency disrupts innate immunity by preventing the regeneration of mucosal epithelium damaged by infection and by reducing the function of neutrophils, macrophages and natural killer cells (12,14).

Given that there is no specific treatment for COVID-19 and to our knowledge no studies have evaluated the effects of vitamin A supplementation in the treatment of COVID-19, this study aimed to assess the efficacy of standard treatment plus vitamin A supplementation compared with standard treatment alone on COVID-19 symptoms, hospitalization status and paraclinical criteria.

Methods

Study design and participants

In this triple-blind clinical trial, the sample comprised patients of Saveh Health Centre, in Islamic Republic of Iran and all of them had COVID-19. The sample size was estimated to be 64, with confidence level 0.95, power 0.80, and the probable mean difference (Cohen's d) of the dependent variable before and after the intervention [i.e. predicted change in probability, mean score for creatinine (Cr) 0.5] using the formula proposed by Lehr (16/d^2) [15]. Given the possibility of sample attrition, 91 individuals were included in the study for each group (n = 182) (Figure 1).

The inclusion criteria were: receiving outpatient care for COVID-19 from the health centre in Saveh, age 18–75 years, agreeing to participate in the study and completing the informed written consent forms. The exclusion criteria included: having any autoimmune diseases (lupus, multiple sclerosis, etc.), having chronic infectious disease, having concomitant or previous viral infections, being a current consumer of vitamin A supplement, pregnant and breastfeeding women, having renal failure, underlying liver disease, having heart failure and having chronic pulmonary disease.

We recruited patients who visited the COVID-19 outpatient centre of Saveh, which is the only medical centre in the city, from 1 May to 1 September 2020 and had positive PCR results for COVID-19. After patients were screened for inclusion/exclusion criteria and completed informed consent, they were then randomly assigned to the 2 treatment groups using the random allocation table.

Randomization and blinding

The method of blinding was as follows: the main researcher packed the drugs in 2 packages A and B and placed them in the pharmacy with the pharmacist. Package A included national standard treatment for COVID-19 outpatient care from the health centre in Saveh, which is the only medical centre in the city, from 1 May to 1 September 2020 and had positive PCR results for COVID-19. After patients were screened for inclusion/exclusion criteria and completed informed consent, they were then randomly assigned to the 2 treatment groups using the random allocation table.
outpatients (hydroxychloroquine) in addition to vitamin A (Zahravi Pharmaceutical Company), and package B included the national standard treatment of COVID-19 for outpatients (hydroxychloroquine) in addition to placebo. The placebo was made to look and feel like the original vitamin A, but the active ingredient was an ineffective substance (glycerin). Patients diagnosed with COVID-19 were referred to a pharmacy by the physician; and the pharmacist assigned the patients to one of the groups A or B based on the random numbers table. The pharmacist was a research assistant who did not take part in the enrolment of participants. Using permuted block randomization with a block size of 2 and an allocation ratio of 1:1, patients were allocated to the intervention and control groups. A random sequence of “intervention” and “control” was generated using a random numbers table. After installing the tables in the clinic, the intervention or control was designated as the first experimental group for the first eligible person by the sampler. It is clear that based on the random sequence method, the next word can be used. Therefore, the patients, laboratory technicians, therapists involved in prescribing, sample recipient and questionnaire responders were blind to the treatment group. The main researcher was not blind to the groups. Participants were not allowed to use any other medication during the 10 days of the study. Patients were trained to follow the prescribed treatment. They were followed up by telephone on the third and sixth days to check their health and general condition and adherence to the recommended treatment regimens, and on the eleventh day they were visited in person.

**Supplement administration**

Ninety-one patients in the control group received only the standard national treatment, and 91 patients in the intervention group received 25 000 IU/d vitamin A for 10 days in addition to the standard treatment recommended in the national protocol.

**Outcome measurements**

We examined the dependent variables before and after the treatment intervention in both groups. The clinical improvements (in combination) up to 10 days after treatment were measured using a self-report questionnaire and patient examination. Clinical improvement was defined as normal body temperature (≤ 37.2° oral), improved cough (lack of cough that was sustained for at least 24 hours and based on the patient report on a physical scale), chills, shortness of breath, headache, body ache, hyposmia, fatigue, anorexia and diarrhoea. A therapist examined the symptoms at baseline and 10 days after the treatment. The cellular count and biochemical parameters of patients were tested by trained constant operators in the reference laboratory of Saveh University of Medical Sciences (17) according to international guideline. Paraclinical improvement was defined as changes in C-reactive protein (CRP) and lymphocytes before and after the treatment, and normal ranges of: white blood cells (WBCs), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK), Cr test, liver function tests [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)]. A turbidimetric method was used to determine CRP; CPK quantified by an ultra violet kinetic method using a special kit; WBC was measured with flow cytometry counters using a haematology analyser and autoanalyser. We did not evaluate alkaline phosphatase and did not perform the liver and bile ultrasonography because no jaundice occurred in any of the patients. The paraclinical variables were evaluated at the beginning and on the tenth day of study. The proportion of patients who were hospitalized due to COVID-19 was examined and compared between the 2 groups.

**Statistical methods**

The data collected from the patients were given to the statistical evaluator in codes because the statistical evaluator was blinded to the treatment groups. Statistical analysis was conducted using SPSS, version 20.0. All measurement data were reported as mean and standard deviation. Treatment groups were statistically compared using independent sample t-tests. The intra-group comparisons were performed using paired t-tests. Enumeration data were reported as case numbers and percentages and these outcomes were compared using chi-squared. Alpha level was set at P < 0.05.

**Ethics**

Written informed consent was obtained from all the patients in the study. All participants were given an information sheet together with the consent form and advised that they could revoke their consent at any time without giving any reasons. The study protocol was approved by the ethics committee of Saveh University of Medical Sciences (IRSAVEHUMSREC1399.003) and registered on the Iran Clinical Trial database (IRCTID: IRCT 46974). The required permission was obtained from the hospital authorities.

**Results**

Two out of 91 patients in the experimental group did not complete the post-intervention evaluation 10 days after treatment, therefore the final analysis was performed on 91 patients in the control group and 89 in the experimental group. Mean age was 39.4 (SD 15.6) years in the experimental group and 40.8 (SD 17.3) years in the control group. Fifty-three individuals (59.5%) in the experimental group and 51 (56%) in the control group were male. Most of the patients (n = 122, 67.8%) were married, and 56 (31%) had a high school diploma. A total of 15 patients (8.3%) were drug addicts, and 81 (45%) reported moderate economic status. Forty-eight patients (26.6%) had underlying diseases, and 49 (27%) had family members with COVID-19. The chi-square test did not show any significant difference between the experimental and control groups in terms of demographic variables (P > 0.05) (Table 1).
Evaluation of the patients’ clinical symptoms indicated that there was no significant difference between the groups in terms of fever, chills, cough, shortness of breath, headache, body ache, decreased sense of smell, weakness, and fatigue, anorexia and diarrhoea before the therapeutic intervention. However, the proportion of those reporting fever, body ache, and weakness and fatigue was significantly lower in the group that received the vitamin A supplement plus hydroxychloroquine 10 days after the intervention ($P < 0.05$) (Table 2).

There was no statistically significant difference between the experimental and control groups in terms of paraclinical criteria - WBC, CRP, AST, ESR, CPK and Cr - before the therapeutic intervention, but there was a significantly greater reduction of CRP and WBCs in the group receiving the vitamin A supplement in comparison with the control group after the therapeutic intervention ($P < 0.05$) (Table 3). The results of the paired t-tests indicate that all paraclinical criteria significantly changed in the experimental group after the treatment intervention ($P < 0.05$) except for lymphocyte counts and Cr values: 33% of patients (31 in the experimental group and 29 in the control group) had lymphocyte counts below 1500 before the intervention, but the rate decreased to 17% (14 in the experimental group and 17 in the control group) after the intervention. There was no significant difference between the 2 groups before and after the treatment intervention for lymphocyte count. Eight patients in the experimental group (9%) and 11 in the control group (12%) were hospitalized, but there was no statistically significant difference in hospitalization rates between the 2 groups ($P > 0.05$).

**Discussion**

In this study, we aimed to determine whether vitamin A supplementation along with standard treatment was more efficacious in reducing COVID-19 symptoms and improving outcomes than standard treatment alone in patients presenting to an outpatient health centre.

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**Table 1**  Comparison of quantitative variables in the intervention and control groups of patients, Saveh, Islamic Republic of Iran, 2020

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention</th>
<th>Control</th>
<th>$P$-value</th>
<th>$\chi^2$</th>
</tr>
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<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>53 59.5</td>
<td>51 56.0</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 41.5</td>
<td>40 44.0</td>
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<td><strong>Employment</strong></td>
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<td>Government employee</td>
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<td>17 18.6</td>
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<td>Industrial worker</td>
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<td>8 8.8</td>
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<td>Other</td>
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<td>14 15.4</td>
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<td></td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6 6.7</td>
<td>12 13.2</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>45 50.5</td>
<td>47 51.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>38 42.6</td>
<td>32 35.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>14 15.7</td>
<td>20 22.0</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Addiction</td>
<td>7 27.0</td>
<td>8 33.3</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td><strong>Underlying disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19 infection among other family members</td>
<td>23 26.0</td>
<td>25 27.5</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td><strong>COVID-19 infection among other family members</strong></td>
<td>25 28.1</td>
<td>24 26.4</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-squared
Table 2 Distribution of clinical characteristics in the clinical and control groups at baseline and 10-day follow-up, Saveh, Islamic Republic of Iran, 2020

