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Lessons learned from conducting a serological survey for Japanese encephalitis after detecting the first cases in New South Wales, Australia, 2022

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Problem: The first known locally acquired cases of Japanese encephalitis virus (JEV) infection in New South Wales (NSW), Australia, were identified in March 2022. NSW Health (the state entity for health care in NSW), with its partner agencies, conducted a serological survey to identify the prevalence of JEV antibody responses in high-risk communities in NSW.

Context: JEV infection is rare in Australia; therefore, vaccination is not recommended for the majority of Australians. Less than 1% of JEV infections in humans result in clinical disease.

Action: We conducted a cross-sectional serological survey of all age groups in five townships within NSW between June and July 2022. A summary report of the serosurvey methods and results was previously published by NSW Health. In this report, we describe the operations and lessons learned from rapidly gathering serological survey evidence to inform the public health management of JEV infection in NSW, within a country with well established health infrastructure.

Lessons learned: Resource limitations had to be addressed pragmatically during this field epidemiology research. Community participation varied between towns. The knowledge of local public health staff was important for identifying appropriate locations for clinics and community engagement activities. The consistency of data collection needs to be emphasized when multiple teams are involved. Data quality assurance issues were limited during this survey, owing to ease of communication in the field with the coordinating research team. When possible, allowing additional time for community engagement and staff orientation would be beneficial before implementing a similar survey. Further consideration of reporting serology results during the study design stage might have prevented the need for manual processing upon study completion.

Discussion: This serological survey highlights that a well trained and coordinated public health workforce can provide important, timely evidence when faced with an emerging public health issue.

PROBLEM

Japanese encephalitis virus (JEV) was detected for the first time in New South Wales (NSW), Australia, in February 2022.[1] Only five human clinical cases of Japanese encephalitis had previously been reported in Australia, and this was the first known incursion of JEV south of the Cape York Peninsula.[2] By June 2022, NSW had recorded 13 confirmed cases of Japanese encephalitis, including two deaths.[1] Because there were few symptomatic cases, a cross-sectional serological survey was undertaken to better understand the outbreak in identified high-risk areas and to inform public prevention measures. We describe the operations and lessons learned from rapidly gathering serological survey evidence to inform public health management of JEV infection in NSW.

CONTEXT

The introduction of JEV to NSW required a rapid and coordinated public health response to identify geographical

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risk areas and inform risk mitigation strategies. As JEV infection is rare in Australia, vaccination is not recommended for the majority of Australians. Prior to the outbreak, vaccination against Japanese encephalitis was recommended for travellers spending 1 month or more in endemic countries, people living and working in the outer islands of the Torres Strait, and laboratory workers who may be exposed to the virus.[3] Less than 1% of JEV infections in humans result in clinical disease.[4] As this was the first time that JEV was detected in NSW, there was little information that could be used to determine the extent of the outbreak or local risk factors for infection. Once Japanese encephalitis was declared a communicable disease incident of national significance,[5] NSW Health (the state entity for health care in NSW) rapidly implemented research and surveillance activities, including this serology study in high-risk areas.

ACTION

Implementing the serological survey

NSW Health, with its partner agencies, conducted a cross-sectional serological survey using convenience sampling in five high-risk towns in NSW (**Fig. 1**). The aim of the study was to estimate JEV antibody prevalence in communities that had limited evidence of transmission. Town selection was based on emerging data from animal and vector surveillance as well as consideration of logistics and resource limitations.

For logistical ease, the first three clinics for the survey were held in Balranald, Corowa and Temora at hospitals or associated health service locations. Clinics in Dubbo and Griffith were held in community centres. Additionally, mobile teams conducted outreach clinics in Dubbo (n = 8), Griffith (n = 13) and Temora (n = 2) at consenting business premises. The main outreach clinic in Griffith was conducted at a local shopping centre and required public liability insurance.

The first clinic was held in Corowa, as there had been local cases of Japanese encephalitis. Therefore, a significant level of interest in participating was anticipated due to high community awareness. The experience in Corowa informed subsequent clinics, allowing for refinement of clinic procedures and participant recruitment.

Serosurvey methods and results have been published elsewhere.[6] Briefly, the results indicated that 8.7% (80/917) of participants had evidence of JEV infection. Those aged ≥65 years showed the largest seropositivity proportion (30/192, 15.6%), and no participants aged <20 years were seropositive. Participants from all five townships had evidence of infection.

Participant recruitment and response

Staff from local public health units (PHUs) promoted participation in the study by engaging with local media (e.g. newspapers and radio stations), councils, general practitioners (GPs), local hospital staff, other government agencies (e.g. Local Land Services and police), businesses and community groups. Posters advertising the clinics were distributed to businesses. Targeted social media posts were also used.

There were 1048 participants who completed a questionnaire and provided a blood sample, giving an overall response rate across the five towns of 1.2%, ranging from 0.7% in Dubbo to 4.4% in Balranald (**Table 1**). Overall, participants tended to be older (**Fig. 2**, with more females (n = 623) than males (n = 425) participating.

Staffing and logistics

The study was coordinated by Health Protection NSW (an entity of NSW Health), and the intention was that local PHU staff would conduct the clinics. However, the availability of local PHU staff to conduct clinics at all five study sites was limited; therefore, 48 staff from across the NSW Health network were assembled into multiple teams to travel to the study sites. Two primary roles were assigned in each team: operational support and blood collection.

All team members participated in a short virtual briefing, during which they could ask questions of the coordinating study team. A briefing document was provided about clinical protocols, background on the study design and information links to JEV factsheets and frequently asked questions. Communication between Health Protection NSW and field staff was maintained through Microsoft Teams, and daily debriefings were arranged, as necessary.

Fig. 1. **Map of study sites, New South Wales, Australia, June and July 2022**

CRS: coordinate reference system.

Source: Map created by the authors based on information from the Australian Bureau of Statistics.[7]

Table 1. **Response rate for a community serology study of the prevalence of Japanese encephalitis antibody, by site, New South Wales, Australia, June and July 2022**

Location	No. (%) of participants	Population size[a] (% tested)
Balranald	64 (6.1)	1452 (4.4)
Corowa	163 (15.6)	7050 (2.3)
Dubbo	300 (28.6)	46 078 (0.7)
Griffith	362 (34.5)	28 126 (1.3)
Temora	159 (15.2)	6100 (2.6)
Total	1048 (100)	88 806 (1.2)

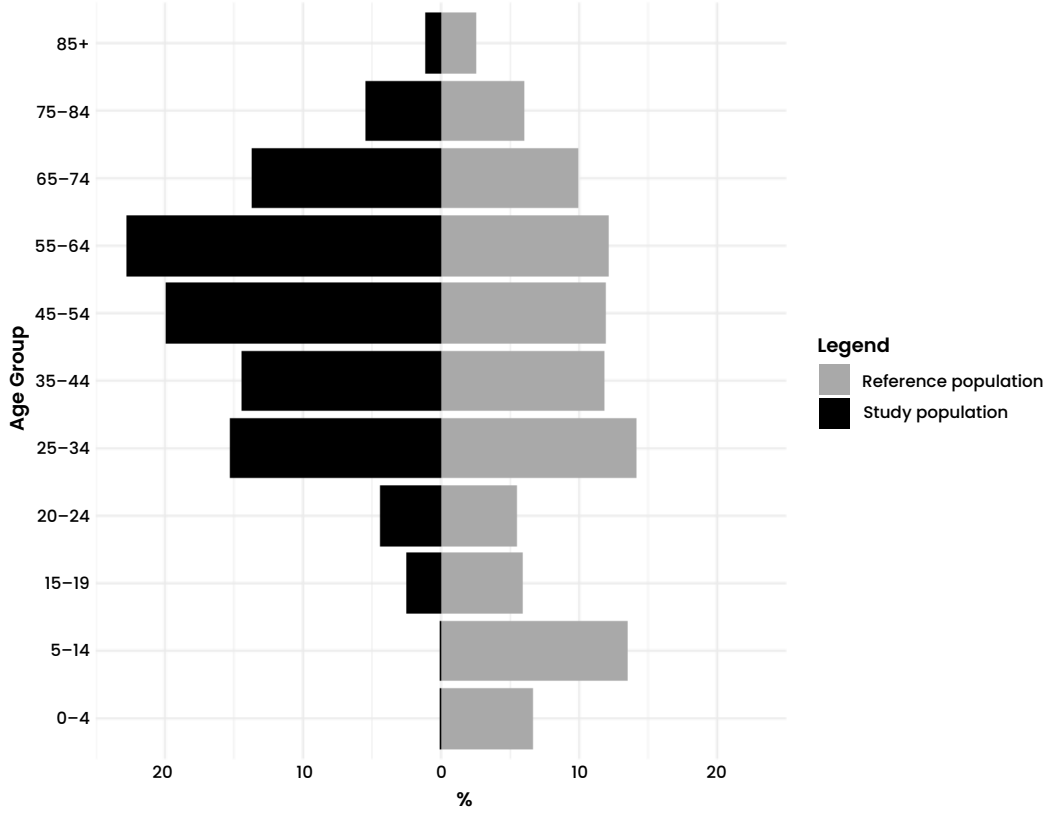
[a] The population is derived from Australian Bureau of Statistics census mesh blocks within a 20-kilometre radius of each town.[8]

Survey instruments and information technology

REDCap[9] software (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) was used to set up online consent forms and to collect demographic and exposure information from participants. Prior to their use, internal user testing was conducted to refine question phrasing and improve data quality. The survey was designed to be administered in the field using tablet devices, with support from operations staff as needed. Wi-Fi dongles were sent to field sites in case there were connectivity issues with fixed wireless internet connections.

In Griffith, where the largest number of workplace clinics took place, QR codes linking to the REDCap survey were printed, and many participants completed the surveys on personal smartphones.

Fig. 2. **Population pyramid of study population and reference population, 2022**



Source: Data derived from the Australian Bureau of Statistics census mesh blocks within a 20-km radius of each town.[8]

Laboratory testing and providing results

Laboratory samples were received via the usual transportation mechanisms. NSW has a strong laboratory infrastructure, and as a result, there were no challenges in ensuring blood samples were sent to and received by the reference laboratory. Results were provided to participants: those with positive results were notified by a phone call from a clinician; those with negative results were notified by SMS or e-mail.[10] Guidance was provided regarding the meaning of the results in relation to potential immunity and vaccination.[10] A copy of each participant's results was sent to their GP, if requested, although this was done manually and not through the usual laboratory process, as details of the GP were not captured by the pathology request forms during blood collection.

LESSONS LEARNED

Implementing the serological survey

The availability of staff, particularly those with phlebotomy skills, was a significant constraint that impacted how the clinics were run. The clinics needed to be organized sequentially, in stand-alone locations that were separate from other pathology services, and over relatively short, fixed periods (i.e. 3–5 days during 1 week at each location). Clinics were held only on weekdays, as staff travelled to the study sites on weekends, which may have limited representativeness at some sites. School holiday periods were avoided to improve the chances of capturing residents and those employed in the townships.

After the first three clinics, staff identified limited public foot traffic at some locations because they were outside the town centres. Therefore, the clinics in Griffith and Dubbo were held in town community centres, albeit still with limited passing foot traffic. Promotional activities were important drivers of participation rather than foot traffic.

Participant recruitment and response

The response rates in the smaller towns of Balranald, Corowa and Temora exceeded expectations and were higher than those in the larger towns of Dubbo and Griffith (**Table 1**). Many participants mentioned hearing about the clinic through traditional and social media, and

they were also aware of, or connected to, local cases. Residents in the larger towns of Dubbo and Griffith appeared less aware of and engaged with JEV as a public health issue. It is possible that social connectedness and perceived proximity to risk in the smaller towns influenced the motivation to participate.[11]

The flexibility to adapt the approach to reach community members and encourage participation was important. Team feedback suggested that phone calls from and visits by clinic staff were helpful to explain the study at outreach locations and, along with ensuring more extensive stakeholder engagement 1–2 weeks before the clinic, may have further increased participation.

Towns where workplace clinics were organized had a greater proportion of younger, working-age participants, demonstrating that the locations used for the clinics influenced participation. Additional strategies could have been used to encourage participation among children, young people and Aboriginal and Torres Strait Islander peoples, who were underrepresented in the survey compared with the source population. Future approaches could consider developing demographic participation targets to increase representativeness and generalizability.

Staffing and logistics

Having more time to prepare the clinics and to discuss site-specific considerations before opening might have been useful. However, time and travel constraints limited these opportunities at some sites. Nevertheless, the different teams reported that they worked well together to resolve issues as they arose, and they benefited from the support of local PHUs and the study coordination staff at Health Protection NSW.

The physical set-up in each clinic was different, and local support was variable. Detailed information about the space, equipment and access to consumables was not always available in advance, which made ordering clinic supplies challenging at times. It was also difficult to know in advance how many participants to plan for.