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Time</th>
<th>Intervention group</th>
<th>Control group</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 89)</td>
<td>(n = 91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes No. (%)</td>
<td>No. (%)</td>
<td>Yes No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Fever</td>
<td>Baseline</td>
<td>34 (38.2)</td>
<td>55 (61.8)</td>
<td>41 (45.1)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>2 (2.3)</td>
<td>87 (97.7)</td>
<td>10 (11.0)</td>
</tr>
<tr>
<td>Chill</td>
<td>Baseline</td>
<td>28 (31.5)</td>
<td>61 (68.5)</td>
<td>37 (40.7)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>3 (3.4)</td>
<td>86 (96.6)</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>Cough</td>
<td>Baseline</td>
<td>42 (47.2)</td>
<td>47 (52.8)</td>
<td>50 (54.9)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>7 (8.0)</td>
<td>82 (92.0)</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Baseline</td>
<td>31 (35.0)</td>
<td>58 (65.0)</td>
<td>29 (32.0)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>4 (4.5)</td>
<td>85 (95.5)</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>Baseline</td>
<td>28 (31.5)</td>
<td>61 (68.5)</td>
<td>35 (39.5)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>3 (3.4)</td>
<td>86 (96.6)</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>Body ache</td>
<td>Baseline</td>
<td>46 (51.7)</td>
<td>43 (48.3)</td>
<td>49 (53.8)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>1 (1.2)</td>
<td>88 (98.8)</td>
<td>8 (9.8)</td>
</tr>
<tr>
<td>Smell</td>
<td>Baseline</td>
<td>71 (79.7)</td>
<td>18 (20.3)</td>
<td>68 (74.7)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>76 (85.3)</td>
<td>13 (14.7)</td>
<td>83 (92.1)</td>
</tr>
<tr>
<td>Weakness &amp; fatigue</td>
<td>Baseline</td>
<td>49 (55.0)</td>
<td>40 (45.0)</td>
<td>60 (65.9)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>4 (4.5)</td>
<td>85 (95.5)</td>
<td>11 (12.1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Baseline</td>
<td>35 (39.4)</td>
<td>54 (60.6)</td>
<td>44 (48.4)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>3 (3.4)</td>
<td>86 (96.6)</td>
<td>8 (8.8)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Baseline</td>
<td>32 (36.0)</td>
<td>57 (64.0)</td>
<td>32 (35.2)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>7 (8.0)</td>
<td>82 (92.0)</td>
<td>9 (10.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Baseline</td>
<td>15 (17.0)</td>
<td>74 (83.0)</td>
<td>18 (20.0)</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>2 (2.3)</td>
<td>87 (97.7)</td>
<td>5 (5.5)</td>
</tr>
</tbody>
</table>

*Chi-square

found that some clinical symptoms (fever, body ache and fatigue) were significantly more improved 10 days after treatment in the group that received the vitamin A supplement in comparison with the control group. The results for other clinical symptoms also indicated improvements over time for chills, cough, shortness of breath, hyposmia, anorexia, and diarrhoea in the vitamin A group, but these findings were not statistically significant compared with the control group. This was consistent with a study by Kabhazi et al., who found that vitamin A could reduce fever in patients with acute pyelonephritis (10). In a study on neonates, Shenai et al. found that taking vitamin A was effective in reducing the infection in breathing pathways (16). Aluisio et al. found that vitamin A supplement led to a reduction in mortality in patients with Ebola virus disease (17). In a study on very-low-birth-weight infants, vitamin A reduced the symptoms of patients with diarrhoea, fever, lethargy, acute respiratory infections, rubella and ear infections (18). In a similar study among schoolchildren, a vitamin A supplement reduced mortality rates and complications of infectious diseases of the gastrointestinal and respiratory tracts (19).

Previous research has suggested that vitamin A plays an important role in maintaining the health of the mucous membranes and skin covering the nose, sinuses and mouth; immune system function; T and B lymphocytes; macrophages; and the production of antibodies (20, 21). It helps in adjusting the secretion of IL-10: IL-10 is produced by T helper 2 (TH2) cells and inhibits the synthesis of the pre-inflammatory cytokines, including IFN-γ and IL-2, in both natural killer- and T-cells. This mechanism is important in limiting inflammatory responses to certain pathogens (22).

In our study, the CRP rate further decreased in the vitamin A supplement group; CRP is known as an attractive biomarker of inflammation because its concentration increases rapidly within a few hours of infection, and even before any clinical symptoms develop (23). Shaker et al. conducted a study evaluating the effectiveness of zinc and vitamin A supplement in treating and reducing upper respiratory tract infections in children (23). Consistent with our findings, they found a significant reduction in CRP in patients. This was expected because vitamin A inhibited CRP production (24). This biomarker is widely used in clinical diagnoses.
as a non-specific acute phase indicator of inflammation. It responds to infection through its rapid production by the liver and its release into the bloodstream and stimulation by several cytokines, including IL6, IL1β, and TNFα. (24,25).

Our findings indicates that the WBC level in the group receiving vitamin A supplement showed a greater decrease than in the control group. Similarly, the rate for WBCs showed a significant reduction in recipients of vitamin A and zinc in a study on upper respiratory tract infections in children (23). In a similar study, the WBC level significantly decreased in tuberculosis patients who received vitamin A (26). In our study, the level of lymphocytes significantly increased in the experimental group, while there was no significant change in the control group. Previous studies have shown the beneficial effects of vitamin A supplement in children with viral diseases through the increase of lymphocyte proliferation (22,27).

Vitamin A deficiency disrupts the innate immunity by preventing the natural regeneration of mucosal barriers damaged by infection and reducing the function of neutrophils, macrophages and natural killer cells. Vitamin A is necessary for consistent immunity and is involved in the growth of T helper (Th) and B cells. In particular, its deficiency decreases the antibody-mediated responses by Th2 cells (12,14).

Our findings did not show any significant difference in Cr levels of patients in the experimental and control groups before and after the intervention. However, in-group comparison indicated a significant decrease in Cr in the experimental group. Creatinine level is a sign of kidney function. As none of our participants had kidney failure or dysfunction, the therapeutic intervention likely had no effect on their Cr levels.

Our findings indicate that liver enzymes were less than 1.5 times the normal amount (normal: 20 in women and 30 in men) in both control and experimental groups, and they were unchanged by the pharmacological intervention. In the case of liver inflammation and hepatocellular hepatitis, the amount of transaminase increased by more than 5 times (28).

Table 3: Comparison of paraclinical characteristics in the clinical and control groups at baseline and 10-day follow-up, Saveh, Islamic Republic of Iran, 2020

<table>
<thead>
<tr>
<th>Test item</th>
<th>Time</th>
<th>Intervention group (n = 89)</th>
<th>Control group (n = 91)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells (× 10⁹ cells/l)</td>
<td>Baseline</td>
<td>7437 (4807)</td>
<td>6378 (2374)</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>5941 (1922)</td>
<td>6283 (1799)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (cells/µL)</td>
<td>Baseline</td>
<td>2085 (1208)</td>
<td>2209 (1698)</td>
<td>0.918</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>2748 (1317)</td>
<td>2482 (1766)</td>
<td>0.225</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.507</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>Baseline</td>
<td>14.5 (21.8)</td>
<td>14.4 (17.9)</td>
<td>0.969</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>3.4 (3.9)</td>
<td>5.8 (9.7)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>Baseline</td>
<td>24.0 (18.5)</td>
<td>27.0 (22.7)</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>15.9 (10.7)</td>
<td>19.8 (13.3)</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>Baseline</td>
<td>0.99 (0.22)</td>
<td>0.93 (0.22)</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>0.92 (0.16)</td>
<td>0.90 (0.16)</td>
<td>0.351</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.002</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Alanine transaminase (IU/L)</td>
<td>Baseline</td>
<td>28.3 (14.6)</td>
<td>26.5 (14.8)</td>
<td>0.422</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>22.3 (15.1)</td>
<td>22.1 (13.5)</td>
<td>0.947</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>Baseline</td>
<td>33.1 (22.9)</td>
<td>27.7 (15.0)</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>23.2 (16.2)</td>
<td>19.2 (16.2)</td>
<td>0.104</td>
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<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase (IU/L)</td>
<td>Baseline</td>
<td>112.9 (73.3)</td>
<td>114.7 (76.8)</td>
<td>0.870</td>
</tr>
<tr>
<td></td>
<td>10-day follow-up</td>
<td>70.4 (35.7)</td>
<td>79.2 (36.9)</td>
<td>0.108</td>
</tr>
<tr>
<td></td>
<td>P-valueb</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.
*t-test.
Paired t-test.
The research limitation was that, because this study used a sample from an outpatient health centre and these patients were quarantined at home, all conditions of the patients were not directly supervised.

Conclusion
Our results suggest that vitamin A supplement is efficacious in improving some clinical (fever, body ache, weakness and fatigue) and paraclinical symptoms (reduction of WBC and CRP) in patients with COVID-19. We suggest future studies examine outcomes with a larger sample size and compare dosage of vitamin A, especially in hospitalized patients.

Funding: None

Competing interests: None declared.

References
Diagnostic and treatment outcomes of patients with pulmonary tuberculosis in the first year of COVID-19 pandemic

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Abstract

Background: The COVID-19 pandemic has put a significant strain on human life and health care systems, however, little is known about its impact on tuberculosis (TB) patients.

Aims: To assess the impact of COVID-19 pandemic on pulmonary tuberculosis (PTB) diagnosis, treatment and patient outcomes, using the WHO definitions.

Methods: A cross-sectional study was conducted in Malatya region, Turkey (population 800 000). Data on regional PTB test numbers, case notification rates and PTB patients’ clinical characteristics and treatment outcomes were collected. Data from the first pandemic year (2020) were compared to data from the previous 3 years (2017–2019). The attitudes and experiences of patients were analysed.

Results: Despite a non-significant 22% decrease in annual PTB case notifications (P = 0.317), the number of TB tests performed (P = 0.001) and PTB patients evaluated (P = 0.001) decreased significantly during the pandemic year compared with the previous 3 years. The proportion of patients with high (3/4+) sputum acid-fast bacilli grades (P = 0.001), TB relapse (P = 0.022) and treatment failure (P = 0.018) increased significantly. The median 64.5-day treatment delay detected in 2017–2019 increased significantly to 113.5 days in 2020 (P = 0.001), due primarily to patients’ reluctance to visit a health care facility.

Conclusion: In addition to the problems with case detection, this study shows notable deterioration in several indicators related to the severity, contagiousness and poor outcomes of TB, which had already been suppressed for decades.

Keywords: COVID-19, pulmonary tuberculosis, self-reported symptoms, predictors, sensitivity, specificity

Citation: Yakupogullari Y; Ermis H; Kargan Z; Otlu B; Bayindir Y; Gulbas G; et al. Diagnostic and treatment outcomes of patients with pulmonary tuberculosis in the first year of COVID-19 pandemic. East Mediterr Health J. 2022;28(9):682–689. https://doi.org/10.26719/emhj.22.060

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Introduction

Mycobacterium tuberculosis, one of the oldest pulmonary pathogens in humans, infects around one-third of the global population. An estimated 9.9 million new cases and more than 1.5 million deaths from tuberculosis (TB) were reported in 2021 (1). Because no effective TB vaccine exists, it is critical to control the disease through effective diagnosis and treatment as well as the elimination of the suboptimal living conditions that contribute to the spread and reactivation of TB. The End TB Strategy, led by the World Health Organization (WHO), aims to reduce TB-related deaths by 95% and disease incidence by 90% by 2035 through early diagnosis, treatment, collaboration and resource allocation (2).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an emerging pulmonary pathogen that has caused a pandemic affecting the entire global population since the beginning of 2020. Data from WHO have shown that SARS-CoV-2 has infected more than 400 million people worldwide, resulting in around 5.5 million COVID-19 deaths as of January 2022 (3). Studies show that the frequency of some neuropsychiatric problems has increased, and quality of life and well-being have been negatively affected while living under pandemic conditions (4,5). Survivors of severe COVID-19 often require immune-suppressive medications and have experienced decreased B- and T-cell counts (6,7). Significant reductions in hospital admissions of patients with health problems other than COVID-19 have also occurred (8). The COVID-19 pandemic has imposed a significant workload on health care facilities, particularly in the departments of chest and infectious diseases, which are critical for TB diagnosis. Therefore, the COVID-19 pandemic has the potential to exacerbate TB burden on societies by negatively impacting health care systems in addition to its effects on personal and social well-being.

A WHO report indicates that substantial disruptions in TB services and case detection have occurred across the world since the beginning of the COVID-19 pandemic (9). A study conducted in the WHO European Region reported a decrease of more than one-third in TB case notifications in the second quarter of 2020 compared to the same period in 2019, and suggested that the deterioration in TB services due to the COVID-19 response may impede the region’s ability to meet the TB targets of the 2030 Sustainable Development Goals (10). Although similar declines in notifications have been reported in several
countries, the details and dynamics of these reductions are not yet clear.

This study aimed to determine changes in diagnostic and treatment processes and treatment outcomes (according to WHO definitions) in patients diagnosed with pulmonary tuberculosis (PTB) in the first year (2020) of the COVID-19 pandemic.

**Methodology**

**Study design, patients**

A cross-sectional study was conducted in Malatya, a city located in mid-eastern Turkey with a population of 800,000 inhabitants. Patients in the region who were tested for and diagnosed with PTB between 1 January 2017 and 28 February 2021 were included in the study. Because the study aimed to evaluate the impact of the COVID-19 pandemic on the course of PTB annually, the first pandemic year was defined as the 1-year period from 1 March 2020 (the first COVID-19 case notification in Turkey) to 28 February 2021.

Any patient who was tested for and diagnosed with PTB during the study period and who was a resident of the Malatya region was included in the study. Patients with PTB and who had COVID-19 were included to determine the potential impact of this co-infection on the diagnosis and treatment processes and the outcomes of pulmonary tuberculosis. Patients who did not meet these criteria were excluded from the study. Because the COVID-19 pandemic did not impact Turkey’s health care system until March 2020, patients diagnosed in January and February 2020 were excluded.

Patients who were tested for and diagnosed with PTB were identified by screening the data from the Public Health Tuberculosis Department of Malatya city and the TB diagnostic laboratory of the region located in the Turgut Ozal Medical Center, a tertiary-level health care facility at the Inonu University Medical Faculty.

This study was approved by the Ministry of Health (2021-011T13_01_23; 12 January 2021), the Malatya Clinical Studies Ethical Board (2021/38; 3 February 2021) and the Ministry of Health Malatya Office (04.21/771-1064; 20 April 2021).

**Data sources and definitions**

Demographic and medical data of patients tested for and diagnosed with PTB during the study period were collected from the electronic and paper records at the Public Health Tuberculosis Department, the Turgut Ozal Medical Center’s TB diagnostic laboratory and the health care facilities where patients were evaluated. The WHO criteria were used to define PTB, relapse, clinically diagnosed TB and treatment outcomes (11).

A questionnaire was used to collect information from patients diagnosed during the pandemic year about their attitudes, behaviours and experiences with the TB diagnosis and treatment processes. The questionnaire had 8 questions with responses graded on a 5-point Likert scale ranging from “strongly disagree” to “strongly agree”. The survey was conducted via phone or in-person interviews. In cases of mortality, juveniles, or mental incapacity, data were obtained from the primary caregiver.

**Data analysis**

The following data for PTB patients who were diagnosed in the region during the study period were collected and analysed: demographic data (age and sex) of the patients, the acid-fast bacilli (AFB) grades in smear samples, diagnostic features (clinical diagnosis/laboratory-based diagnosis), new case or relapse, comorbidities, treatment outcomes and duration from the onset of symptoms to the initiation of anti-TB treatment. Patients’ data from the pre-pandemic (2017–2019) and pandemic (2020) periods were statistically compared.

Quantitative data were presented as median (minimum–maximum) and qualitative data as numbers (percentages). The interquartile range was calculated for the patients’ ages. The conformity of quantitative data to the normal distribution was evaluated with the Shapiro–Wilk test. The one-sample chi-square, Mann–Whitney U, Kruskal–Wallis, Conover pairwise comparison and Pearson chi-square tests were used. The significance level was < 0.05. We used SPSS, version 26.0, software in the analysis.

**Results**

**Pulmonary tuberculosis case notification rate and test statistics in the region**

A total of 2970 patients were evaluated for PTB in the region during the study period. The median age of the patients was 54 years and 60.5% of them were male.

The region’s PTB case notification rate decreased to 6.51 per 100,000 population during the pandemic year, a nonsignificant 22.0% drop from the previous 3 years. This rate was 8.53 in 2017, 7.85 in 2018 and 8.94 in 2019. When compared to the average values of the previous 3 years, the annual number of PTB tests, the number of patients tested and the average number of diagnostic test sets per patient all decreased significantly during the pandemic year, by 47.4%, 39.6% and 20.0%, respectively. Table 1 presents the number of PTB laboratory tests performed and number of patients evaluated for PTB by study year in the region.

**Characteristics of patients**

During the study period, 252 patients with PTB were diagnosed, with a median age of 48 years and 156 (61.9%) of them were male. In 2020, 52 PTB patients (61.5% male, median age 51 years) were diagnosed, with 67, 62 and 71 PTB patients notified in 2017, 2018 and 2019 respectively.

During the pandemic year (2020), the number of PTB patients with 3 or 4+ AFB grades in smear microscopy increased significantly to 27 (51.9%), compared to 6 (9.0%), 2 (3.2%) and 7 (9.8%) in 2017, 2018 and 2019 respectively. In
the previous 3 years, the rate of clinical diagnosis ranged between 13.4% (in 2017) and 18.3% (in 2019), but it dropped insignificantly to 77% during the pandemic year (2020).

In the pandemic year (2020), the number of PTB patients who relapsed and the number who delayed attending the Public Health Tuberculosis Department to start anti-TB treatment by more than 7 days increased significantly when compared to pre-pandemic years (2017–2019).

When the treatment outcomes of patients who completed a 6-month standard anti-TB treatment were compared to the previous 3 years (2017–2019), a statistically significant increase in treatment failure was found during the pandemic year (2020).

Between the pandemic year (2020) and the pre-pandemic years (2017–2019), there was no statistically significant difference in the patients’ co-morbidities, the rate of mortality during treatment, the number of patients with PTB-related hospitalization, or the length of hospital stay (Table 2).

**Duration of diagnosis and treatment processes**

Patients diagnosed with PTB between 2017 and 2019 received treatment within a median of 64.5 days of symptom onset, but this increased significantly to 113.5 days during the pandemic year (2020). In 2020, there were significant delays in the median time taken for a doctor’s appointment and to apply to the Public Health Tuberculosis Department to start treatment after a PTB diagnosis (Table 3).

**Experiences of pulmonary tuberculosis patients in the pandemic year**

Out of 52 PTB patients diagnosed during the pandemic year (2020), 48 were queried. A total of 31 (65.0%) PTB patients reported that they would have sought medical care earlier if there was no pandemic; 20 (41.7%) patients delayed seeking medical care due to fear of contracting COVID-19 in the health care facilities; 16 (33.3%) patients delayed seeking medical care due to “stay at home” advice; 20 (41.6%) had difficulty finding a doctor; 35 (72.9%) had a later appointment time than previous visits and 9 (18.8%) perceived that they received less medical attention compared with prior experiences.

**Pulmonary tuberculosis patients with COVID-19**

In total, 9 PTB patients diagnosed during the pandemic year also had COVID-19. One patient with severe COVID-19 died. Another patient who was diagnosed with PTB following severe COVID-19 was recorded as a COVID-19-mediated PTB recurrence. Two PTB patients who also contracted COVID-19 remained positive for M. tuberculosis complex during the fifth month of the anti-TB treatment.

**Discussion**

In this study, we found significant reductions in the number of PTB patients diagnosed in Malatya during the first year of the COVID-19 pandemic. Similar reductions in TB case notification have been reported in other parts of the world; for example, the Pan American Health Organization reported that PTB case notification in continental America decreased by 15–20% during 2020 (12).