Organizing clinics primarily in one location versus at several workplace outreach locations presented a trade-off between increasing the numbers of participants and having enough staff, vehicles, information technology and blood collection equipment to support multiple locations. Ensuring that the teams at the clinics were using consistent practices became challenging across different locations, but it did result in greater numbers of participants. When the numbers of participants were high, staff had less time to clean data and support participants taking the survey. It was necessary to have a robust system to match a participant's survey with their blood sample, particularly when there were many participants, and time often had to be allocated for staff to clean data every few hours.

Survey instruments and information technology

Most participants successfully used the provided touchscreen tablets to complete the survey directly in the REDCap database, and clinic staff provided assistance as needed. A small number of surveys was completed on paper due to a lack of Wi-Fi access rather than to participant preference, with data subsequently entered by clinic staff. Refinements to the survey were made following the first clinic, and these might have been reduced by more extensive user testing before the clinics.

The use of QR codes to access the survey decreased the time spent at the clinic by participants, as they did not need to wait for tablet devices to become available. However, greater attention was required for those using the QR codes to manage data quality and ensure blood samples were correctly matched to survey records. Communication between team members in the field and at Health Protection NSW facilitated optimal data collection and quality assurance processes.

Laboratory testing and providing results

It was an oversight not to ask for details about GPs on the pathology request forms during blood collection, and this meant that laboratory results systems could not be used to send results to GPs. Instead, workarounds and manual collation of the results were required to send results individually.

DISCUSSION

In NSW, an agile response by skilled and experienced researchers working in partnership with local PHUs and communities enabled the successful implementation of the first community-based cross-sectional serological

survey for JEV infection, conducted with limited lead time. Maintaining a flexible approach enabled the team to overcome challenges as they arose. The lessons outlined in this report can be applied to other contexts and jurisdictions for similar operational research projects conducted during an outbreak.

There were substantial challenges to operationalizing the study ahead of the 2022–2023 summer season, as it was desirable to have results to inform public health response activities. The results were used to inform vaccination policy, public health prevention messaging and a communication campaign. In the context of an active outbreak response, our knowledge and understanding of JEV infection in south-eastern Australia was evolving. This posed challenges for designing the study.

A skilled public health workforce and collaborative health research approach resulted in timely evidence that could be used to inform the public health response to Japanese encephalitis in NSW. Leveraging stakeholder relationships with pathology services and with PHU directors and staff was key to rapidly conducting the study. Strong community engagement from local PHU staff was integral not only to respond to the local outbreak but also to build relationships to drive community participation in the serological survey. Central coordination worked well and field communications were maintained via digital technologies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This study was conducted under the Public Health Act (2010), with ethics approval received from the Sydney Children's Hospital Network Human Research Ethics Committee (approval number 2022/ETH01167) as part of a national semi-harmonized serosurveillance programme.

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Incorporating One Health into a front-line field epidemiological training programme in Papua New Guinea: lessons learned

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Problem: Over the past two decades, there has been increased recognition of the importance of a more holistic approach to preventing, predicting, detecting and responding to public health threats. The COVID-19 pandemic highlighted the need to bring together environmental, human and animal health sectors in addressing public health threats and the need to develop skilled front-line workers to act as surge capacity during health emergencies.

Context: Papua New Guinea is a high-risk country for emerging and re-emerging pathogens. The effects of climate change, human-mediated encroachment on natural habitats and destructive land-use practices have threatened ecosystems and caused environmental damage. The movement of goods, animals and people over porous borders provides opportunities for the introduction and spread of new pathogens.

Action: In recognition of the importance of multisectoral responses to health threats in Papua New Guinea, and the need to train front-line workers, we designed and piloted a 3-month One Health in-service training programme for front-line workers from across all sectors.

Lessons learned: The co-creation of curricula was essential in ensuring the relevance of the programme to front-line workers from multiple sectors, and the development of provincial training teams was key to ensuring mentorship and programme sustainability. Bringing front-line workers together in joint trainings facilitated the building of relationships, the understanding of the roles and responsibilities of the various sectors, the identification of sectoral focal points and the development of informal networks.

Discussion: Papua New Guinea's One Health front-line Field Epidemiology Training Program demonstrated that investment in cross-sectoral training programmes can be a catalyst for the implementation of One Health approaches on the front line.

PROBLEM

Over the past two decades, there has been increased recognition of the benefits of adopting a holistic approach to preventing, detecting and responding to public health threats, one that acknowledges the interconnection of human, animal and environmental health.[1–5] While human health, animal health and environmental sectors have effectively worked together to respond to specific health emergencies, such as natural disasters, zoonotic influenzas and the Zika outbreak,[4,6] in more recent years, the importance of developing ongoing intersectoral working relationships has become increasingly apparent. The COVID-19 pandemic highlighted the need for greater mutual understanding across sectors to facilitate the collaboration needed to develop a surge workforce with the capacity to respond to health emergencies. Joint capacity-building[2,7,8] has emerged as an important component of strategies to foster ongoing working relationships between sectors involved in mounting national responses to public health threats.

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Front-line field epidemiology training programmes (f-FETPs) are 3-month competency-based in-service training programmes that build capacity in disease surveillance, outbreak investigation, data analysis and interpretation, as well as communication to support evidence-based decision-making. Such programmes are typically offered as the first tier of a cascaded field epidemiology training model that includes a 9-month intermediate programme and a 2-year advanced programme.[9]

As Global Outbreak Alert and Response Network (GOARN) partners, the Field Epidemiology Training Program of Papua New Guinea (FETPNG) and the University of Newcastle, Australia, are committed to strengthening national and subnational capability to prevent, predict, detect and respond to health alerts. Recognizing the urgency of developing a multisectoral front-line workforce capable of addressing public health threats, FETPNG collaborated with the University of Newcastle to develop and pilot a One Health training programme tailored to the needs of front-line workers in Papua New Guinea.

CONTEXT

Located in the South Pacific, Papua New Guinea is intrinsically linked to Asia, the Pacific and the rest of the world by air, sea and a land border with Indonesia. The country has widespread trade and travel with its neighbours, with the movement of goods, people, plants and animals placing it at high risk for the introduction of high-impact diseases and disease emergence.[6,10]

Papua New Guinea faces serious health threats including vaccine-preventable disease outbreaks, zoonotic disease outbreaks, neglected tropical diseases, the expansion of vector-borne diseases, antimicrobial resistance, environmental contamination, transboundary animal disease incursions, natural disasters and food security, among others.[6,10] While specific One Health activities have been implemented, such as the adoption of a national approach for combating antimicrobial resistance,[10] there is a lack of training programmes that integrate One Health principles.

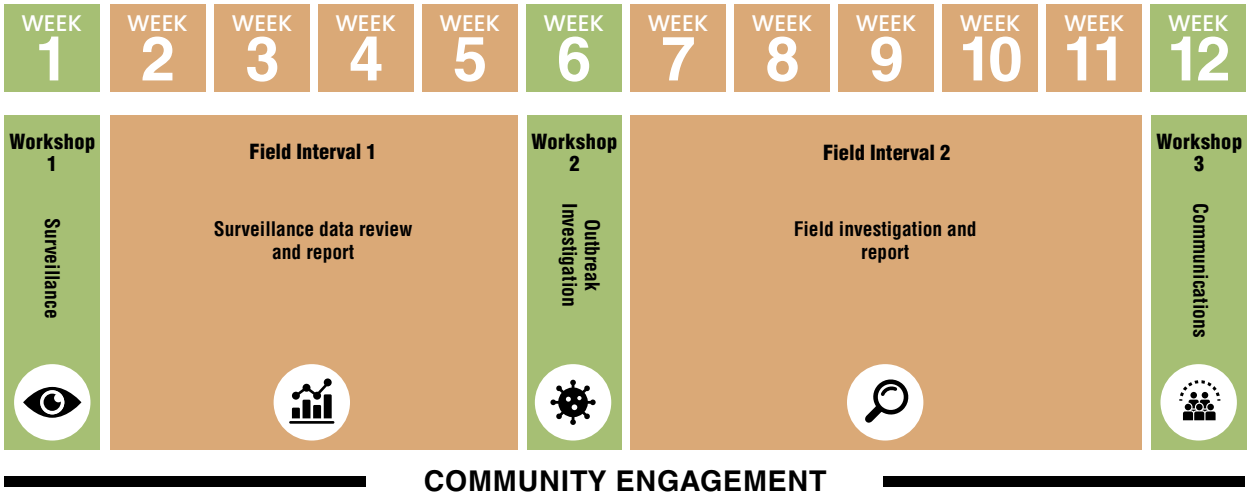
In contrast with global trends towards increasing urbanization, less than 14% of Papua New Guinea's population lives in urban centres.[11] For much of the country's rural population, front-line workers are most likely to be the primary contact in the event of a health emergency, providing the bridge between local communities and the various sectors responsible for protecting public health. This is even more likely in the more remote, less accessible areas, where front-line workers are often the first to hear of health threats affecting communities. The importance of training front-line workers in prevention, prediction, detection and response to health threats is, therefore, especially urgent in countries like Papua New Guinea. Coordinated training of cross-sectoral teams provides opportunities for building relationships, sensitizing participants to the respective roles and responsibilities of various sectors and enhancing capacity in information sharing, collaboration and coordinated joint responses.

In 2013, led by the National Department of Health (NDoH), the FETPNG was launched with an intermediate-level programme targeting public health professionals (Field Epidemiology Training Program of Papua New Guinea. Our workforce, our future: strategic plan 2023–2028. Internal document). However, no equivalent programme was offered to those working in the animal health and environmental sectors. Recognizing the need for a multisectoral training programme to strengthen field epidemiology capability on the front line, the One Health f-FETPNG was initiated. The primary focus of f-FETPNG is to equip front-line workers across sectors with the necessary competencies to prevent, predict, detect and respond to public health threats. Additionally, f-FETPNG aims to foster stronger communication with communities and collaboration across public health, animal health, plant health and conservation sectors at the provincial level. This report describes the methods employed in developing and implementing this training programme in four provinces and lessons learned along the way.

ACTION

In September 2022, the NDoH received a grant from the Global Fund COVID-19 Response Mechanism[12] to pilot a 3-month in-service FETP. An initial stakeholder consultation determined the principles and main components of the training programme, which were further refined during programme implementation in an iterative process. The elements covered included the development of pilot site selection criteria, provincial assessment visits, curriculum development, training of

Fig. 1. **Phases of the One Health front-line Field Epidemiology Training Program of Papua New Guinea, 2023**



trainers (ToTs) in adult principles of learning, development of participant selection criteria and quality assurance processes. The decision to adopt a One Health approach was taken early on and played a major role in shaping the format and content of the f-FETPNG pilot. The primary aim was to strengthen disease surveillance, early detection and response across sectors. Emphasis was placed on collaboration and communication skills to facilitate teamwork across disciplines and sectors. Field projects were designed to give participants practical experience in applying epidemiological principles, while the face-to-face workshops provided an opportunity to build relationships across sectors, sensitize participants to One Health principles and expose them to other sectors' operations.

In contrast to the national intermediate-level FETPNG, the f-FETPNG was designed to be administered at provincial level. Thus, the building of provincial capacity to successfully roll out and replicate training for subsequent cohorts of front-line workers was the main aim of the pilot training programmes. The initial selection of pilot provinces was governed by several factors, including: (i) the presence of intermediate FETPNG graduates who could serve as trainers and mentors and deliver the training programme in collaboration with identified trainers and mentors from other sectors; (ii) the presence of a strong provincial health authority (PHA); and (iii) the prioritization by the National Agriculture Quarantine and Inspection Authority (NAQIA). Five pilot provinces were selected using these criteria: Eastern Highlands, Morobe, National Capital District, West New Britain and West Sepik. The 3-month in-service training programme was delivered in each province to a single cohort between 2022 and 2024. This enabled the training materials to be reviewed and adapted after each cohort, creating an iterative improvement process. The f-FETPNG training programmes consisted of 3-week face-to-face workshops, 1 month apart. In the intervals between workshops, fellows were expected to carry out two field projects, comprising a surveillance task and a field or outbreak investigation (**Fig. 1**). For this part of the training, fellows were required to either collect their own data or use existing data from their workplace. They were supported by faculty members who provided guidance on collecting and analysing data.

As One Health front-line field epidemiology curricula were unavailable during the programme development phase, existing sector-specific resources were adapted, including the United States Centers for Disease Control and Prevention's *FETP-frontline curriculum guide*,[13] the Frontline In-Service Applied Veterinary Epidemiology Training (ISAVET) programme[14] and the intermediate FETPNG. Core competencies focused on epidemiological principles using a One Health approach, surveillance and data analysis, outbreak/field investigation and community engagement (**Table 1**). As part of the community engagement component, f-FETPNG programme fellows were tasked with identifying community priorities and developing and implementing engagement and communication plans for field projects. The aim was

Table 1. **Core competencies of the One Health front-line Field Epidemiology Training Program of Papua New Guinea, 2023**

Competency domain	Competency
Epidemiological concepts	▪ Describe key disease prevention and control concepts using a One Health approach
Epidemiological surveillance	▪ Map a surveillance system for a human, animal, plant or environmental health issue ▪ Summarize, analyse and interpret human, animal, plant and environmental health surveillance data
Outbreak/field investigation	▪ Investigate a public/animal/plant/environmental health alert
Data management and analysis	▪ Create and manage epidemiological data ▪ Conduct a descriptive data analysis of time, place and person/animal/plant
Evidence-based practice	▪ Provide recommendations from field projects
Communication and community engagement	▪ Create a communication plan for sharing surveillance data and for use during an outbreak investigation ▪ Demonstrate capability in successfully partnering with communities

to strengthen relationships and trust between front-line workers and the communities they serve.

Initially, trainers and mentors were selected from various organizations such as the NDoH, PHAs, NAQIA, the Department of Agriculture and Livestock, the Conservation Environment Protection Authority and other partners. Subsequently, graduates of the f-FETPNG were appointed as junior trainers and mentors. Additionally, faculty members included individuals who had completed the national intermediate FETP and advanced FETP, as well as those from NAQIA who had finished the Asia Pacific Consortium of Veterinary Epidemiology training programme. A ToT workshop was conducted after the third f-FETPNG pilot to provide junior faculty members with training in adult learning principles, session plan development and interactive experiential learning techniques.

Each sector was responsible for selecting its trainees for the programme. Fellow selection was based on specific criteria, including being employed in a role where they could apply their skills, having support to complete field projects during work time and being able to attend all three face-to-face workshops. The f-FETPNG fellows were matched with mentors based on sector and area of expertise. The number of fellows per cohort was limited to 20 to ensure an average of two or three mentees per mentor. A team mentoring approach was adopted to ensure less experienced mentors received support and could learn from those with more mentoring experience.

Continuous quality assurance was built into the training programme with pre-workshop facilitator sessions, participant feedback during workshops, peer feedback for trainers, workshop evaluations and a post-pilot curriculum review workshop. For instance, before the delivery of each face-to-face workshop, faculty met over 4–5 days to review content, share sectoral experiences, develop session plans and practise delivering content. During the interactive workshops, fellows provided daily feedback, which was used to adapt training content and delivery as needed. Following each workshop, a half-day post-training faculty evaluation workshop was held to reflect on four key areas: session planning, teaching, learning and mentoring. Evaluation findings informed the delivery of subsequent workshops. When the training was completed in the first four pilot provinces, a curriculum review workshop was held with representation from all sectors, faculty and graduates. The curriculum was reviewed and updated to ensure sectoral relevance. The revised curriculum was implemented in the fifth pilot province, Eastern Highlands.

While identifying suitable case studies and examples from plant health, wildlife and conservation sectors was an initial challenge, the adoption of an iterative co-creation approach enabled participants and faculty from all sectors throughout the pilot process to shape and adapt the curricula to local needs. The fellows' engagement with trainers and mentors from different sectors during the training provided an opportunity for them to learn more about how each sector operates, their data collection and reporting pathways, and where field epidemiology skills could be used to strengthen systems in each sector. The above-mentioned daily evaluations and the end-of-workshop evaluations provided valuable examples and guidance for sourcing environmental case

studies and examples in the plant health and conservation sectors. The fellows' information on their own projects added to the pool of resources to be used when creating case studies for the course curricula.

LESSONS LEARNED

As of October 2024, of the 99 fellows recruited from the five pilot provinces to attend f-FETPNG, 75 had successfully graduated from the programme. They included community health workers, health extension officers, rural development officers, laboratory assistants, tree and food crop officers, fisheries officers, agriculture quarantine officers, animal health officers, extension officers, environmental health officers, livestock officers, defence force medical officers, customs officers, environment and conservation officers, ports officers, public health surveillance officers and health promotion officers. A total of 150 projects were undertaken by the f-FETPNG graduates while taking part in the 3-month training programme, with all 75 graduates completing their two required projects. Surveillance projects covered topics as diverse as malaria, food handling, water quality, coconut rhinoceros beetles, livestock management and waterborne diseases after natural disasters. Outbreak/field investigation projects included yaws, beef cattle diarrhoea, diarrhoea in displaced populations after natural disasters, fish kills, pig deaths, locust plague, sugarcane diseases and several vaccine-preventable diseases.

The implementation of the One Health f-FETPNG has provided valuable insights and lessons in addressing the complex health challenges faced by the country. Key lessons are summarized below.

Lesson 1: Tailor the programme to the local context

When developing training programmes aimed at front-line workers, it is essential to gather input from the fellows to ensure relevance to their role and sector. The co-creation approach ensured that the programme's curricula were tailored to address the specific needs and realities they faced across sectors in Papua New Guinea. Embedding continuous quality assurance from the outset facilitated continual reflection and adaptation of the programme to suit learner needs. A one-size-fits-all approach is unlikely to meet the needs of front-line workers. It is, thus, recommended that curricula development be an ongoing iterative process, that is, during not only the pilot phase but also subsequent phases.

Lesson 2: Front-line worker relationships are important in ensuring the success of a One Health approach

As the global community shifts towards the integration of human, animal and environmental health, the need to build cross-sectoral relationships and trust has taken centre stage. The cross-sectoral training of front-line workers by the f-FETPNG has led to the formation of active informal networks and communication channels between participants through social media platforms such as WhatsApp. After the completion of the training programme, graduates continued to utilize this network to share important alerts and information, such as dead whale sightings, contaminated fish sales, community diarrhoeal deaths, foodborne illnesses and suspected disease outbreaks, as well as other health issues and concerns. These shared alerts have prompted multisectoral investigations in various locations, showcasing the lasting positive impact of the training programme on collaboration and information sharing among participants. In addition to sharing alerts, graduates have used social media to seek advice from peers on topics ranging from a dog with ocular growths, a broken sewage pipe, the environmental health impacts of a volcano and laboratory results follow-up, to shared outbreak reports and policy documents. Cross-sectoral training has enabled cross-learning, the recognition of fellows' roles and responsibilities and the establishment of trusted relationships, which in turn have fostered collaboration, information sharing and effective multisectoral responses.

Lesson 3: Training of trainers has a translational impact on programme delivery

ToT in the principles of adult learning led to greater ownership of the delivery of workshop sessions and high levels of participant satisfaction. Training in interactive methods helped trainers increase their confidence and ability to prepare and deliver experiential adult learning. Pre-workshop days enabled trainers to review workshop content and incorporate earlier evaluation feedback and province-specific examples, build confidence in developing session plans and provide opportunities to

practise a variety of experiential learning techniques. Peer review ensured the continued growth and development of trainers.

Lesson 4: Build a provincial training model for front-line workers

The f-FETPNG pilot has underscored the benefits of provincial-level programme implementation, enabling relationships to be forged between individuals who would possibly work together after graduation. The impact of this approach, highlighted in Lesson 2, may not have been as strong if the programme had drawn participants from across different provinces. Training provincial faculty has also equipped individual provinces with the capability to deliver similar trainings to future cohorts of front-line workers.

These lessons learned from the f-FETPNG are likely to be applicable to other island nations. The programme's design and approach, emphasizing the importance of a coordinated and interdisciplinary approach to addressing evolving health challenges, can serve as a valuable model for countries seeking to enhance their epidemiological capacity at subnational level. Similarly, with its focus on equipping front-line workers with foundational competencies, the f-FETPNG model provides a tool that strengthens national capacity to prevent, predict, detect and control health threats, and also produces evidence for decision-making, improves communication with communities and fosters collaboration across sectors.

DISCUSSION

Globally, the intersection between human, animal and environmental health and the need for holistic solutions in addressing new and emerging health challenges is increasingly recognized.[2,15] Now, perhaps more than ever, front-line workers form the foundation of a nation's health security architecture. The f-FETPNG has demonstrated that bringing front-line workers from multiple sectors together can forge strong cross-sectoral relationships that continue to have a translational impact after programme completion. Joint trainings enable a better understanding of sectoral roles and responsibilities, build trusted relationships, and increase knowledge of specific health threats facing each sector and those that are interconnected across sectors. The successful implementation of the f-FETPNG has yielded important insights into how to address complex health challenges more effectively through combined efforts. By adopting a customized, collaborative One Health approach, the programme has effectively enhanced the capabilities of front-line workers to jointly tackle health issues in Papua New Guinea.

In Papua New Guinea, where over 85% of people live in rural and/or remote locations, front-line workers are critical in identifying and responding to health threats. Multisectoral training has built foundational epidemiological capacity and has provided front-line workers with a common language and understanding. In addition, the relationships and trust formed during the training have translated into enhanced communication and collaboration through active informal networks and joint responses to alerts after completion of the programme.

The f-FETPNG will continue to evolve as lessons are identified and the programme is rolled out in different provinces, each of which will have its own unique requirements. We acknowledge the need for sustained engagement across all sectors, particularly since the programme is embedded within national and provincial health authorities. We also recognize the need to ensure graduates are engaged in activities and professional development opportunities that build upon the competencies gained during their f-FETPNG participation. We hope the lessons shared here can serve as a guide for other nations initiating One Health in-service training for front-line workers.

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continued to translate their learning into practice. We would also like to acknowledge Dr Joanne Taylor for her contribution in the early phase of the project.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Formal ethical approval was not sought as research was not undertaken. Approval and permission to publish was received from the Papua New Guinea National Department of Health before the paper was submitted for publication.

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Active case finding to detect symptomatic and subclinical pulmonary tuberculosis disease: implementation of computer-aided detection for chest radiography in Viet Nam

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Objective: In Viet Nam, tuberculosis (TB) prevalence surveys revealed that approximately 98% of individuals with pulmonary TB have TB-presumptive abnormalities on chest radiographs, while 32% have no TB symptoms. This prompted the adoption of the "Double X" strategy, which combines chest radiographs and computer-aided detection with GeneXpert testing to screen for and diagnose TB among vulnerable populations. The aim of this study was to describe demographic, clinical and radiographic characteristics of symptomatic and asymptomatic Double X participants and to assess multilabel radiographic abnormalities on chest radiographs, interpreted by computer-aided detection software, as a possible tool for detecting TB-presumptive abnormalities, particularly for subclinical TB.

Methods: Double X participants with TB-presumptive chest radiographs and/or TB symptoms and known risks were referred for confirmatory GeneXpert testing. The demographic and clinical characteristics of all Double X participants and the subset with confirmed TB were summarized. Univariate and multivariable logistic regression modelling was used to evaluate associations between participant characteristics and subclinical TB and between computer-aided detection multilabel radiographic abnormalities and TB.

Results: From 2020 to 2022, 96 631 participants received chest radiographs, with 67 881 (70.2%) reporting no TB symptoms. Among 1144 individuals with Xpert-confirmed TB, 51.0% were subclinical. Subclinical TB prevalence was higher in older age groups, non-smokers, those previously treated for TB and the northern region. Among 11 computer-aided detection multilabel radiographic abnormalities, fibrosis was associated with higher odds of subclinical TB.

Discussion: In Viet Nam, Double X community case finding detected pulmonary TB, including subclinical TB. Computer-aided detection software may have the potential to identify subclinical TB on chest radiographs by classifying multilabel radiographic abnormalities, but further research is needed.

In 2022 alone, approximately 10.6 million people fell ill with TB globally.[1] Although new diagnostic tests are improving the capacity for early detection, TB remains one of the world's deadliest infectious diseases.[2–4] While chest radiographs (CXRs) are used to screen for TB, their interpretation capacity is limited in many high-TB burden settings. Recognizing this barrier to early detection, in March 2021, the World Health Organization (WHO) endorsed the use of artificial intelligence-powered computer-aided detection (CAD) in place of human readers to interpret digital CXRs for TB among individuals aged 15 years and older.[5] WHO describes four models for integrating CAD into TB screening or triage algorithms.[6] These models differ in the way CAD is used alongside human readers to interpret CXRs. They comprise: CAD screening followed by human reading for all abnormal

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CXRs; CAD screening followed by human reading for all abnormal CXRs plus a proportion of normal CXRs; CAD and human reading conducted in parallel; and human reading replaced by CAD.

In recent years, the spectrum of pulmonary TB has broadened and now includes terms describing early stages of disease such as "minimal" and "subclinical" TB.[7–9] Subclinical TB is "disease due to viable *Mycobacterium tuberculosis* bacteria that does not cause clinical TB-related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays."[7] Furthermore, it was previously thought that TB transmission only occurred when symptoms such as cough were present, but recent studies demonstrate that people with subclinical TB disease are infectious[10] and exhale *M. tuberculosis* bacteria (evidenced by face-mask sampling).[11] Prevalence surveys from 23 African and Asian countries show that 36–80% of individuals with TB disease have no TB symptoms.[12] Neglecting to diagnose and cure subclinical TB disease is thus a barrier to ending TB.

Screening of any TB symptom (cough, haemoptysis, fever, night sweats or weight loss) has an estimated 71% sensitivity for identifying TB disease.[6] CXR screening using TB-presumptive abnormalities significantly improves case detection, in particular of subclinical TB, increasing sensitivity to 85%.[6] While not as accurate as chest computed tomography (CT) imaging for detecting subclinical and incipient TB,[13–15] CXRs remain the most pragmatic, readily available radiographic option for TB screening and triage in high-TB burden settings, especially when coupled with CAD technologies. However, to date, few studies have assessed the extent to which CAD products improve the accuracy of CXR screening for subclinical TB in routine programme implementation.