Nguyen et al. reported that the diagnosis of around 20% of PTB cases required 4 or more sputum samples or deep pulmonary sampling because 2 or 3 previous samples showed negative results (13). Therefore, a strong clinical suspicion is essential in PTB diagnosis. We compared the average number of TB tests performed for each patient by year. This parameter could be regarded

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**Table 1** Number of pulmonary tuberculosis laboratory tests performed and number of patients evaluated for PTB, Malatya, 2017–2021

<table>
<thead>
<tr>
<th>Item/characteristic</th>
<th>2017</th>
<th>Pre-pandemic year</th>
<th>2019</th>
<th>Pandemic year</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): median (min–max), IQR</td>
<td>54 (0–95), 51.5</td>
<td>56 (0–96), 52</td>
<td>55 (0–95), 51</td>
<td>52 (0–92), 51</td>
<td>0.262²</td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB tests performed for PTB</td>
<td>1884 (27.2)</td>
<td>2136 (30.9)</td>
<td>1864 (27.0)</td>
<td>1093 (14.9)</td>
<td>0.001⁶</td>
</tr>
<tr>
<td>Patients tested for PTB</td>
<td>875 (29.5)</td>
<td>840 (28.3)</td>
<td>757 (25.5)</td>
<td>498 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>363 (41.5)</td>
<td>340 (40.4)</td>
<td>305 (40.3)</td>
<td>171 (34.3)</td>
<td>0.081⁴</td>
</tr>
<tr>
<td>Male</td>
<td>512 (58.5)</td>
<td>500 (59.5)</td>
<td>452 (59.7)</td>
<td>347 (65.6)</td>
<td></td>
</tr>
<tr>
<td>Patients diagnosed with PTB</td>
<td>67 (26.6)</td>
<td>62 (24.6)</td>
<td>71 (28.2)</td>
<td>52 (20.6)</td>
<td>0.36²</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB test sets per patient</td>
<td>1.97 (1.34)</td>
<td>2.32 (1.52)</td>
<td>2.2 (1.40)</td>
<td>1.73 (1.26)</td>
<td>0.001⁴</td>
</tr>
<tr>
<td>Regional PTB case notification rate</td>
<td>8.53</td>
<td>7.85</td>
<td>8.94</td>
<td>6.51</td>
<td>0.31⁴</td>
</tr>
</tbody>
</table>

IQR = interquartile range. AFB = acid-fast bacilli. SD = standard deviation. Kruskal–Wallis H test. One-sample chi-square test. *TB test set included AFB microscopy + TB cultures/TB PCR. This parameter was calculated according to the TB test set performed for diagnostic purposes by excluding the TB tests performed after diagnosis (i.e. tests for follow up the treatment effectiveness). Annual population size in the province was obtained from the Turkish Statistics Institute.
as a measurable indicator of the medical attention that should be provided to each patient and the degree of clinical suspicion that necessitates a thorough clinical evaluation. We found that the average number of TB tests performed per patient decreased significantly by up to a quarter in the pandemic year (2020). In spite of the significant decrease in number of TB tests, the reduction in number of PTB patient notifications in 2020 was not statistically significant. This finding could be due to an increase in the number of patients with obvious clinical symptoms, and suggests that a proportion of PTB patients, particularly those with ambiguous clinical PTB presentation, may have gone unnoticed during 2020.

We found that the AFB grades of PTB patients increased substantially in the pandemic year (2020). A high sputum bacilli load was associated with the highest relative risk of transmission or active PTB among contacts (14). Given that people had been advised to stay at home since the emergence of COVID-19, the risk of indoor TB exposure may have increased during that year.

About 13% of patients with TB were diagnosed clinically, and required further interventions (i.e. biopsy, histopathology) and evaluations because the TB tests were negative (13). Although not statistically significant, the number of patients diagnosed clinically decreased by more than half in 2020. This could indicate that a proportion of PTB patients who would have been diagnosed clinically may not have been detected in the first year of the COVID-19 pandemic.

Recurrent PTB may yield poorer outcomes, including death and treatment failure (15). Estimates from WHO indicate that about 7% of PTB patients diagnosed annually are relapsed (9). In Turkey, TB recurrence gradually declined from 9.7% to 7.8% between 2006 and 2017 (16). We found more than 2-fold increase in the rate of relapsed PTB patients during the first pandemic year. This could be due to personal factors influenced by the pandemic such as increased psychological stress, deteriorated living standards and limited or delayed access to medical care for any chronic disease.

Despite the increasing number of patients with high bacilli load, treatment failure and recurrence, we found no significant increase in the rate of hospitalized PTB patients and length of hospitalization in 2020.

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### Table 2: Comparison of the characteristics of 252 pulmonary tuberculosis patients who were diagnosed in Malatya, 2017–2021

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2017</th>
<th>Pre-pandemic year</th>
<th>2018</th>
<th>2019</th>
<th>Pandemic year</th>
<th>2020–2021</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years): median (min–max), IQR</strong></td>
<td>No. (%)</td>
<td>52 (17–85), 51.5</td>
<td>No. (%)</td>
<td>50 (13–86), 48.5</td>
<td>No. (%)</td>
<td>46 (12–90), 43</td>
<td>No. (%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>No. (%)</td>
<td>20 (29.9)</td>
<td>No. (%)</td>
<td>29 (46.8)</td>
<td>No. (%)</td>
<td>27 (38.0)</td>
<td>No. (%)</td>
</tr>
<tr>
<td><strong>AFB microscopy</strong></td>
<td>No. (%)</td>
<td>23 (34.3)</td>
<td>No. (%)</td>
<td>30 (48.4)</td>
<td>No. (%)</td>
<td>35 (49.3)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>No. (%)</td>
<td>33 (49.3)</td>
<td>No. (%)</td>
<td>27 (43.5)</td>
<td>No. (%)</td>
<td>20 (28.2)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>1+</td>
<td>No. (%)</td>
<td>5 (7.5)</td>
<td>No. (%)</td>
<td>3 (4.8)</td>
<td>No. (%)</td>
<td>9 (12.7)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>2+</td>
<td>No. (%)</td>
<td>2 (3.0)</td>
<td>No. (%)</td>
<td>1 (1.6)</td>
<td>No. (%)</td>
<td>4 (5.6)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>3+</td>
<td>No. (%)</td>
<td>4 (6.0)</td>
<td>No. (%)</td>
<td>1 (1.6)</td>
<td>No. (%)</td>
<td>3 (4.2)</td>
<td>No. (%)</td>
</tr>
<tr>
<td><strong>Basis of diagnosis</strong></td>
<td>No. (%)</td>
<td>58 (86.6)</td>
<td>No. (%)</td>
<td>51 (82.3)</td>
<td>No. (%)</td>
<td>58 (81.7)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Laboratory-based</td>
<td>No. (%)</td>
<td>9 (13.4)</td>
<td>No. (%)</td>
<td>11 (17.7)</td>
<td>No. (%)</td>
<td>13 (18.3)</td>
<td>No. (%)</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>No. (%)</td>
<td>61 (91.0)</td>
<td>No. (%)</td>
<td>58 (93.5)</td>
<td>No. (%)</td>
<td>66 (93.0)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>New case</td>
<td>No. (%)</td>
<td>6 (9.0)</td>
<td>No. (%)</td>
<td>4 (6.5)</td>
<td>No. (%)</td>
<td>5 (7.0)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>No. (%)</td>
<td>20 (29.9)</td>
<td>No. (%)</td>
<td>22 (35.5)</td>
<td>No. (%)</td>
<td>29 (41.4)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Hospitalized patients</td>
<td>No. (%)</td>
<td>7 (10.4)</td>
<td>No. (%)</td>
<td>5 (8.1)</td>
<td>No. (%)</td>
<td>6 (8.5)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Patients for whom treatment initiation delayed &gt; 7 days</td>
<td>No. (%)</td>
<td>1 (1.9)</td>
<td>No. (%)</td>
<td>0 (0.0)</td>
<td>No. (%)</td>
<td>1 (1.9)</td>
<td>No. (%)</td>
</tr>
<tr>
<td><strong>Treatment process</strong></td>
<td>No. (%)</td>
<td>5 (7.5)</td>
<td>No. (%)</td>
<td>8 (12.9)</td>
<td>No. (%)</td>
<td>5 (7.0)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Mortality during treatment</td>
<td>Mean (SD)</td>
<td>2.55 (7.26)</td>
<td>Mean (SD)</td>
<td>3.02 (6.34)</td>
<td>Mean (SD)</td>
<td>1.92 (3.74)</td>
<td>Mean (SD)</td>
</tr>
</tbody>
</table>

IQR = interquartile range. AFB = acid-fast bacilli. SD = standard deviation. Kruskal–Wallis H test. Pearson chi-square test. *This analysis included the patients who were able to complete a 6-month TB treatment regime, therefore, the patients who were diagnosed clinically or died before the treatment conclusion were excluded.
could be due to patients’ reluctance to be hospitalized, or clinicians’ attitudes about reserving beds for patients with more acute cases.

In the first pandemic year, we found significant increases in the number of PTB patients who were still positive for smear AFB microscopy and/or TB culture in the fifth month of the treatment, which is defined as treatment failure according to WHO criteria (11). Research has shown that cavitary lung lesions, diabetes, high bacilli load in smear microscopy and recurrent TB are predictors of treatment failure (17,18). Given that no difference was observed in PTB patients’ characteristics in terms of diabetes and cavitary lesions in the years studied, we surmised that increasing treatment failure in the first pandemic year was most likely related to increases in high AFB load and relapses during that time.

One study reported a median of 62 days for PTB patients to initiate anti-TB treatment after clinical symptoms first appeared (19). We compared 5 different periods in the diagnostic and treatment processes of PTB by study year. The “time to doctor’s visit after TB symptoms”, which could be considered one of the indicators of patients’ care-seeking behaviour, was found to have almost doubled in 2020. In another period, “doctor’s appointment time” – which could also be viewed as an indicator of the health system’s ability to cope with the increased patient load caused by the COVID-19 pandemic – was found to have increased to a median of 5 days in the 2020 pandemic year, whereas it was usually a same-day procedure between 2017 and 2019. The “time to PTB diagnosis after sample delivery” (which could also be used to assess the laboratory’s performance in PTB diagnosis) showed no delay; in contrast, an average decrease of 2 days was observed in 2020. This finding was an unexpected result and likely occurred due to the significant decrease in TB test orders in that year. There was a significant delay in the “time to access treatment after diagnosis” in 2020, which could be another indicator of patients’ care-seeking behaviour. The period “total time”, as the sum of treatment delays including patient- and health service-dependent delays, increased substantially, as much as 1.7-fold, in 2020.

Patients diagnosed during the pandemic year (2020) were able to access anti-PTB treatment about 40 days later than patients diagnosed previously. Using a statistical method of survival analysis in future studies will help determine more accurate results for such delays.

To clarify the factors contributing to these delays, we queried patients who were diagnosed with PTB in 2020. A significant proportion of PTB patients delayed seeking care due to pandemic-related factors (such as stay-at-home orders and the fear of becoming infected with SARS-CoV-2 in health care facilities), had difficulty seeing a doctor and received less medical attention in 2020. Patients’ responses indicated that during the pandemic, PTB patients experienced hesitation to seek medical help and problems in accessing effective diagnosis and treatment.

We analysed 9 PTB patients diagnosed in the pandemic year (2020) who also had COVID-19 because a co-infection could influence the diagnostic and treatment process as well as treatment outcomes. Although 3 of these 9 patients had shown TB symptoms for up to 6 months, they were ultimately diagnosed with PTB during medical evaluations performed during their hospital stay for COVID-19. This finding is additional evidence that patients postponed their visits to the doctor in 2020 until it was necessary. A patient who received 1-month prednisolone due to severe COVID-19 developed treatment failure for TB. Five of these 9 patients developed COVID-19 during their anti-TB treatment but did not experience any health problems due to their co-infection. The last one of the 9 PTB patients was considered to have a COVID-19-mediated PTB relapse because that patient had no PTB symptoms before acquiring COVID-19. Due to severe COVID-19, this patient was hospitalized for about 34 days, had lymphopenia for 2 weeks and received prednisolone therapy for 2 months. This patient was diagnosed with PTB on the 22nd day following termination of corticosteroid therapy and developed treatment failure.

COVID-19-mediated dysfunctions in effector lymphocytes may not improve completely even 6 months after infection (20), and many patients with severe
COVID-19 receive corticosteroids to prevent lung damage. These immune-system problems may offer favourable conditions for TB bacilli to progress, the bacterium can survive in tissues for decades even in immunocompetent individuals. We identified PTB relapse and treatment failures in our patients, which could be attributed to severe COVID-19. When the distribution of both infections is considered, it can be predicted that such interactions between TB and COVID-19 could result in a global health problem.

In this study, only PTB patients were investigated. Therefore, it is unknown how the pandemic affected the diagnosis and treatment processes and outcomes in patients with extrapulmonary TB. We conducted this study in a region where two-thirds of the health care capacity was never exceeded due to the pandemic, and the region’s TB diagnostic laboratory managed to continue to provide routine service in the meantime. As a result, PTB patients in our region did not experience extensive difficulty accessing basic diagnostic and therapeutic services during the first pandemic year. Given these limitations, we believe that the COVID-19 pandemic would result in greater regressions in TB case detection in areas where health care capacity was exceeded or TB laboratories were used for SARS-CoV-2 diagnosis.

This study shows that more PTB patients may have gone undetected in the province during the pandemic year (2020) as a result of emerging problems in case detection due to changing health care-seeking behaviour among patients and the high workload at health care facilities. In addition to the increased TB burden, an increase in the number of undiagnosed patients in a population can trigger further problematic consequences, such as increased TB-related deaths, as predicted by WHO (9).

Our study reveals that the COVID-19 pandemic may worsen the severity and contagiousness of PTB as well as the success of anti-TB treatment. Therefore, to prevent subsequent threats of TB resurgence, the global community must increase its efforts in raising awareness in addition to educating and encouraging people to access medical aid. As further pandemics may emerge in the years to come, appropriate strategies must be reconsidered to sustain the goals of controlling TB.

Funding: None
Competing interests: None declared.

Résultats diagnostiques et thérapeutiques des patients atteints de tuberculose pulmonaire au cours de la première année de la pandémie de COVID-19

Résumé

Contexte: La pandémie de COVID-19 a mis à rude épreuve la vie humaine et les systèmes de soins de santé, mais on sait peu de choses sur son impact sur les patients atteints de tuberculose.

Objectifs: Évaluer l’impact de la pandémie de COVID-19 sur le diagnostic, le traitement et les résultats des patients atteints de tuberculose pulmonaire (TBP), en utilisant les définitions de l’OMS.


Résultats: Malgré une diminution non significative de 22 % des notifications annuelles de cas de tuberculose pulmonaire (p = 0,317), le nombre de tests de dépistage de la tuberculose effectués (p = 0,001) et de patients atteints de tuberculose pulmonaire évalués (p = 0,001) a considérablement diminué pendant l’année pandémique par rapport aux trois années précédentes. La proportion de patients présentant des niveaux élevés (3/4+) de bacilles acido-alcoolo-résistants dans les expectorations (p = 0,001), de rechute tuberculeuse (p = 0,022) et d’échec thérapeutique (p = 0,018) a augmenté de manière significative. Le retard médian du traitement de 64,5 jours détecté en 2017-2019 a considérablement augmenté pour atteindre 113,5 jours en 2020 (p = 0,001), principalement en raison de la réticence des patients à se rendre dans un établissement de santé.

Conclusion: Au-delà des problèmes de détection des cas, la présente étude montre une détérioration notable de plusieurs indicateurs liés à la gravité, à la contagiosité et aux mauvais résultats de la tuberculose, que les programmes de lutte avaient déjà supprimés depuis des décennies.
نتائج التشخيص والعلاج لمرضى السل الرئوي في السنة الأولى من جائحة كوفيد-19

يوسف باكويدجيلازي، هلال إرميس، زينب كازجان، باريس أونلو، يسار بايندير، غازي جلباس، إلفين تانبرفردي، إيميلك جولدوجان

الخلاصة

الخلفية: نسب جائحة كوفيد-19 في ضغط كبير على حياة البشر ونظم الرعاية الصحية، إلا أننا لا نعرف إلا القليل عن تأثيره على مرضى السل.

الأهداف: هدفت هذه الدراسة إلى تقييم أثر جائحة كوفيد-19 على تشخيص السل الرئوي وعلاجه ونتائج المعالجة للمرضى، باستخدام تعرفات منتظمة الصحة العالمية.


النتائج: على الرغم من الانخفاض غير الكبير بنسبة 22% في العدد السنوي للإخطارات بحالات الإصابة بالسل الرئوي (القيمة الاحتمالية = 0.317)، فإن عدد اختبارات السل الرئوي الذين أجريت (القيمة الاحتمالية = 0.001) وعدد مرضى السل الرئوي الذين أجريت (القيمة الاحتمالية = 0.001) قد انخفض تحت ضغط كوفيد-19 خلال السنة الأولى من الجائحة مقارنةً بالسنوات الثلاث السابقة. وحدث ذلك زيادة كبيرة في نسبة المرضى الذين لديهم تشتت عالٍ بالعصبونات، وخصوصًا في عينات البلغم (4/3) (القيمة الاحتمالية = 0.001)، وبسبب الإكتساح السل (القيمة الاحتمالية = 0.022) وفشل العلاج (القيمة الاحتمالية = 0.018) وزيادة كبيرة في نسب الاحترام غير كافٍ للأعراض والعلاج، التي كانت 64.5% في الفترة من 2019 إلى 2017، إذ أن نسبة تصل إلى 113.5 برومو في عام 2020 (القيمة الاحتمالية = 0.001)، ويرجع ذلك في المقام الأول إلى إنجاز لوح FedEx من مهتمين بمرض السل الرئوي.

الاستنتاجات: بالإضافة إلى المتغيرات المتعلقة باكتشاف الحالات هذه الدراسة تدemonstrate ملحوقًا في العديد من المؤشرات المتعلقة بصدمة مرض السل والعدوى به، وتطبيق النتائج بين المصابين به، وذلك بعد أن تنبهت ببرامج المكافحة في قمع تلك المؤشرات لعقود من الزمن.

References


Mental health and driving behaviour of students and alumni of a university in the United Arab Emirates: a cross-sectional study

Gabriel Andrade, Dalia Bedawi and Ibrahim Bani

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Abstract

Background: The United Arab Emirates has set the goal to reduce traffic-related deaths to 3 per 100 000 people by 2021. To do this, authorities must assess the factors related to risky driving behaviour.

Aims: To verify if there are any correlations between driving behaviour and certain variables, including years of driving experience, daily hours of sleep, general markers of mental health, and symptoms of attention deficit hyperactivity disorder (ADHD).

Methods: Two hundred and seventy-five participants responded to a survey made up of the Manchester driver behaviour questionnaire, the general health questionnaire, the adult ADHD self-report scale, and 2 additional questions. Spearman’s coefficient was calculated for correlations between these variables, at statistical significance level P < 0.05.

Results: Years of driving experience and hours of sleep had no correlations with driving performance. Markers of general mental health had a weak correlation with risky driving behaviour, and symptoms of ADHD had moderate correlation with risky driving behaviour.

Conclusion: Policymakers and public health officials should screen for ADHD during driver licensing examination.

Keywords: driving, mental health, United Arab Emirates, traffic safety, ADHD, students, university

Citation: Andrade G; Bedawi D; Bani I. Mental health and driving behaviour of students and alumni of a university in the United Arab Emirates: a cross-sectional study. East Mediterr Health J. 2022;28(9):690–694. https://doi.org/10.26719/emhj.22.059

Introduction

Over the last few years, the United Arab Emirates has been making significant progress in road traffic injury prevention. Following the 725 traffic-related deaths and 6681 injuries in 2016, the Government of the United Arab Emirates made a deep commitment as part of its national agenda to reduce traffic-related deaths to 3 per 100 000 people by 2021 (1).