Viet Nam's second national TB prevalence survey, conducted in 2017–2018, found a bacteriologically-confirmed TB prevalence of 322 cases per 100 000 persons; among individuals with confirmed TB disease, 97.7% had CXR abnormalities suggesting TB, 57.9% reported cough for 2 or more weeks and 32.1% had no TB symptoms.[16] These findings led Viet Nam's National Tuberculosis Program (NTP) to implement a "Double X" (2X) strategy to diagnose TB among symptomatic and asymptomatic TB-vulnerable populations, which used CXR to identify individuals for confirmatory diagnostic testing with GeneXpert (Xpert; Cepheid, Sunnyvale, CA, United States of America). From 2020 to 2022, CAD was integrated into NTP's 2X community case-finding strategy. The aim of this study was to describe the demographic, clinical and radiographic characteristics of symptomatic and asymptomatic 2X participants, including those diagnosed with TB. CAD-scored radiographic abnormalities were also assessed to determine whether they were associated with Xpert-confirmed TB disease, both overall and separately for symptomatic and subclinical TB.

METHODS

Setting

This study was conducted as part of routine programmatic implementation from March 2020 to December 2022. Annual 2X active case finding community campaigns were conducted in eight provinces comprising An Giang, Can Tho, Dong Nai, Dong Thap, Nghe An, Tay Ninh, Tien Giang and Thai Binh, which were selected for being representative of Viet Nam's three regions and for their baseline TB notification rates. Collectively, the eight provinces accounted for approximately 20% of the country's notified TB cases. The 2X community campaigns ranged in duration from 4 to 18 days and evaluated between 100 and 440 individuals daily.

Community TB screening algorithms

The 2X community participants comprised two categories of TB-vulnerable populations. The first category was household contacts of adults diagnosed with pulmonary TB disease (with or without bacteriological confirmation) within 2 years of the start of the 2X campaign. Contacts were persons who had lived, slept (1 night per week) or stayed (1 hour per day, 5 days per week) in the same house with the index patient for 3 months before diagnosis. The second category of TB-vulnerable populations included individuals who were aged 60 years and older (the age category defined as "elderly" according to Vietnamese law[17]), had a diagnosis of diabetes, or were smokers (any smoking history), regular alcohol users (daily) or malnourished (low body mass index), as well as those with pulmonary or other chronic diseases, a history of prior treatment for TB disease or living with HIV. Medical history was self-reported. TB symptoms (fever, cough of any duration, weight loss or night sweats)

were documented but not required for CXR evaluation. For participants with "TB-presumptive" CXRs, sputum specimens were collected on site for Xpert testing. Physicians also referred participants for Xpert testing if they had normal CXRs but positive screens for TB symptoms and/or TB risk factors, based on participant interview during campaign intake.

CXR interpretation by physicians

Posterior-anterior digital CXR images (Vikomed, Hanoi, Viet Nam) were obtained in mobile CXR vans and interpreted in the van by provincial-level radiologists who had access to each participant's name, age and brief medical history including TB symptoms and risk factors. CXRs reviewed by physicians were interpreted as "TB-negative" or "TB-presumptive."

CAD analysis

Offline CAD analysis with qXR[18] version 3.0 (Qure.ai, Mumbai, India) was performed using qBoxes installed in mobile CXR vans. Each CXR DICOM (Digital Imaging and Communications in Medicine) image was given a qXR TB abnormality score, which ranged from 0.00 to 1.00, with higher values indicating more abnormal CXRs. The manufacturer's pre-set threshold for TB interpreted a qXR score ≥0.50 as TB-presumptive and <0.50 as TB-negative. qXR employs convolutional neural networks-based algorithms that are able to perform "multilabel" classification of other, non-TB radiographic abnormalities, including blunted costophrenic angle, calcification, cardiomegaly, cavity, consolidation, fibrosis, hilar lymphadenopathy, nodule, opacity, pleural effusion and pneumothorax.[19–21] This feature extends the capability of qXR beyond providing simple binary TB-presumptive and TB-negative results.[22,23] Thresholds for the 11 multilabel, non-TB radiographic abnormalities analysed in this study were pre-set by the manufacturer and did not change during the study (2020–2022).

To select CAD TB thresholds for 2X implementation, we conducted a retrospective qXR analysis of CXRs from 2020 community campaigns, which showed that threshold scores from 0.40 to 0.60 resulted in the most consistent case-finding yields across provinces. Thresholds in this range were employed in 2X campaigns in 2021 onwards. In terms of the choice of CAD integration model, a priori, there was no preference for a "CAD-first" (software interprets CXRs first and only those rated as CAD TB-presumptive are read by physicians) or a "CAD-parallel" model (CXRs are interpreted by both CAD and on-site physicians; **Fig. 1**), and both models were employed in 2021 – CAD-first at three sites and CAD-parallel at two sites. For the CAD-first model, we selected a qXR ≥0.40 TB threshold, which is lower and thus more sensitive than the manufacturer's pre-set threshold (≥0.50), to reduce the risk for missing potential cases. Conversely, a qXR ≥0.60 TB threshold was selected for the "CAD-parallel" model; this is higher than the pre-set ≥0.50 threshold and was selected to increase CAD specificity for the parallel model and reduce the risk of false positives. To standardize methods in 2022, all CXRs were processed according to the CAD-first model (and qXR threshold ≥0.40), which was simpler to implement than CAD-parallel integration in mobile CXR vans. qXR interpreted CXRs from all 2X participants who were aged 6 years and older.

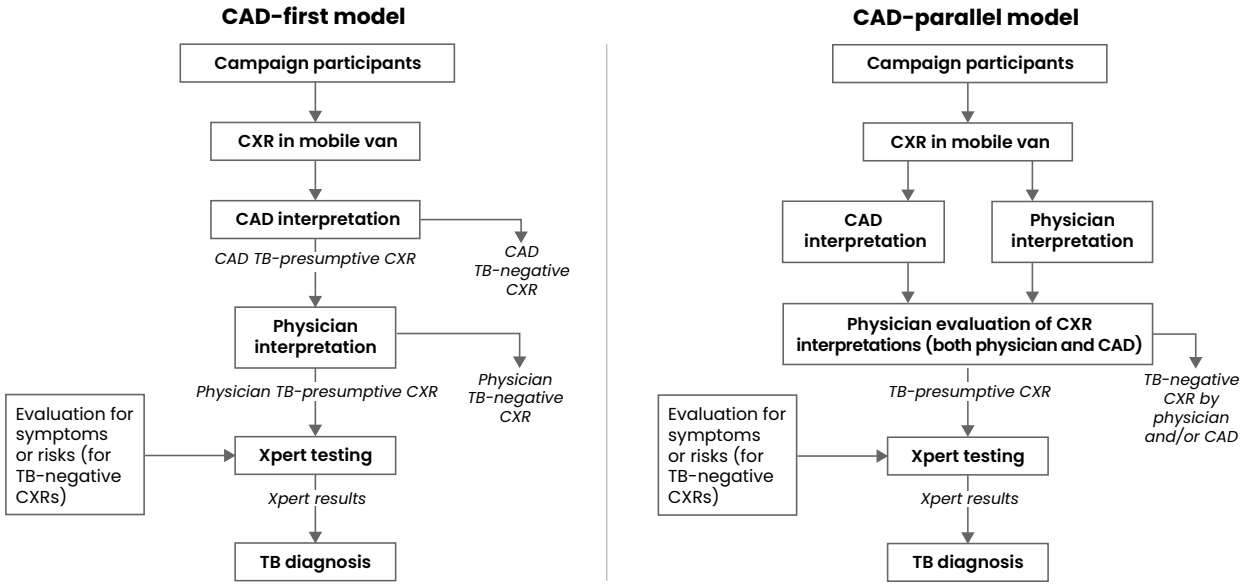
Diagnostic confirmation with Xpert testing

Participants referred for Xpert testing produced a single-spot specimen that was analysed on site or in a nearby facility with Xpert capacity (Xpert MTB/RIF or Xpert Ultra). Symptomatic TB disease was defined as Xpert-confirmed TB in individuals with any TB symptom (fever, cough of any duration, weight loss or night sweats), and subclinical TB disease was defined as Xpert-confirmed TB with no TB symptoms.

Statistical analysis

Demographic and clinical characteristics of the 2X study participants were summarized and compared across the study years using the χ^2 test (categorical variables) and ANOVA (continuous variables). The characteristics of the subsets of participants with symptomatic and subclinical Xpert-confirmed TB were also compared using the χ^2 test. Univariate and multivariable logistic regression modelling explored which, if any, characteristics (region, sex, age group, smoking status, prior treatment for TB, diabetes, alcohol use, malnutrition) were associated with subclinical Xpert-confirmed TB. We also reported the prevalence of the 11 qXR multilabel, non-TB radiographic abnormalities for each year of our study (2020–2022). Finally, we used univariate and multivariable Firth logistic regression to determine which of the 11 multilabel, non-TB radiographic abnormalities were associated with

Fig. 1. **Models employed for CAD-CXR interpretation for TB in Viet Nam[a,b]**



CAD: computer-aided detection; CXR: chest radiography; TB: tuberculosis; Xpert: GeneXpert.

[a] According to the CAD-first model (left), CXRs are interpreted by CAD software first, and only CAD TB-presumptive CXRs are then interpreted by on-site physicians.

[b] According to the CAD-parallel model (right), all CXRs are interpreted by both CAD and on-site physicians; physicians have the option of agreeing or disagreeing with the CAD interpretation when making their final decision (TB-presumptive or TB-negative) and making a referral for Xpert testing.

Xpert-confirmed TB (overall) and which were associated with subclinical Xpert-confirmed TB. The Firth logistic regression model uses a penalized log likelihood to handle separation, which prevents cases from being dropped and enables use of the full sample. All models were fitted on data from 2020, 2021, 2022 and all years combined. Data were analysed using STATA 18 (Stata Corp; College Station, TX, United States).

RESULTS

We retrospectively analysed 51 441 CXRs from 2020 and used real-time CAD to analyse 17 078 CXRs in 2021 and 28 112 CXRs in 2022. Participants' demographic and clinical characteristics differed across the three years (**Table 1**). The proportion of participants aged 60 years and older was lower in 2022 (40.5%) compared to 2020 (47.1%) and 2021 (46.7%). Females outnumbered males in all years, with the lowest proportion of males (41.1%) recorded in 2020. Participants in 2021 were the least symptomatic, with only 16.8% reporting any symptom compared to 31.8% in 2020 and 33.9% in 2022; cough was the most frequently reported symptom. Across all years, a total of 15 278 participants had CXRs that were rated as TB-presumptive (15.8%), among whom 14 024 (91.8%) underwent Xpert testing and 1254 (8.2%) dropped out. Additionally, 1200 who had TB-negative CXRs but presented with TB symptoms and/or risk factors underwent Xpert testing, for a total of 15 224 (92.1% TB-presumptive CXRs, 7.9% TB-negative CXRs) (**Table 1**). Across the study period, Xpert positivity averaged 7.5% (1144/15 224). Xpert positivity was lower among those with TB-negative CXRs (2.9%) and among those with subclinical TB (5.9%).