Research has provided much relevant information on this topic. Previous studies have suggested that mental health is associated with improved driving performance, and consequently, with increased traffic safety (2). However, it is not known which aspects of mental health are associated with driving performance. Since mental health is a broad category, policy-makers must focus on particular mental health markers and their relationship with particular dimensions of driving behaviour. This study addressed this question, and its correlations in the United Arab Emirates, because only few studies conducted on driving performance have paid attention to their relationship with mental health.

In this study we investigated whether 5 dimensions of mental health (social dysfunction, anxiety, loss of confidence, hours of sleep, attention deficit/hyperactivity) had any correlation with dangerous driving behaviour in the United Arab Emirates.

Methods

This was a cross-sectional study that measured age, sex, hours of sleep, years of driving experience, mental health, driving behaviour and levels of attention deficit hyperactivity disorder (ADHD).

An integrated questionnaire of 27 items was approved by the research ethics committee of Ajman University, # M-H-F-31-May. The questionnaire was sent (via email) to students and alumni of the university who live permanently in the United Arab Emirates. Participants were recruited on the basis of convenient non-probability sampling, considering availability and willingness to answer questionnaires during the COVID-19 lockdowns.

Participants were informed about the nature of the study and that they could refuse to answer questions at any time. They were requested to sign consent and instructed to carefully complete all questions in the survey to avoid any potential loss of data. The survey was designed using software that would not allow the participant to go on to the next question without answering the previous one. This method ensured that the returned questionnaires would not have any missing data. Consequently, the level of missing data was 0. We sent out 350 questionnaires; 275 were returned, giving a response rate of 79%.

The survey gathered demographic information (age, sex). One question asked participants how many hours
of sleep they got daily. Another question asked how many years of driving experience they had. The rest of the questions were made up of 3 questionnaires combined.

The first set of questions were taken from a 12-item version of the general health questionnaire (GHQ-12), which assesses 3 non-psychotic dimensions of mental health obtained from factor loading analyses: social dysfunction, anxiety and loss of confidence (3). Social dysfunction assesses individuals’ capacity to properly function in society (e.g. Have you recently felt capable of making decisions?); anxiety assesses situations of stress and/or depression (e.g. Have you recently felt unhappy and depressed?); loss of confidence assesses situations in which the respondent does not feel they are functioning for optimal performance (e.g. Have you recently felt losing confidence?).

Participants were asked to rate how frequently they experienced particular situations expressed in the items. Responses were given on a Likert scale, from 0 (not at all) to 3 (more than usually), with higher scores indicating worse mental health.

The second set of questions were taken from a 9-item version of the Manchester driver behaviour questionnaire (Mini-DBQ). On the basis of previous factor loading analyses, the Mini-DBQ is structured around 3 dimensions: violations (e.g. I drive especially close or “flashing” the car in front as a signal for that driver to go faster), errors (e.g. I fail to notice, because lost in thought or distracted, someone waiting at a zebra crossing, or that a pelican crossing light has just turned red), and lapses (e.g. I forget where I left my car in a multi-level car park).

Participants responded by identifying how frequently they engaged in each of the habits expressed in the items, on a Likert scale from 0 (never) to 5 (nearly all the time), with higher scores indicating poorer driving performance. The Mini-DBQ has good reliability, with a Cronbach alpha = 0.9. It has been properly validated (4).

The third set of questions were taken from a 6-item version of the World Health Organization’s Adult ADHD self-report scale (ASRS), which assesses symptoms of ADHD among adults. Participants were asked about the frequency of particular situations (e.g. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?), and they respond on the basis of a Likert scale (1 = never; 5 = very often), with higher scores indicating greater levels of ADHD. The ASRS is considered to have good reliability (5), and it has been validated across various settings (6).

Given that most variables included an interval (rather than a ratio) level of measurement, Spearman’s test (instead of Pearson’s) was selected to establish correlation, in line with the recommendation of most statisticians for interval levels of measurement. Coefficients were calculated for correlations between driving behaviour (violations, lapses, errors) and general mental health (social dysfunction, anxiety, loss of confidence), years of driving experience and daily hours of sleep.

Statistical significance was $P < 0.05$.

### Results

We surveyed 275 participants: 64 males and 211 females. Mean age was 27.3 (standard deviation 7.24) years.

Spearman’s coefficients for correlations between dimensions of driving behaviour (violations, errors and lapses) and symptoms of ADHD, years of driving experience and hours of sleep, are presented in Table 1. Results show that ASRS had a weak but statistically significant correlation with violations ($r = 0.31; P < 0.01$), a moderate and statistically significant correlation with errors ($r = 0.49; P < 0.01$) and a moderate and statistically significant correlation with lapses ($r = 0.47; P < 0.01$). Neither years of driving experience nor hours of sleep had any statistically significant correlation with any dimension of driving behaviour.

Spearman’s coefficients for correlations between dimensions of driving behaviour (violations, errors and lapses) and dimensions of general mental health (social dysfunction, anxiety, loss of confidence) are presented in Table 2.

Social dysfunction had a very weak but statistically significant correlation with violations ($r = 0.15; P < 0.05$) but no statistically significant correlation with errors or lapses. Anxiety had a weak but statistically significant correlation with violations ($r = 0.25; P < 0.01$), with errors ($r = 0.27, P < 0.01$) and with lapses ($r = 0.29; P < 0.01$). Loss of confidence had a weak but statistically significant correlation with violations ($r = 0.21; P < 0.01$), with errors ($r = 0.27; P < 0.01$) and with lapses ($r = 0.25; P < 0.01$).

### Discussion

We found that years of driving experience had no correlation with any of the assessed dimensions of driver behaviour. This would imply that road safety does not improve with greater experience, and most likely, driver behaviour remains constant. Similar findings have been reported in previous research. For example, one large study found “no evidence of a group of drivers whose aberrant behaviour decreased over time” (7).

More surprisingly, our study reveals that hours of sleep had no correlation with any of the dimensions of driving behaviour. This finding runs counter to previous research, in which sleep deprivation was related to poor

### Table 1 Correlation between the driving behaviour questionnaire and physical factors in a survey of 275 permanent residents of the United Arab Emirates

<table>
<thead>
<tr>
<th>Factor</th>
<th>Spearman’s coefficient (df = 273)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Violations</td>
</tr>
<tr>
<td>ASRS</td>
<td>0.31**</td>
</tr>
<tr>
<td>Years of driving experience</td>
<td>0.002</td>
</tr>
<tr>
<td>Hours of sleep</td>
<td>0.002</td>
</tr>
</tbody>
</table>

ASRS = attention deficit hyperactivity disorder self-report; DBQ= driving behaviour questionnaire

**$P < 0.01$.**

- **asrs**
- **37x12**
- **Book 28-09.indb**
- **691**
- **r**
- **0.50**
- **09/10/2022 11:07 AM**
- **691**
- **r**
- **Errors**
Some caution in considering the relationship between anxiety and driving performance must be considered. In this study, the relationship between both variables was negative and monotonic (i.e. the value of one variable increased as the value of the other decreased). But research suggests that the relationship between anxiety and performance (not only in driving, but any task) may also be non-monotonic (13). Too high levels of anxiety are detrimental to optimal performance, but at the other extreme, too low levels of anxiety may also be detrimental to performance. For example, excessive relaxation may cause reduced caution in drivers (and consequently, increased errors and lapses) since drivers do not feel the stress necessary to concentrate on the task.

Interestingly, symptoms of ADHD did have a much stronger correlation with dimensions of driving behaviour. The correlation with violations was only weak. This is very much expected as violations in driving behaviour relate to deliberate attempts to break traffic rules, and in this regard attention deficit and hyperactivity do not have a strong impact. However, symptoms of attention deficit and hyperactivity do have a moderate positive correlation on the propensity to commit errors and lapses while driving.

Prior research has established that, indeed, symptoms of ADHD are a considerable risk in driving performance. One study concluded that “drivers (with ADHD symptoms) rate themselves as more angry, risky and unsafe drivers and reported experiencing more losses of concentration and vehicular control” (14). Our results replicate such findings to the extent that there was a moderate correlation between self-report of ADHD symptoms and self-report of risky driving habits. One plausible theoretical explanation for these results is that, inasmuch as driving in increasingly complex urban settings requires sustained attention and concentration, individuals with deficits in those particular mental skills would be more likely to engage in poorer driving performance.

The impulsivity dimension of ADHD may also have a significant detrimental effect on driving performance. Previous research has established that impulsivity increases dangerous driving behaviour (15). This is expected, given that, in complex urban settings, driving decisions must be taken with confidence, yet at the same time assessing the risks involved. Overly impulsive behaviour impairs this capacity, to the extent that drivers may attempt particular manoeuvres without the necessary deliberation for their decisions.

### Study limitations

This study had some limitations. Sampling was limited to students and alumni of Ajman University, and consequently, the results can only be taken as an initial assessment of the driving behaviour in the United Arab Emirates, but not as a robust indicator. Further studies with broader segments of the United Arab Emirates population would provide more robust conclusions. Availability for recruitment amongst participants was easier with women, and therefore sampling included significantly more women than men. This needs to
be considered a limitation, and further studies with a more balanced sample in the sex variable could provide stronger conclusions.

Another limitation of the study was its cross-sectional nature. Data were collected at a particular moment, but in order to obtain more robust conclusions, more advanced designs (e.g. cohort and case-control studies) should be done. For practical timing purposes in the administration of the surveys, a shortened version of the general health questionnaire was used. In future studies, a comprehensive assessment of mental health should be included to thoroughly examine the dimensions of mental health and their possible relationship to driving performance. Perhaps most importantly, this study relied on self-reporting of driving behaviours. This is an important limitation, given that a more robust assessment of driving behaviour relies on independent observation.

While acknowledging these limitations, some tentative conclusions and recommendations can be made. Based on the study results, policymakers and public health officials in the United Arab Emirates should support programmes aimed at improving general mental health in the population because such programmes can improve driving performance.

The results show that symptoms of ADHD had a moderate correlation with risky driving behaviour, traffic safety policymakers in the United Arab Emirates should implement a twofold policy. First, greater awareness of the risks of ADHD is needed. Second, screening procedures during drivers’ licensing examination should begin to consider assessment of attention deficit and hyperactivity.

Funding: None

Competing interests: None declared.

Santé mentale et comportement au volant des étudiants actuels et anciens d’une université aux Émirats arabes unis : étude transversale

Résumé
Contexte : Les Émirats arabes unis ont fixé l’objectif de réduire le nombre de décès liés à la circulation à trois pour 100 000 habitants à l’horizon 2021. Pour ce faire, les autorités doivent évaluer les facteurs liés aux comportements de conduite à risque.

Objectifs : Vérifier s’il existe des corrélations entre le comportement au volant et certaines variables, dont les années d’expérience de conduite, les heures de sommeil quotidiennes, les marqueurs généraux de la santé mentale et les symptômes du trouble déficitaire de l’attention avec hyperactivité (TDAH).

Méthodes : Deux cent soixante-quinze participants ont répondu à une enquête composée du Manchester Driver Behaviour Questionnaire, du General Health Questionnaire, de l’Adult ADHD Self-Report Scale et de deux questions supplémentaires. Le coefficient de Spearman a été calculé pour les corrélations entre ces variables, au niveau de signification statistique p < 0.05.


Conclusion : Les décideurs et les responsables de la santé publique devraient dépister le TDAH lors de l’examen du permis de conduire.
References


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Risk assessment of road traffic accidents related to sleepiness during driving: a systematic review

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Abstract

Background: Injuries due to accidental crash are the 8th leading cause of death worldwide. Sleepiness results in disrupted neurological function and is a major risk factor for road traffic accidents.

Aims: This systematic review assessed the relationship between sleepiness during driving and road traffic accidents.

Methods: A systematic review was conducted using online databases such as Wiley Online Library, JSTOR, Medline, and PubMed. Full-text, English language articles published between May 2000 and November 2020 were retrieved. Road traffic accident was set as the outcome of interest and sleepiness during driving as the exposure. The review included studies containing adjusted risk estimates (95% confidence interval). Ten cross-sectional studies (N = 55,945), 5 case-control studies (N = 3821), and 2 cohort studies (N = 16,875) were included.

Results: Over 50% of the participants in the different studies experienced sleep deprivation ranging from 3.5% to 67.3%. Abe et al. reported the highest (58%) frequency of sleepiness during driving in their cross-sectional study in Japan, and Nabi et al. reported the lowest (1.1%) in their cohort study in France.

Conclusion: Sleepiness and sleep deprivation were related to road traffic accidents; and sleep deprivation was the main contributor to drowsiness while driving.

Keywords: road traffic accidents, sleepiness, driving, observational study, risk assessment

Introduction

Sleep is a dynamic process that affects the way our bodies function (1). Sleepiness can be defined as difficulty remaining awake even while carrying out activities (2). Sleep deprivation is defined as a state caused by inadequate quantity or quality of sleep, including voluntary or involuntary sleeplessness and circadian rhythm sleep disorders (3). Sleepiness results in disrupted brain functioning, such as reduced reaction time or decreased ability for decision-making. It is a major contributor to road traffic accidents, which often occur when a driver experiences drowsiness at the wheel, or due to sleep abnormalities, lack of sleep, alcohol consumption or medication (4). About 1.3 million deaths occur each year as a result of road traffic accidents globally, causing a 3% loss of the gross domestic product of most countries (5). The US National Highway Traffic Safety Administration has estimated that worldwide every year, about 100,000 road accidents are caused by drowsiness, accounting for > 1500 deaths and > 70,000 injuries (6).

In every country, road traffic accidents are a major public health problem and cause huge societal and financial burdens (7). Sleepiness causes disruption of neurological functions (8,9). Factors that contribute to the incidence of road traffic accidents range from continued driving even when feeling drowsy, having a physical condition, fewer sleeping hours, more working hours, and nutritional imbalances (10). Several studies during the last 20 years have suggested that sleepiness is among the main factors that cause road traffic accidents (11–15). Sleepiness while driving contributes to 3% to > 30% of all road traffic accidents globally (16–18), which may involve a variety of sleep conditions but also may be caused by sleep deprivation (19–20). More than 20% of the drivers feel a need to stop driving at least once due to sleepiness (21). A religious lifestyle was found to be negatively associated with the risk of road traffic accidents, as were younger drivers (22,23). This systematic review was designed for a better understanding of the relationship between sleepiness and risk of road traffic accidents.

Methods

Study protocol

This systematic review protocol was developed keeping in view the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines 2020, without execution of a meta-analysis. The PRISMA statement is a guideline developed by an international group of 29 methodologists and experienced researchers in 2005. It comprises 27 checklists and 4-phase flow diagram to ensure transparent reporting of a systematic review [24].

[References cited here]
**Search strategy**

The reviewer searched for articles published between January 2000 and December 2020 in Wiley Online Library, JSTOR, Medline and PubMed databases. The keywords used were: road traffic accidents, sleepiness while driving, and observational study. PRISMA information flow during the phases of this systematic review is presented in Figure 1.

**Search eligibility criteria**

The reviewer included observational studies with adjusted risk estimates and outcome measure of road traffic accidents. Due to expected difficulties of quantification, excluded studies were experimental studies, case series without comparison groups and case reports.

**Data extraction**

The potentially relevant articles were screened by title and abstract and full text of the articles were retrieved from databases. Final eligibility was assessed independently keeping in view the PRISMA guideline checklist 2020, and the reviewer extracted the following details from the included studies: study design (cross-sectional, case-control and cohort), number of road accidents, frequency of sleepiness while driving, and the adjusted risk estimates of accidents resulting from sleepiness. For quality assessment purposes, the Newcastle Ottawa Scale was used with a total score for quality ranging from 0 to 9 (25). Participants’ characteristics such as age, gender, and sleep disorders and lack of sleep due to workload/other causes were extracted. The overall frequency of sleepiness during driving was calculated using adjusted risk estimates.

**Study selection**

A total of 5651 articles were identified from Wiley Online Library, JSTOR, Medline and PubMed databases, where sleepiness while driving was among the causes of road traffic accidents. A total of 1132 duplicates (20.03%) were removed including 717 (63.33%) from JSTOR, and 415 from Medline and PubMed (36.66%). Out of the 4519 remaining articles (79.96%), 4283 were found to be unrelated (94.77%) and were excluded. The remaining 236 articles (5.22%) were fully reviewed and this led to a total of 17 observational studies (7.20%) that qualified for the systematic review. The 17 eligible studies consisted of a total of 76,641 participants worldwide (Table 1). There were 10 cross-sectional studies (55,945 participants; 72.99%); 5 case-control studies (3821 participants; 4.98%), and 2 cohort studies (16,875 participants; 22.01%). Sixteen studies included both sexes while 2 Saudi Arabian studies were based on men due to the previous ban on female drivers. The ages of participants were < 30 years in 3 studies, 30–50 years in 8 studies, and > 50 years in 6 studies.

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**Figure 1 PRISMA flow data**

<table>
<thead>
<tr>
<th>Identification of studies via databases and registers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
</tr>
<tr>
<td>Records identified from database searches: (n = 5851)</td>
</tr>
<tr>
<td>No. of records after duplicates removed (n = 4519)</td>
</tr>
<tr>
<td>Full-text articles assessed for eligibility (n = 236)</td>
</tr>
<tr>
<td>Included</td>
</tr>
<tr>
<td>Studies included in systematic review (n = 17)</td>
</tr>
<tr>
<td>Duplicates records removed (n = 1132)</td>
</tr>
<tr>
<td>Records excluded after title and abstract screening (n = 4283)</td>
</tr>
<tr>
<td>Reports excluded:</td>
</tr>
<tr>
<td>No English full-text articles (n = 12)</td>
</tr>
<tr>
<td>No observational studies (n = 15)</td>
</tr>
<tr>
<td>No road traffic accidents (n = 34)</td>
</tr>
<tr>
<td>No estimation measures (n = 62)</td>
</tr>
<tr>
<td>No measure sleepiness during driving (n = 94)</td>
</tr>
<tr>
<td>Duplicate studies (n = 2)</td>
</tr>
</tbody>
</table>
### Results

Results from all 17 studies showed that sleepiness and sleep deprivation were major contributors to road traffic accidents. The high frequency of sleepiness reported while driving, with significant odd ratios, makes this a significant risk factor for road traffic accidents. In these studies, >50% (3.5–67.3%) of the participants agreed that they experienced sleep deprivation. Abe et al. reported the highest (58%) frequency of sleepiness during driving in their cross-sectional study (OR 12.90) in Japan, and Nabi et al. reported the lowest (1.1%) in a cohort study in France (OR 2.90) (Figure 2).

Liu et al. concluded that a significant decrease in injuries related to road traffic accidents can be attained if fewer people drive when they are sleepy (26). Gottlieb et al. associated sleep apnoea with a 123% greater risk of road traffic accidents than apnoea unrelated to sleep (27). This shows that sleeping for 6 hours daily is connected to a 33% greater risk of accidents than sleeping for 7 or 8 hours per night. Comparatively, Cummings et al. reported such an accident risk to be 39.5% in a case–control study in the United States of America [14]. Lloberes et al. found in a cross-sectional study in Spain that 35.3% of drivers fell asleep while driving (28). Pizza et al. reported 1.9 times greater risk of accidents in individuals with poor sleep quality making them to fall asleep while driving (29).