Among the 1144 individuals who were diagnosed with Xpert-confirmed TB disease during 2020–2022, around half had subclinical TB (51%). However, this proportion differed by year, geographical region, age group, prior TB treatment, smoking status, alcohol use and malnutrition (**Table 2**; **Supplementary Table 1**). Subclinical TB prevalence was higher in the northern region than in the central and southern regions (72.5%, 36.7% and 49.8%, respectively). Subclinical TB prevalence was higher among older age groups and in those with a history of TB treatment than those without (55.2% versus 48.3%). Subclinical TB prevalence was lower in smokers than non-smokers (43.2% versus 54.6%), those with alcohol use disorders than those without (38.2% versus 51.9%), and those with malnutrition than those without (20.0% versus 51.5%). In multivariable logistic regression models, residing in the northern region (adjusted odds ratio [aOR]:

Table 1. **Participant characteristics for 2X community case finding, 2020–2022**

Characteristics	2020–2022 (*N* = 96 631)	2020 (*n* = 51 441)	2021 (*n* = 17 078)	2022 (*n* = 28 112)
Region				
North (%)	14 624 (15.1)	11 825 (23.0)	2799 (16.4)	–
Central (%)	6072 (6.3)	3675 (7.1)	2397 (14.0)	–
South (%)	75 935 (78.6)	35 941 (69.9)	11 882 (69.6)	28 112 (100)
Age[a]				
Mean (SD)	54.32 (18.17)	54.88 (18.14)	54.34 (19.05)	53.31 (17.62)
Median (IQR)	58 (45–67)	58 (46–67)	58 (45–67)	56 (43–66)
Sex				
Female (%)	54 535 (56.6)	30 320 (58.9)	8886 (52.3)	15 329 (54.9)
Male (%)	41 829 (43.4)	21 114 (41.1)	8116 (47.7)	12 599 (45.1)
Screening group				
Household contacts (%)	20 996 (21.7)	12 587 (24.5)	4575 (26.8)	3834 (13.6)
Other vulnerable populations (%)	75 627 (78.3)	38 846 (75.5)	12 503 (73.2)	24 278 (86.4)
Specific vulnerable populations[b]				
Elderly[c] (≥60 years) (%)	43 481 (45.1)	24 153 (47.1)	7967 (46.7)	11 361 (40.5)
Prior TB treatment (%)	9218 (9.5)	5114 (9.9)	2074 (12.1)	2030 (7.2)
Smoker (%)	11 805 (12.2)	5957 (11.6)	1826 (10.7)	4022 (14.3)
Alcohol use disorder (%)	2706 (2.8)	1253 (2.4)	445 (2.6)	1008 (3.6)
Malnutrition (%)	1001 (1.0)	652 (1.3)	116 (0.7)	233 (0.8)
Diabetes (%)	9268 (9.6)	5169 (10.0)	1275 (7.5)	2824 (10.0)
Hypertension (%)	33 639 (34.8)	17 365 (33.8)	5404 (31.6)	10 870 (38.7)
Asthma (%)	4067 (4.2)	1304 (2.5)	856 (5.0)	1907 (6.8)
Chronic obstructive pulmonary disease (%)	1677 (1.7)	772 (1.5)	620 (3.6)	285 (1.0)
Symptoms				
Cough of any duration (%)	25 447 (26.3)	14 499 (28.2)	2639 (15.5)	8309 (29.6)
Fever (%)	1580 (1.6)	1197 (2.3)	55 (0.3)	328 (1.2)
Night sweats (%)	2624 (2.7)	1462 (2.8)	98 (0.6)	1064 (3.8)
Weight loss (%)	3947 (4.1)	2524 (4.9)	301 (1.8)	1122 (4.0)
Any symptom (%)	28 750 (29.8)	16 333 (31.8)	2875 (16.8)	9542 (33.9)
CXR and Xpert results				
CAD TB-presumptive CXR (%)	ND	6934 (13.5)	2892 (16.9)	5033 (17.9)
Physician TB-presumptive CXR (%)	15 278 (15.8)	7406 (14.4)	3789 (22.2)	4083 (14.5)
Xpert testing (rate,%)[d]	15 224 (15.8)	7205 (14.0)	3722 (21.8)	4297 (15.3)
Xpert positivity[e]				
Overall (%)	1144 (7.5)	620 (8.6)	194 (5.2)	330 (7.7)
TB-negative CXR (%)	35 (2.9)	20 (4.4)	10 (2.8)	5 (1.3)
Subclinical TB (%)	584 (5.9)	302 (6.8)	130 (4.4)	152 (5.9)
Symptomatic TB (%)	560 (10.7)	318 (11.5)	64 (8.7)	178 (10.2)
Xpert-confirmed TB yield overall per 100 000 CXR	1184	1205	1136	1174

2X: Double X; *N*: number; SD: standard deviation; IQR: interquartile range; TB: tuberculosis; CXR: chest radiography; Xpert: GeneXpert; CAD: computer-aided detection; ND: not determined due to differing CAD models/thresholds each year.

[a] Some age data were missing: $n = 149$ (2020); $n = 23$ (2021); $n = 62$ (2022).

[b] Characteristics for people living with HIV are not summarized due to small sample size ($n = 65$ for all years).

[c] Age cut-off for "elderly" (aged ≥60 years) was defined using the Viet Nam Law for the Elderly.[17]

[d] Number of participants who underwent Xpert testing ($n = 15\,224$) as a percentage of the total number of participants with CXRs ($n = 96\,631$). Note that this number includes 1200 participants with physician TB-negative CXRs who also underwent Xpert testing. The decision to offer Xpert testing for these participants was at the discretion of the on-site physician based on an assessment of symptoms and risk factors.

[e] Number of participants with a positive Xpert test result ($n = 1144$) as a percentage of the number of participants who underwent confirmatory Xpert testing ($n = 15\,224$).

Table 2. **Demographic and clinical characteristics of individuals with Xpert-confirmed TB disease, comparing subclinical and symptomatic disease, and associations with subclinical TB, 2020–2022**[a]

Characteristics	Subclinical TB	Symptomatic TB	Total	OR (95% CI) (*n* = 1144)	aOR (95% CI) (*n* = 1141)
Positive Xpert result	584 (51.0)	560 (49.0)	1144	–	–
Physician TB-presumptive CXR	561	548	1109	–	–
Physician TB-negative CXR	23	12	35	–	–
Region					
North (%)	58 (72.5)	22 (27.5)	80	2.66* (1.60–4.41)	2.37** (1.42–3.96)
Central (%)	11 (36.7)	19 (63.3)	30	0.58 (0.27–1.24)	0.47 (0.22–1.02)
South (%)	515 (49.8)	519 (50.2)	1034	Reference	Reference
Sex					
Male (%)	484 (50.8)	468 (49.2)	952	0.95 (0.70–1.30)	1.09 (0.78–1.54)
Female (%)	100 (52.1)	92 (47.9)	192	Reference	Reference
Age group[b]					
0–19 (%)	5 (45.5)	6 (54.5)	11	0.67 (0.20–2.20)	0.63 (0.19–2.09)
20–29 (%)	9 (45.0)	11 (55.0)	20	0.65 (0.27–1.60)	0.68 (0.27–1.69)
30–39 (%)	27 (38.6)	43 (61.4)	70	0.50** (0.30–0.83)	0.50*** (0.30–0.85)
40–49 (%)	48 (42.1)	66 (57.9)	114	0.58** (0.39–0.87)	0.55** (0.36–0.84)
50–59 (%)	156 (49.1)	162 (50.9)	318	0.77 (0.59–1.01)	0.81 (0.61–1.07)
≥60 (%)	338 (55.6)	270 (44.4)	608	Reference	Reference
Prior treatment for TB					
No (%)	336 (48.3)	359 (51.7)	695	Reference	Reference
Yes (%)	248 (55.2)	201 (44.8)	449	1.32*** (1.04–1.67)	1.36*** (1.05–1.75)
Smoker					
No (%)	431 (54.6)	359 (45.4)	790	Reference	Reference
Yes (%)	153 (43.2)	201 (56.8)	354	0.63* (0.49–0.82)	0.68** (0.52–0.90)
Diabetes					
No (%)	517 (51.3)	491 (48.7)	1008	Reference	Reference
Yes (%)	67 (49.3)	69 (50.7)	136	0.92 (0.64–1.32)	0.91 (0.63–1.32)
Alcohol use disorder					
No (%)	558 (51.9)	518 (48.1)	1076	Reference	Reference
Yes (%)	26 (38.2)	42 (61.8)	68	0.57*** (0.35–0.95)	0.79 (0.46–1.34)
Malnutrition					
No (%)	581 (51.5)	548 (48.5)	1129	Reference	Reference
Yes (%)	3 (20.0)	12 (80.0)	15	0.24*** (0.07–0.84)	0.28*** (0.08–0.99)

aOR: adjusted odds ratio; CXR: chest radiograph; OR: odds ratio; TB: tuberculosis; Xpert: GeneXpert.

* $P < 0.001$; ** $P < 0.01$; *** $P < 0.05$.

[a] All characteristics shown in this table were included as predictors in the multivariable logistic regression model. We opted for the most parsimonious model and thus did not include hypertension, asthma and chronic obstructive pulmonary disease as predictors since they did not change the included predictors' statistical significance for association with the outcome. HIV was not included as a predictor due to small sample size ($n = 65$ for all years).

[b] Logistic regression models that include age groups have a sample of $n = 1141$ (3 cases missing information on age).

2.37; 95% confidence interval [CI]: 1.42–3.96) and prior treatment for TB (aOR: 1.36; 95% CI: 1.05–1.75) were associated with higher odds of subclinical TB disease. Age groups 30–39 and 40–49 years (aOR: 0.50; 95% CI: 0.30–0.85 and aOR: 0.55; 95% CI: 0.36–0.84, respectively), smoking (aOR: 0.68; 95% CI: 0.52–0.90) and malnutrition (aOR: 0.28; 95% CI: 0.08–0.99) were associated with lower odds of subclinical TB. Neither sex nor self-reported diabetes was associated with subclinical TB.

Table 3. Distribution of CAD multilabel, non-TB radiographic abnormalities among CXRs with Xpert-confirmed TB, 2020–2022

Radiographic abnormality	qXR threshold	2020 *n* = 620 (%)	2021 *n* = 194 (%)	2022 *n* = 330 (%)
Blunted costophrenic angle	0.80	12.3	9.3	14.5
Calcification	0.85	–	33.5	40.6
Cardiomegaly	0.85	1.9	0.5	2.7
Cavity	0.90	33.4	42.8	42.4
Consolidation	0.50	71.0	77.3	79.1
Fibrosis	0.70	90.5	92.3	90.3
Hilar lymphadenopathy	0.85	1.6	3.1	3.3
Nodule	0.50	86.9	86.6	90.0
Opacity	0.50	96.9	97.9	99.1
Pleural effusion	0.75	12.6	12.9	13.9
Pneumothorax	NA	–	1.0	0.6

CAD: computer-aided detection; CXR: chest radiography; NA: not available; qXR: Qure.ai CAD software; TB: tuberculosis; Xpert: GeneXpert.

Among those with Xpert-confirmed TB, the most frequently classified CAD radiographic abnormalities were consolidation, fibrosis, nodule and opacity (**Table 3**). In adjusted analyses, cavity, consolidation, fibrosis, nodule and opacity were significantly associated with higher odds of Xpert-confirmed TB. Fibrosis was also associated with higher odds of subclinical TB (aOR: 1.77; 95% CI: 1.10–2.85), while consolidation was associated with lower odds of subclinical TB (aOR: 0.71; 95% CI: 0.52–0.97) for all years combined (**Table 4**).

DISCUSSION

This study describes the Viet Nam NTP's 2X community-based active case-finding strategy that effectively diagnosed TB among symptomatic and asymptomatic TB-vulnerable populations during 2020–2022. Of the 96 631 individuals who were targeted by 2X campaigns and screened with CXRs, 15 224 underwent Xpert testing, which was predominantly for TB-presumptive CXRs (14 024; 92.1%), and 1144 individuals were diagnosed with Xpert-confirmed TB, of whom 584 (51.0%) had subclinical TB disease. A CAD radiographic classification of fibrosis was found to be a good predictor of subclinical TB disease.

Our study provided several insights into the distribution of symptomatic versus subclinical TB disease among 2X participants. While the total number of Xpert-confirmed TB cases was lower in 2021, coinciding with Viet Nam's most severe phase of the COVID-19 pandemic,[24] the proportion of participants diagnosed with subclinical TB in 2021 was higher than in other years. The reasons for this are likely multifactorial, potentially including increased stigma around respiratory diseases during the height of the COVID-19 pandemic, resulting in underreporting of TB symptoms. Also, individuals with respiratory symptoms may have been preferentially triaged to COVID-19 evaluation, leaving a higher proportion of individuals without symptoms to participate in 2X campaigns. Pandemic lockdowns in 2021 may have additionally delayed care-seeking, possibly leading to more severe – and symptomatic – TB disease being diagnosed in 2022.

We also noted that 2X campaigns in Viet Nam's northern region detected higher proportions of subclinical TB disease than southern campaigns. This could be related to the relatively low TB prevalence in the north, especially compared with the south where some of the highest TB prevalences in the country have been recorded.[16,25] This pattern has been found in other countries, including Cambodia, China and India.[12] Furthermore, we observed a greater prevalence of subclinical TB among older 2X participants (≥60 years). This finding is in contrast with a study conducted in Republic of Korea, which found that age <65 years was associated with subclinical TB disease.[26] However, the two studies are not directly comparable due to differences in the definition of subclinical TB; the Korean study defined subclinical TB as "radiographic or microbiologic

Table 4. **Summary of associations between CAD radiographic abnormalities and Xpert-confirmed/subclinical Xpert-confirmed TB disease, 2020–2022**

Radiographic abnormality	aOR[a] (95% CI) for Xpert-confirmed TB disease			
	All years (N^b = 15 224)	2020 (n^b = 7205)	2021 (n^b = 3722)	2022 (n^b = 4297)
Blunted costophrenic angle	0.72 (0.54–0.95)*	0.95 (0.64–1.40)	0.36 (0.17–0.75)**	0.66 (0.41–1.08)
Calcification	0.63 (0.53–0.75)***	0.33 (0.02–5.94)	0.80 (0.57–1.13)	0.60 (0.46–0.78)***
Cardiomegaly	0.79 (0.51–1.23)	0.84 (0.46–1.52)	0.57 (0.11–3.00)	0.82 (0.41–1.65)
Cavity	1.71 (1.47–1.98)***	1.23 (1.00–1.51)	2.80 (1.97–3.97)***	2.18 (1.65–2.88)***
Consolidation	4.40 (3.76–5.15)***	3.79 (3.07–4.67)***	5.27 (3.53–7.85)***	5.14 (3.80–6.96)***
Fibrosis	1.38 (1.08–1.77)*	1.64 (1.16–2.31)**	1.39 (0.73–2.67)	1.01 (0.66–1.55)
Hilar lymphadenopathy	0.95 (0.62–1.43)	1.03 (0.52–2.03)	0.82 (0.35–1.92)	1.12 (0.58–2.15)
Nodule	2.06 (1.67–2.53)***	1.98 (1.50–2.62)***	1.65 (1.01–2.68)*	2.26 (1.51–3.38)***
Opacity	2.51 (1.59–3.95)***	2.27 (1.30–3.98)**	2.95 (0.97–9.01)	2.90 (0.93–9.04)
Pleural effusion	0.89 (0.68–1.18)	0.74 (0.50–1.09)	1.29 (0.66–2.53)	1.01 (0.61–1.66)
Pneumothorax	0.49 (0.18–1.32)	4.53 (0.18–111.69)	0.73 (0.17–3.07)	0.35 (0.09–1.33)
Radiographic abnormality	**aOR[a] (95% CI) for subclinical Xpert-confirmed TB disease**			
	All years (N^c = 1144)	2020 (n^c = 620)	2021 (n^c = 194)	2022 (n^c = 330)
Blunted costophrenic angle	1.06 (0.62–1.79)	1.35 (0.65–2.82)	0.35 (0.08–1.57)	1.38 (0.56–3.40)
Calcification	1.26 (0.92–1.74)	NA[d]	1.22 (0.62–2.40)	1.27 (0.78–2.06)
Cardiomegaly	0.61 (0.25–1.44)	0.77 (0.25–2.39)	1.28 (0.05–33.28)	0.35 (0.08–1.57)
Cavity	0.85 (0.65–1.12)	0.80 (0.56–1.16)	1.41 (0.72–2.78)	0.67 (0.40–1.13)
Consolidation	0.71 (0.52–0.97)*	0.58 (0.39–0.88)*	0.91 (0.40–2.08)	0.97 (0.53–1.77)
Fibrosis	1.77 (1.10–2.85)*	2.15 (1.11–4.15)*	0.69 (0.15–3.19)	1.63 (0.71–3.73)
Hilar lymphadenopathy	1.00 (0.47–2.14)	0.80 (0.23–2.74)	0.96 (0.19–4.98)	1.15 (0.34–3.88)
Nodule	0.93 (0.62–1.42)	1.30 (0.73–2.30)	0.99 (0.34–2.89)	0.55 (0.25–1.23)
Opacity	0.49 (0.20–1.22)	0.62 (0.21–1.83)	0.29 (0.01–7.09)	0.12 (0.01–2.62)
Pleural effusion	0.65 (0.39–1.11)	0.57 (0.27–1.19)	0.97 (0.25–3.78)	0.65 (0.25–1.69)
Pneumothorax	1.55 (0.25–9.48)	NA[d]	0.45 (0.03–7.17)	1.89 (0.18–19.99)

aOR: adjusted odds ratios; CAD: computer-aided detection; CI: confidence interval; NA: not available; TB: tuberculosis; Xpert: GeneXpert.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] All 11 multilabel, non-TB radiographic abnormalities, if available, were included as predictors in the multivariable logistic regression models.

[b] Number of individuals with Xpert results.

[c] Number of individuals with Xpert-confirmed TB disease.

[d] Point estimates are not available because there were no CXRs with calcification or pneumothorax in 2020.

results consistent with TB among individuals without clinical symptoms", whereas ours relied solely on Xpert confirmation. Our findings regarding smoking also differ from Viet Nam's TB prevalence survey results, which suggest that current smoking is associated with both symptomatic and subclinical TB disease.[27] In contrast, in our 2X population, smoking was only associated with lower odds for subclinical TB; differences in study design most likely explain the discrepancies between our study and prevalence survey results.

Fibrosis was the only CAD multilabel radiographic abnormality that was associated with higher odds of subclinical TB disease among 2X participants. A common sequela of pulmonary TB,[28] fibrotic lesions tend to progress and regress repeatedly and thus represent a dynamic risk.[29] Nevertheless, there is some evidence to suggest that the presence of fibrosis may be prognostic for TB disease; one study showed that fibrosis or infiltrates on ^{18}F-FDG PET/CT can identify subclinical TB that is likely to progress to symptomatic TB disease among people

living with HIV.[14] Others have shown that fibrotic lesions are associated with an increased risk for progression to TB disease among individuals with TB infection.[5,30] For 2X participants, consolidation (which develops when air-filled spaces in the lungs become fluid-filled)[31] was associated with lower odds of subclinical TB. This is not surprising, since fluid occupying air-filled spaces normally causes respiratory symptoms.

Interest in the use of chest radiography for active case finding, particularly subclinical TB, has increased in recent years;[13,14,32–35] multiple studies have been conducted in a variety of settings (high- and low-TB burden) and differing study populations (in terms of age structure or HIV status). Studies have also compared the accuracy of CXRs versus CT scans and CXR field reading versus expert reading for identifying subclinical TB abnormalities. According to one such study in a low-TB burden country, cavitation, extensive parenchymal abnormalities and endobronchial spread were more frequently missed on CXRs than on CT scans.[13] Another study found that cavitation and upper-lobe parenchymal abnormalities were more likely to be missed by CXR field readers than expert readers.[33] In our setting, while cavitation was associated with higher odds of Xpert-confirmed TB, we found no evidence of an association with subclinical TB. Using qXR's pre-set threshold for cavitation of ≥0.90, we detected cavities in 33.4–42.8% of CXRs with Xpert-confirmed TB (depending on the year). It is possible that had we employed a lower, more sensitive threshold, we might have detected more cavitation and/or observed significant differences in cavitation between symptomatic and subclinical TB. Further limiting our analysis was the qXR output, which did not include an abnormality score for cavitation.

Deep learning-based CAD classification of multilabel radiographic abnormalities on CXR has demonstrated variable diagnostic accuracy for TB. An early version of qXR image classifiers matched human expert annotations for four radiographic abnormalities in drug-resistant TB CXRs.[20] Although qXR 2.0's discriminatory power for classifying specific chest abnormalities, measured against radiologists' interpretations, proved to be variable,[21] qXR 3.0 found significant associations between upper-lobe cavitation and TB disease among diabetics.[36] Radiographic abnormalities classified by Lunit INSIGHT version 3.1.0.0 (Seoul, Republic of Korea) were associated with culture-confirmed TB disease but had limited sensitivity using the manufacturer's pre-set thresholds.[37] Other convolutional neural networks-based algorithms reportedly classified TB-related radiographic abnormalities accurately.[23,38] Taken together, these studies suggest that CAD for CXRs may yet have value beyond providing simple binary results (TB-presumptive versus TB-negative). To date, however, no product has the proven capacity to accurately identify subclinical TB abnormalities. More research is needed to determine if CAD can improve CXR accuracy for detecting subtle lesions of early, subclinical TB disease. Clarification is needed from manufacturers on how multilabel radiographic abnormalities factor into the CAD TB threshold deep-learning algorithms. One way forward might be to focus on subclinical radiographic abnormalities that are detected on CT and PET/CT scans but are missed on CXR. For example, it might be possible to evaluate whether calibration of the fibrosis threshold improves the accuracy of CXR detection of subclinical TB disease. Cavitation, although not associated with subclinical TB in our population (possibly due to the high qXR ≥0.90 threshold), is another candidate for a similar evaluation. Of note, CXRs cannot detect metabolic activity in radiographic lesions; some lesions may thus exhibit the same radiographic appearance on CXRs, whether they are active or inactive, and regardless of the CAD threshold accuracy for TB or multilabel abnormalities.

In this study, the CAD-first and CAD-parallel integration models supported CXR interpretation and Xpert referral decisions along the 2X community workflow. The CAD-first model decreased physicians' workloads by limiting the number of CXRs for them to interpret to those rated as TB-presumptive; programmatic implementation in other settings has shown similar benefits.[34,39] The CAD-first model works well in high-TB burden settings where clinical evaluation, CXR interpretation, Xpert referral decisions and sputum collection are conducted in one site – for example, community campaigns that use mobile CXR vans or ultraportable CXR units as one-stop shops. CAD-parallel interpretation was difficult to implement with fidelity in the mobile vans, since in our protocol the physicians were not blinded to the CAD result; thus, their CXR reading may have been influenced by the CAD result, even though, ideally, they should have been independent. CAD-first integration was selected for the Viet Nam community setting, while CAD-parallel integration was selected for facility-based 2X case finding.[40]

Our study had limitations. We conducted Xpert testing only in participants with TB-presumptive CXRs or TB symptoms or risk; we did not carry out

systematic diagnostic testing in participants with normal CXRs. Not all participants with TB-presumptive CXRs underwent Xpert testing; however, this proportion was relatively small (8.2%) and thus unlikely to have significantly biased our findings. The CAD model and TB-presumptive threshold varied from 2020 to 2022, a timeframe also affected by COVID-19. Together, these factors limited comparisons of CXR results and Xpert yield across years. Therefore, in this report, we prioritized analyses of the multilabel, non-TB radiographic abnormalities, each of which had its own threshold that did not change from 2020 to 2022 and was, in theory, less affected by the CAD TB threshold. The changing CAD TB thresholds may still affect interpretation of multilabel radiographic abnormalities, especially for year-to-year comparisons.

CONCLUSIONS

Double X TB case finding detected a high proportion of subclinical TB disease among TB-vulnerable populations in Viet Nam's communities. While there is a clear role for CAD as a tool to aid the interpretation of digital CXRs in screening programmes for TB disease, further research is needed to determine whether CAD can improve CXR identification of subclinical TB using multilabel, non-TB radiographic abnormalities.

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Conflicts of interest

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Ethics statement

The FHI 360 Office of International Research Ethics determined that the "External quality assurance for chest X-rays for tuberculosis screening" implementation study did not meet the regulatory definition of research as defined under the Department of Health and Human Services Code of Federal Regulations [45 CFR part 46.102(d)(f)]. Due to implementation under routine programme conditions, ethics approval was waived in accordance with Viet Nam regulations. Verbal consent was obtained from all individuals before participation.

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Implementation of maternal death audits and changes in maternal health care in Cambodia, 2010–2017

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Objective: Cambodia is one of seven countries globally that met Millennium Development Goal 5A: reduction of maternal deaths by at least 75% between 1990 and 2015. The maternal death audit (MDA) was instituted in 2004 to support the improvement of maternal care. We evaluated progress in MDA implementation and maternal health services in Cambodia between 2010 and 2017.

Methods: International experts and the national MDA committee members assessed all case abstracts, investigation questionnaires and audit meeting minutes covering all maternal deaths reported in Cambodia in 2010 and 2017 for quality of classification, data, care and recommendations. They convened provincial MDA committees to conduct similar assessments and develop evidence-based recommendations. Differences in data from the two years were assessed for significance using χ^2 and Fisher's exact tests.

Results: In 2010 and 2017, 176 and 59 maternal death cases were reported, respectively. Cases were more likely in 2017 than in 2010 to have antenatal care (90.0% vs 68.2%, $P = 0.004$), give birth in a facility (81.6% vs 55.3%, $P = 0.01$) and receive a prophylactic uterotonic (95.7% vs 73%, $P < 0.02$) for postpartum haemorrhage and magnesium sulfate (66.7% vs 37%, $P = 0.18$) for preeclampsia/eclampsia. However, additional interventions and improved timeliness of referral with equipped and competent staff were identified as critical. Data quality prevented the classification of one fourth of cases during both periods. The quality of MDA recommendations improved from 2.8% in 2011 to 42% in 2018.

Discussion: Improvements in maternal care are reflected in the increased antenatal care, facility births and better postpartum haemorrhage and preeclampsia/eclampsia management. However, additional care management improvements are needed. The MDA reporting needs to improve data completeness and make more specific recommendations to address causes of death.

Pregnant women are among the most vulnerable populations, and this increases during public health emergencies whether from disasters or infectious disease outbreaks. The Asia Pacific Health Security Action Framework[1] notes the critical role that resilient health systems play in delivering equitable and timely health services before, during and after a public health emergency, especially for vulnerable populations. It further recognizes the mutually reinforcing role of health security and health systems. The resilience of health systems to deliver services during events is highly associated with how strong the system was before the event. Thus, priority needs to focus on continuity planning to maintain obstetric and other essential health services during emergencies and strengthen routine care and surveillance. Maternal death surveillance and response systems provide critical information for strengthening routine maternal health-service delivery systems to mitigate pregnancy-related risks, including those from public health emergencies.

Cambodia is one of a few countries that met the target of Millennium Development Goal (MDG) 5A: reduction of maternal deaths by at least 75% between 1990 and 2015.[2] In this context, Cambodia's Ministry of Health issued the Fast-track Initiative Roadmap for Reducing Maternal and Newborn Mortality (2010–2015 and 2016–2020),[3,4] which recommended skilled attendance at birth and birth spacing. The government achieved this by: (1) recruiting midwives for all health

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centres; (2) enabling them to provide basic emergency obstetric care, family planning counselling and implement safe abortion care through direct training, supportive supervision and skills building during periodic refresher skills training; (3) providing financial incentives to midwifery teams for each facility birth that ended with a live mother and newborn; (4) removing financial barriers by establishing the Health Equity Fund (initiated in 2008)[5] and other financial schemes; and (5) developing behavioural change communication.