AlShareef et al. in a population-based analysis in Saudi Arabia showed the correlation between sleep and sleepiness during driving and reported that the strongest sleep predictor while driving was being a male driver (30). Most drivers in this study were men (86.5%) as women have only been allowed to drive in Saudi Arabia since June 2018. Sagaspe et al. found that 28% of drivers had at least 1 incident of uncontrollable sleepiness during driving, and about 5% of drivers had an accident or near miss due to sleepiness (31). Stutts et al. reported that almost 5% of the drivers in road traffic accidents admitted consuming alcohol before causing a crash. However, this study highlighted potential bias because the data depended on self-reports and the drivers could have blamed longer work hours and poor sleep habits for their accidents (32).

Limitations of this review include the possibility of selection bias because of the methods used or participants involved. There may have been a residual confounding effect because studies were based on observational

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**Table 1: Estimates of risk associated with sleepiness during driving**

<table>
<thead>
<tr>
<th>Country</th>
<th>Sample size</th>
<th>Men</th>
<th>Women</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>2462 (21)</td>
<td>86.5%</td>
<td>13.5%</td>
<td>1.1 (NR)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1219 (773)</td>
<td>86.0%</td>
<td>14.0%</td>
<td>1.90 (1.38–2.60)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>399 (114)</td>
<td>77.0%</td>
<td>23.0%</td>
<td>1.90 (0.85–1.67)</td>
</tr>
<tr>
<td>USA</td>
<td>3501 (222)</td>
<td>86.0%</td>
<td>14.0%</td>
<td>1.79 (1.07–2.99)</td>
</tr>
<tr>
<td>Spain</td>
<td>3568 (644)</td>
<td>86.0%</td>
<td>14.0%</td>
<td>2.90 (1.30–6.32)</td>
</tr>
<tr>
<td>Greece</td>
<td>1216 (121)</td>
<td>86.0%</td>
<td>14.0%</td>
<td>3.52 (1.15–10.29)</td>
</tr>
<tr>
<td>China</td>
<td>824 (480)</td>
<td>86.0%</td>
<td>14.0%</td>
<td>3.52 (1.15–10.29)</td>
</tr>
<tr>
<td>USA</td>
<td>1036 (550)</td>
<td>86.0%</td>
<td>14.0%</td>
<td>2.90 (1.30–6.32)</td>
</tr>
<tr>
<td>Spain</td>
<td>3201 (222)</td>
<td>86.0%</td>
<td>14.0%</td>
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</tr>
<tr>
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<td>86.0%</td>
<td>14.0%</td>
<td>3.52 (1.15–10.29)</td>
</tr>
</tbody>
</table>
methods. Other possible risk factors for accidents, age, body mass index, medical conditions, alcohol and drug abuse, and sleep duration were not calculated in terms of ORs (adjusted) in all of the studies used for this review.

**Conclusion**

Driver fatigue or drowsiness is a road transport safety hazard. The risk of road traffic accidents increases proportionately when drivers experience sleepiness. Among the frequent explanations for sleepiness during driving were sleep disorders such as sleep apnoea and some behavioural factors, most importantly sleep deprivation. The risk factors for sleep deprivation were found to be driving at night, not getting enough sleep, and working or staying awake for long periods. Other factors were young age, male sex, office worker, smoker, shorter sleep duration, poor subjective sleep quality, moderate or severe excessive daytime sleepiness, and alcoholism. A minimum of 6 hours of sleep every day could significantly decrease the number of road traffic accidents.

To reduce the incidence of accidents related to sleepiness during driving, it is important to conduct safety checks before driving, monitor sleeping patterns, record and track driving hours, and conduct psychological assessments and behavioural training. The results show that road traffic accidents are consistently associated with sleepiness during driving. Therefore, awareness campaigns and strengthening of road safety programmes should be implemented to reduce the increasing number of road traffic accidents related to sleepiness during driving. Further studies will be required for a more in-depth analysis of this subject.

**Funding:** None

**Competing interests:** None declared.

Tiquiemos a la mitad de los accidentes de tráfico por la somnolencia en el volante: un estudio sistemático

**Resumen**

**Contexto:** Los traumatismos a causa de un accidente son la octava causa de muerte en el mundo. La somnolencia entraña una perturbación de las funciones neurológicas y constituye un factor de riesgo importante de accidentes de circulación.

**Objetivos:** La presente revisión sistemática ha evaluado la relación entre la somnolencia en el volante y las consecuencias de los accidentes de circulación.

**Métodos:** Se realizó una revisión sistemática utilizando bases de datos en línea como Wiley Online Library, JSTOR, Medline y PubMed. Se extrajo 55 945 artículos completos, en lengua inglesa, publicados entre mayo de 2000 y noviembre de 2020. Los accidentes de circulación fueron considerados como el resultado de interés, y la somnolencia en el volante como la exposición. La revisión comprendió 10 estudios transversales, 5 estudios caso-control y 2 estudios de cohorte. Los siguientes estudios han sido incluidos.

**Resultados:** Más de 50% de los participantes en diferentes estudios han experimentado privación de sueño de entre 3,5 y 67,3%. En su estudio transversal en Japón, Abe et al. reportaron la prevalencia de somnolencia más alta (58%) y Nabi et al. la más baja (1,1%) en su estudio de cohorte en Francia.

**Conclusión:** La somnolencia y la privación de sueño se han asociado con los accidentes de circulación, y la privación de sueño era el principal factor de somnolencia en el volante.
The results of the study showed a variation in the rates of sleep deprivation among different groups of drivers. In Japan, Abe et al. (2018) reported that 3.5% of the drivers experienced sleep deprivation, with a range of 3.5% to 67.3%. In contrast, Preidt (2018) found that 58% of the drivers were sleep-deprived in one study.

The conclusion is that sleep deprivation is a significant factor in accidents, and it is important to address this issue to reduce the number of accidents due to fatigue driving.


Introduction

There has been an increase in access to sexual and reproductive health (SRH) services, including contraceptives and voluntary counselling and testing for sexually transmitted infections, in the Eastern Mediterranean Region (EMR) (1). Improvements have been reported in several countries such as Afghanistan, Lebanon, Islamic Republic of Iran, Jordan, Libya, Morocco, Somalia, and Sudan (1). However, countries need to document and share lessons and experiences from these improvements to help shape the SRH research agenda in the region, and increase adoption, sustainability and impact of SRH initiatives by increasing the health and well-being of populations.

In March 2021, the WHO Regional Office for the Eastern Mediterranean convened a virtual workshop on sharing best practices in SRH in the EMR. The workshop aimed to facilitate sharing of innovative methodologies, tools and approaches used to improve SRH services by countries in the region and discuss how to scale-up and sustain the outstanding initiatives. The workshop included 72 participants from 8 countries and territories in EMR and WHO.

Summary of discussions

Effective knowledge-sharing is a good strategy for providing essential evidence for policies and interventions and encouraging adoption of best practices. Based on mathematical modelling conducted in Afghanistan, Iraq, Morocco, Pakistan, Somalia, and Sudan, the benefits of continuing to provide SRH services at health facilities and in the community far outweigh the risks of infections during a pandemic such as the COVID-19. However, the magnitude of the benefits and the number of lives saved will depend on the effectiveness of interventions included in the model, baseline coverage of services, level of coverage disruption, number and impact of the mitigation measures, household size, and age structure of the population.

During the ongoing pandemic, Morocco and Pakistan have been using the digital platforms for training, data collection, counselling, information sharing, and other SRH services. Lebanon, with guidance from the Ministry of Public Health, continues to involve professional, non-governmental and community-based organizations in the provision of SRH services.

Participants agreed on the need to continue and advance the use of information technology and digital platforms for training, counselling, provision of SRH information, and to secure additional resources for services. They noted the importance of actively involving non-governmental organizations in service provision during emergencies and their catalytic role in maintaining essential SRH services. To make such support effective, coordination and clear guidance are essential, as they would help prevent duplication and overlapping of services and ensure the convergence and standardization of services based on the relevant national, regional, and global guidelines (2).

Recommendations

• WHO Member States are to identify SRH-related best practices for documentation and publication, organize dissemination forums for SRH-related best practices, and scale-up and sustain innovative initiatives by institutionalizing them.

• WHO will provide technical and financial support for advocacy with the relevant authorities for identification, documentation, dissemination, adoption, and scale-up of innovative initiatives.

References


This is a summary of the report of a workshop for sharing best practices in sexual and reproductive health in the Eastern Mediterranean Region, available at: https://applications.emro.who.int/docs/WHOEMWRH111E-eng.pdf.
Eastern Mediterranean Health Journal

It is the official health journal published by the Eastern Mediterranean Regional Office of the World Health Organization. It is a forum for the presentation and promotion of new policies and initiatives in public health and health services; and for the exchange of ideas, concepts, epidemiological data, research findings and other information, with special reference to the Eastern Mediterranean Region. It addresses all members of the health profession, medical and other health educational institutes, interested NGOs, WHO Collaborating Centres and individuals within and outside the Region.

La Revue de Santé de la Méditerranée Orientale

EST une revue de santé officielle publiée par le Bureau régional de l’Organisation mondiale de la Santé pour la Méditerranée orientale. Elle offre une tribune pour la présentation et la promotion de nouvelles politiques et initiatives dans le domaine de la santé publique et des services de santé ainsi qu’à l’échange d’idées, de concepts, de données épidémiologiques, de résultats de recherches et d’autres informations, se rapportant plus particulièrement à la Région de la Méditerranée orientale. Elle s’adresse à tous les professionnels de la santé, aux membres des instituts médicaux et autres instituts de formation médico-sanitaire, aux ONG, Centres collaborateurs de l’OMS et personnels concernés au sein et hors de la Région.

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Women always function as the gatekeepers to the formal/informal health sector. Despite global and regional progress in advancing women’s health, the COVID-19 pandemic forced governments and development partners in the EMR and beyond to re-set their priorities. A renewed commitment to women’s health is inescapable to expedite progress towards the SDGs in an integrated manner.

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