In Cambodia, maternal deaths were estimated to have reduced from 1020 to 161 per 100 000 live births between 1990 and 2015, while births attended by skilled personnel and the number of women reporting at least four antenatal care visits tripled between 2000 and 2014.[6–8]

The World Health Organization (WHO) recommends that countries conducting maternal death surveillance and response (MDSR) address critical moments where a woman's life could have been saved.[9,10] Case studies found that while MDSR is well accepted, its integration into health systems is limited.[11] Evaluations in Zimbabwe found that inadequate health-worker knowledge and the scarcity of guidelines and notification forms impeded MDSR functionality.[12] Studies in Nigeria, Rwanda, United Republic of Tanzania and Zimbabwe found that 55% of facilities could demonstrate improvements in "evidence of routine integration" of the maternal and perinatal death surveillance and response (MPDSR) process, but few facilities had mechanisms to promote a no-blame environment.[13] In Ethiopia, the triangulation of MDSR and emergency obstetric care data identified postpartum haemorrhage (PPH) (10–27%) and severe preeclampsia/eclampsia (10–24%) as common immediate causes of death, with delayed arrival at a health facility and transfer to an appropriate level of care accounting for 32–40% and 22–29% of underlying factors, respectively. Half (48%) of women who died of PPH received uterotonics, while 72% who died of severe preeclampsia/eclampsia received anticonvulsants.[14]

This report aims to highlight progress noted during two internationally led peer review assessments of the Maternal Death Audit (MDA) implementation and maternal health-service quality conducted in 2010 and 2017 in Cambodia.

METHODS

Routine maternal death audits

Cambodia instituted the National Protocol on Maternal Death Audit, including confidential enquiry and verbal autopsies, in 2004.[15] The protocol included: the MDA steps; organizational structure and terms of reference for members; standardized templates, including notification and investigation forms to be completed for each case and a narrative form to briefly describe the events from onset until death; and a table of recommendations from audit meetings. The protocol states that maternal deaths should be reported as soon as possible, investigated within 2 weeks and reviewed at provincial MDA committee audit meetings within a week thereafter. During reviews, gaps and contributing factors are identified and recommendations made to prevent future deaths. These are distributed to provincial health departments and operational districts and assessed for implementation at subsequent audit meetings.[15]

International expert-facilitated review

International experts facilitated the review of all reported maternal deaths from 2010 in a 2011 review workshop. This led to revisions to the national MDA protocol (2014),[16] including: the revision of the national and provincial MDA committees' structure and terms of reference; the establishment of a regular meeting for the national MDA committee to monitor and provide technical support to all provincial MDA committees; and the strengthening of the recommendations and response portions of the protocol. A similar review workshop was conducted in 2018 to assess all reported maternal deaths in 2017.

Prior to the workshop, international experts and the national MDA committee assessed all maternal death case abstracts, investigation data collection forms, and minutes of audit meetings from each of the 24 provinces and Phnom Penh (the capital region) in 2010 and 2017. They classified cases as maternal deaths (direct or indirect), fortuitous deaths (those that occur due to causes unrelated to pregnancy), not a maternal death (the woman was neither pregnant nor had she been pregnant in the preceding 42 days) or unclassifiable (maternal death of unknown cause). They then identified the cause, timing and place of death and assessed whether provincial

MDA committee recommendations addressed the key moments in which a woman's life could have been saved, including recognition of underlying problems within the health system, such as the lack of essential medicines and health-care workers with the capacity to manage obstetric emergencies. They commented on data quality, including data needed to improve case classification and recommendations. Finally, they compared the reported numbers of maternal deaths across the country with the United Nations maternal death estimates for Cambodia.

On 2–3 June 2011 and 14–16 November 2018, the national MDA committee convened MDA assessment workshops with three members from each subnational MDA committee to review MDA reports and committee recommendations. Participants were divided into eight groups of nine people from three provinces (three per province). Each review followed the same process as the international experts and national MDA committee. Finally, each provincial group developed specific recommendations for improving the MDA process and care provided.

Sample, data sources and definitions

All maternal deaths reported to the provincial committees in 2010 and 2017 were included. Data used for the review included case abstracts, data collection forms used in provincial death investigations, and the minutes of audit meetings covering all maternal deaths reported from each subnational committee. These data were sourced from medical records and included medical history, physical, laboratory and imaging test results, treatments and drug orders, as appropriate. For the international review, National Reproductive Health Program members translated these data from Khmer into English. Qualitative data on quality of care and MDA came from participants from these subnational areas. Standard definitions were used for all variables.[17]

Data analysis

The international experts extracted and entered data on the variables of interest from the translated case abstracts into Microsoft Excel, then cleaned and presented them as categorical values. Descriptive statistics (n/N, %; or mean, standard deviation) were calculated for each variable for 2010 and 2017 and compared for statistical significance using χ^2 and Fisher's exact tests as appropriate, using Epi Info 7.0™ (2021).

RESULTS

Number and characteristics of maternal death cases reviewed

Nationwide in 2010 and 2017, 176 and 59 maternal death cases were reported, respectively, and were reviewed by the national MDA committee and international experts. Compared to 2010, cases in 2017 had lower parity (2.1 in 2017 versus 3.6 in 2010) and were significantly more likely to have one (90.0% vs 68.2%) and at least four (48.0% vs 27.3%) antenatal care visits, and for childbirth (52.3% vs 28.7%) and place of death (65.9% vs 46.3%) to be in a public hospital. The timing of death was more commonly during antepartum and postpartum periods (**Table 1**).

Cause of death

In both 2010 and 2017, 35–39% of deaths were from postpartum haemorrhage and 10–15% were from preeclampsia/eclampsia (**Table 2**). Less common causes included antepartum bleeding, gestational trophoblastic disease, dehydration, cerebrovascular accident, congestive heart failure, pneumonia and ectopic pregnancy. However, a cause of death could not be assigned ("unclassifiable") based on the available information in 26.7% of deaths in 2010 and 27.1% in 2017. When a maternal death occurred in another province (for example, in a national referral hospital), the hospital where the death occurred reported the death but did not provide clinical information to the MDA committee of the home province. In such situations, provincial MDA committees relied on information provided by the family to assign the cause of death and identify contributing factors.

Contributing factors

The most common contributing factors in 2010 were anaemia (11, 6.3%) and HIV (4, 2.2%). In 2017, anaemia was a contributing factor for two (3.4%) deaths, while HIV was a contributing factor for none. The most common harmful traditional factor noted in 2010 was "roasting" (16, 9.1%), where women in the postnatal period are put in a room with a hot fire for up to a month. No harmful traditional factors were noted in 2017. The number of women who reportedly had an abortion in 2010 and 2017 were eight (4.5%) and one (1.7%), respectively.

Table 1. Characteristics of reported maternal deaths, 2010 and 2017, Cambodia

Characteristic	2010 (*N* = 176)	2017 (*N* = 59)	*P*
Age, mean (standard deviation)	31.1 (7.5)	32.2 (6.5)	NS
Parity, mean (standard deviation)	3.6 (2.5)	2.1 (1.7)	0.001
Antenatal care by skilled provider			
At least one contact	60 (68.2)	45 (90.0)	0.004
Four or more contacts	24 (27.3)	24 (48.0)	0.014
Place of birth			
Home, not attended by skilled attendant[a]	55 (40.4)	6 (13.6)	0.001
Home, attended by midwives	4 (2.9)	0	NS
Health centre	30 (22.1)	12 (27.3)	NS
Public hospital	39 (28.7)	23 (52.3)	0.004
Private health facility	3 (2.2)	2 (4.5)	NS
During transfer	5 (3.7)	1 (2.3)	NS
Place of death			
Home, not attended by skilled attendant[a]	29 (21.3)	4 (10.3)	NS
Home after birth with skilled attendant	5 (3.7)	1 (2.2)	NS
Health centre	14 (10.3)	6 (9.1)	NS
Public hospital	63 (46.3)	29 (65.9)	0.024
Private health facility	1 (0.7)	1 (2.3)	NS
During transfer	24 (17.6)	3 (6.8)	NS
Timing of death			0.0001
Antepartum	40 (23.7)	8 (14.3)	–
Intrapartum	3 (1.8)	10 (17.9)	–
Postpartum	119 (70.1)	37 (66.1)	–
Post-abortion	7 (4.1)	1 (1.8)	–

NS: not statistically significant.

Values are *n* (%) unless otherwise indicated.

[a] Attended by a traditional birth attendant or relative or unattended

Table 2. Major causes of death of reported maternal deaths, 2010 and 2017, Cambodia

Cause of death	2010 (*N* = 176)	2017 (*N* = 59)	*P*
Postpartum haemorrhage	63 (35.8)	23 (39.0)	0.72
Preeclampsia/eclampsia	27 (15.3)	6 (10.2)	0.30
Abortion-related	8 (4.5)	1 (1.7)	0.32
Obstructed labour/ruptured uterus	4 (2.3)	3 (5.1)	0.28
Sepsis	4 (2.3)	2 (3.4)	0.64
Unclassifiable	47 (26.7)	16 (27.1)	0.95
Other	23 (13.1)	8 (13.6)	–

Values are *n* (%) unless otherwise indicated.

Table 3. Use of medications in the management of women who died of postpartum haemorrhage and preeclampsia/eclampsia from reported maternal death cases, 2010 and 2017, Cambodia

Cause of death and treatment received	2010	2017	*P*
Postpartum haemorrhage cases	63	23	–
Postpartum haemorrhage cases that received:			
Oxytocin, prophylactic	46 (73.0)	22 (95.7)	0.02
Oxytocin, second dose	8 (12.7)	7 (30.4)	0.14
Preeclampsia cases	27	6	–
Preeclampsia cases that received:			
Magnesium sulfate	10 (37.0)	4 (66.7)	0.18
Antihypertensive	1 (6.7)	1 (16.7)	0.48

Values are n (%) unless otherwise indicated.

Table 4. Missing data per variable in reported maternal deaths, 2010 and 2017, Cambodia

Variable	Missing observations	
	2010 (*N* = 176)	2017 (*N* = 59)
Age	2 (1.1)	0 (0.0)
Parity	9 (4.1)	5 (8.5)
Place of birth	40 (22.7)	15 (25.4)
Death[a]		
Timing	7 (4.6)	3 (5.1)
Place	2 (1.1)	1 (1.7)
Classifiable cause	47 (26.7)	16 (27.1)
Status of baby	39 (22.2)	37 (72.5)[a]

Values are *n* (%) unless otherwise indicated.

[a] *N* = 51 in 2017, as eight mothers died before delivery of the baby.

Quality of care

Of the 63 women who died of PPH in 2010, 46 (73.0%) received a prophylactic uterotonic in the third stage of labour versus 22 (95.7%) of the 23 women who died of PPH in 2017 (χ^2 = 5.2, *P* <0.02). The use of additional uterotonics was recorded in seven (30.4%) of 23 reports reviewed in 2017 and eight (12.7%) of the 63 reports with available data in 2010 (χ^2 = 2.1, *P* = 0.14). Delays in the use of additional doses of oxytocin and correction of hypovolemic shock were additionally noted to have contributed to PPH-related deaths in hospitals (**Table 3**).

Among the 27 women who died from preeclampsia/eclampsia in 2010, 10 (37.0%) received magnesium sulfate, but one (3.7%) received it late and in inappropriate doses. Among the six hypertension-related maternal deaths in 2017, four (66.7%) received magnesium sulfate, but one (16.7%) received it late. The use of antihypertensive medication in the management of eclampsia was recorded in one (16.7%) of six reports reviewed in 2017 and one (6.7%) of 15 with available data in 2010 (χ^2 = 0.50, *P* = 0.48; **Table 3**).

MDA reports in 2010 and 2017 also described disrespectful behaviour by care providers such as shouting and disregarding the women's complaints. Additionally, during the 2018 review, participants reported that ambulances were stationed at provincial hospitals and were summoned to health centres for emergency transfers. This could have contributed to delays in critical therapeutic management. Moreover, some medicines (for example, oxytocin and magnesium sulfate) or materials in emergency care kits were not replenished in a timely manner. Even when available, they may not have been used as staff do not routinely accompany sick mothers during referral for emergency care or communicate with the receiving hospital.

Data quality

Information was insufficient to assign the cause of maternal death in over one quarter of cases reviewed in both time periods. Other indicators were also missing data (**Table 4**). Statistical significance was probably limited by the relatively small number of total cases, especially for preeclampsia.

Quality of the MDA recommendations

The expert panel judged that only five (2.8%) MDA recommendations in 2010 and five (42%) of the randomly selected sample of 12 recommendations from 2017 specifically addressed correcting the point along the causal pathway that resulted in maternal death. Most MDA recommendations reviewed in 2010 were vague. Examples include: "arrange and strengthen the referral system of Operational District"; "Health centres should have free referral system for pregnant woman"; and "strengthen management and quality of services." During the discussion in 2018, participants reported that more specific recommendations related to contributing factors were made during the MDA committee meetings but were not reflected in written recommendations.

Underreported deaths

Assuming a birth cohort of 360 000, the 176 deaths in 2010 corresponded to a maternal mortality ratio (MMR) of 49/100 000 live births. The Cambodian Demographic and Health Survey[7] estimated an MMR of 206/100 000 live births (95% confidence interval [CI]: 124–288), an under-reporting of 567 cases (95% CI: 271–863). The United Nations (WHO, the United Nations Children's Fund, the United Nations Population Fund and the World Bank Group) estimated MMR in 2017 to be 160 (95% CI: 116–221), equivalent to 590 deaths.[18] The 59 deaths reported underreports the total deaths by 531.

Feedback from peer reviews and international experts

The peer review groups arrived at similar conclusions as the international experts and the national MDA committee on the quality of recorded data and recommendations made, and the improvements needed to strengthen MDA implementation.

The international experts who participated in both workshops noted that many participants in 2011 appeared unengaged in the evaluation process. One participant remarked: "If I only knew someone would read my report, I would have written a better-quality report." In 2018, participants actively assessed the MDA cases and acknowledged gaps in the MDA committee process and recommendations: "This workshop made me realize that there are a lot of mistakes, incomplete and misinformation that could not be analysed in the MDA. Our MDA recommendations are very vague and not specific."

Observations about care quality included: "health facilities often did not follow the Safe Motherhood Protocol"; "...(sometimes) did not correctly diagnose maternal conditions"; and "…often were late in providing (or did not provide) appropriate lifesaving management and referral."

The peer review groups recommended that mechanisms should ensure that clinical information about deaths that occurred after referral are available for provincial MDA committee audit meetings, and that records and information are complete. Recommendations should focus on addressing the causal pathway and committees should systematically follow up on the implementation of recommended actions. They further recommended retraining on the management of common conditions (for example, PPH) and life-saving interventions (for example, active management of the third stage of labour and stabilization before referral).

DISCUSSION

As one of only seven countries to have met the MDG5A target, Cambodia has made remarkable progress towards improving services and survival for women of reproductive age. Our observations of MDA implementation in Cambodia in 2010 and 2017 provide insights into some concrete contributions to the continued improvement in maternal survival, including during public health emergencies.

Compared to 2010, significantly more births and deaths in 2017 occurred in health-care facilities than at home (**Table 1**). The median parity among the deceased decreased from 3 to 2 over the same period. These

findings align with the Cambodian Demographic and Health 2010 and 2014 surveys, where the number of home births decreased by 62% (from 45% to 17%) and the total fertility rate decreased from 3.0 to 2.7.[7,8]

In 2007, the Government of Cambodia offered an incentive to midwife teams for every live birth occurring at health facilities that resulted in a live mother and baby.[19] This resulted in a vast national increase in births at health facilities that is recognized globally.[20] The Ministry of Health invested nationwide to ensure that a wide range of family planning modalities were available at all health centres and midwives had the capacity to provide them. This is despite Cambodia ranking 159th among 196 countries globally in per capita gross national income.[21]

PPH and preeclampsia/eclampsia were the top two causes of maternal death in 2010 and 2017. However, compared to women who suffered maternal deaths in 2010, the women who died in 2017 were more likely to have received prophylactic uterotonics and magnesium sulfate. Among women who died following PPH, those who did not receive active management during the third stage of labour decreased from 27% to 4.3% and subsequent addition of oxytocin from 84% to 70%, though the latter was not statistically significant. Among those who died due to preeclampsia/eclampsia, the percentage of those who did not receive magnesium sulfate or antihypertensives decreased by half, but neither reached statistical significance, presumably due to the small sample size.

Additional interventions besides prophylactic uterotonics and magnesium sulfate are needed to further reduce maternal deaths due to PPH and preeclampsia/eclampsia. When PPH occurs, health-care providers need to recognize the problem early and take timely actions such as adequate fluid infusions, additional uterotonics, tranexamic acid, uterine compression, surgical interventions and blood transfusions.[22] Likewise, women with severe preeclampsia/eclampsia should receive antihypertensive medication and adequate fluid management while steps are taken for early termination of pregnancy.[23,24] Our study focused on additional doses of oxytocin and the addition of antihypertensives for PPH and preeclampsia, respectively. Both interventions need improvement. Delays in referral because of the late arrival of ambulances, use of ambulances without functional emergency kits and lack of staff accompanying women during referrals are additional challenges. These findings are similar to other evaluations that have been conducted.[25]

Finally, community interventions for iron, folic acid and calcium supplementation, and aspirin in selected pregnancies and populations could reduce anaemia and preeclampsia and thereby reduce complications immediately before, during and after childbirth.[26]

Relevant and specific MDA recommendations increased from 3% among the death reports reviewed in 2010 to 42% in 2017. While many recommendations are more relevant, effective use of data to guide recommendations can be greatly improved.

Compared to 2010, maternal death cases in 2017 had decreased by two thirds. However, these represent only one tenth of the estimated maternal deaths in Cambodia, and efforts should be taken to improve maternal death reporting. Routine health information systems under-report maternal deaths, while surveillance systems may or may not improve accurate counting of maternal deaths. Under-reporting of maternal deaths is common and has been reported from Asia and Africa.[27–31] Under-reporting should be suspected when reported deaths are significantly below estimated deaths. One must note that estimates of maternal mortality have wide ranges of uncertainty and are based on events that occurred years earlier, not in real time as with surveillance data.[32] More importantly, ensuring corrective actions in response to the findings of even a small proportion of deaths could contribute to improvements in maternal health and survival.[33]

The two internationally facilitated reviews used death summary reports submitted by provincial MDA committees in Khmer and translated into English. Accuracy of the contents of these summaries could not be verified. The participants noted that better recording of clinical information would make it easier to understand why the women died and to ensure correct classification of cause of death and appropriate recommendations. Over one quarter of deaths were unclassifiable based on the audit reports. When a maternal death occurred, all relevant information related to care at the different health-care facilities should have been shared with the provincial MDA committees. Timely information sharing between the different levels will contribute to better

quality reviews, identification of modifiable factors that lead to maternal deaths and recommended interventions to address them.

Globally, data systems often do not undergo rigorous review. Decision-makers then either base decisions on unvalidated information or ignore the data. This becomes a burden without benefit. Furthermore, improving data quality requires feedback mechanisms to the reporting units. MDSR systems are no exception. This was exemplified in the first workshop, at which the reporter noted that if he had known someone was going to look at the report, he would have done a better job. The participant obviously was doing this for compliance and not quality improvement. In the second workshop, perhaps because the participants had been through this evaluation previously and had an active national MDA committee, with quarterly reviews headed by a Secretary of State, the participants participated more actively and questioned each other. They recognized the need to continue to collect information more precisely and to make more relevant MDA recommendations.

The richness of these evaluation findings shows the value for countries to engage end-users in routinely evaluating information data systems including MDSR. Likewise, it shows the vastly improved maternal care provided in Cambodia between 2010 and 2017. Lastly, it helped identify the actions needed to continue improving routine maternal health services, which is the first step to making them robust and resilient to events that could disrupt service delivery. MDSR needs to be considered as an adjunct to strengthening maternal health-service delivery systems to meet the needs of pregnant women before, during and after public health emergencies.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

All information was collected as part of the maternal death audit process. No new information was collected for the purposes of this report. The review was conducted as part of a quality improvement exercise to improve maternal death audits. All information contained herein was de-identified.

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Investigating suspected gastrointestinal anthrax: a case-control study in Cayapa village, Abra province, Philippines, March 2017

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Objective: Due to rising cases of foodborne illness in Cayapa village, Abra province, Philippines, a team was dispatched on 21 March 2017 to conduct an epidemiological investigation. The objectives were to confirm the diagnosis, determine the existence of an outbreak, identify risk factors and recommend prevention and control measures.

Methods: A 1:2 case-control study was conducted. We defined a suspected case as a previously well village resident who developed abdominal pain or diarrhoea, and one or more symptoms of fever, vomiting, sore throat, difficulty swallowing or lymphadenopathy between 27 February and 14 March 2017. Confirmed cases were suspected cases who tested positive for *Bacillus anthracis* through bacterial culture or rt-PCR. Serum and soil samples were collected for testing, and an environmental survey and key informant interviews were conducted. Stata version 13 was used for data analysis.

Results: The epidemic curve indicated a point source outbreak for the 29 cases identified. Common signs and symptoms were abdominal pain (26, 90%), fever (16, 55%) and diarrhoea (14, 48%). One case presented with lymphadenopathy. Interviews revealed that a dead carabao had been butchered and sold to the villagers. The 11 serum specimens and five soil samples tested were negative for *B. anthracis*. After multivariable analysis, consumption of the uncooked meat of the carabao was significantly associated with being a case (adjusted odds ratio: 6, 95% CI: 1.7–18.4).

Discussion: This outbreak was most likely associated with the consumption of the carcass of a dead carabao. Educating such farming communities on preventive measures for zoonotic diseases is recommended.

Anthrax is an infectious disease caused by *Bacillus anthracis*, a gram-positive, rod-shaped bacterium that can form spores. It can occur in humans in three forms: pulmonary, cutaneous and gastrointestinal.[1] The incubation period ranges from 15 hours to 60 days but is usually 1–7 days. Cutaneous anthrax is the most common form. It typically presents as a papular skin lesion, surrounded by a ring of fluid-filled vesicles. The central papule eventually ulcerates and forms a dark, depressed black eschar.[2]

Gastrointestinal anthrax includes fever and chills, nausea and vomiting, diarrhoea or bloody diarrhoea, abdominal pain, sore throat, lymphadenopathy and difficulty swallowing.[3] This may progress to shock, coma and death. In most of the reviewed case reports and related articles about gastrointestinal anthrax, the disease has a mortality rate of 25–60%.[4,5] However, the spectrum of disease may range from no symptoms to death and may not always be severe.[6] Consumption of raw or undercooked meat from an infected animal is the most common mode of transmission for gastrointestinal anthrax.[7]

In the Philippines, 20 health events related to anthrax were reported to the Department of Health Epidemiology Bureau from January 1999 to July 2024, through the Field Epidemiology Training Program (FETP), the Event-based Surveillance and Response system and the Philippine Integrated Disease Surveillance and Response system. Of the reported events, five (25%) were from the Cordillera Administrative Region. The first

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report was in May 2010 with 39 suspected cases in Abra province, and the most recent was in October 2023 with five cases of cutaneous anthrax in Kalinga province.

Cayapa is one of 17 villages of Lagangilang municipality in Abra province which, in 2017, had a projected population of 954.[8] The main source of livelihood is agricultural farming, including the raising of livestock such as swine, goats and carabaos. On 21 March 2017, a team of FETP fellows was sent to Cayapa village to investigate an increase in reports of foodborne illness. The team's objectives were to verify the diagnosis, establish the existence of an outbreak, identify risk factors and recommend prevention and control measures. This is the first report of suspected gastrointestinal anthrax in the Philippines.

METHODS

Epidemiological investigation

Cases began to appear after the meat of a dead carabao was sold in the community. A sex-unmatched, 1:2 case-control study was conducted to test the hypothesis that consumption of by-products of the implicated carabao was the mode of transmission. Medical records from the Rural Health Unit and Abra Provincial Hospital were reviewed to identify cases and controls. Active case finding was also conducted using a structured questionnaire to collect demographic, clinical and food exposure data from the study participants. For cases and controls who were minors, parents or guardians completed the questionnaire in their stead.

Cases were defined as follows. A suspected case was a previously well resident of Cayapa village who developed abdominal pain or diarrhoea and any of the following symptoms including vomiting, sore throat, difficulty swallowing, lymphadenopathy or fever from 26 February to 15 March 2017. A confirmed case was a suspected case who tested positive for *B. anthracis* through bacterial culture or reverse transcription-polymerase chain reaction (rt-PCR). A control was a resident of Cayapa village living in or near the house of a case with no clinically compatible symptoms and who tested negative for *B. anthracis* during the study period.

Statistical analysis

Data analysis was conducted using Stata version 13. Variables with $P < 0.05$ in bivariate analysis were included in a multivariable logistic regression model. Backward elimination was employed to refine the model by systematically removing variables with the highest P values exceeding 0.05 at each elimination step. Statistically significant variables identified during the multivariable analysis were reported.

Key informant interviews, environmental investigation and laboratory testing

Local officials and health officers were interviewed to substantiate the information gathered. An ocular survey was also conducted at the site where the carabao was found dead and where it had grazed to gain in-depth insight into the health event.

Serum specimens were collected from the cases and soil samples from the site for laboratory confirmation. The serum specimens were sent to the Research Institute for Tropical Medicine, while soil samples were sent to the Reference Laboratory of the Department of Agriculture, Cagayan Valley Region. Both sets of samples were tested for bacteriological isolation.

RESULTS

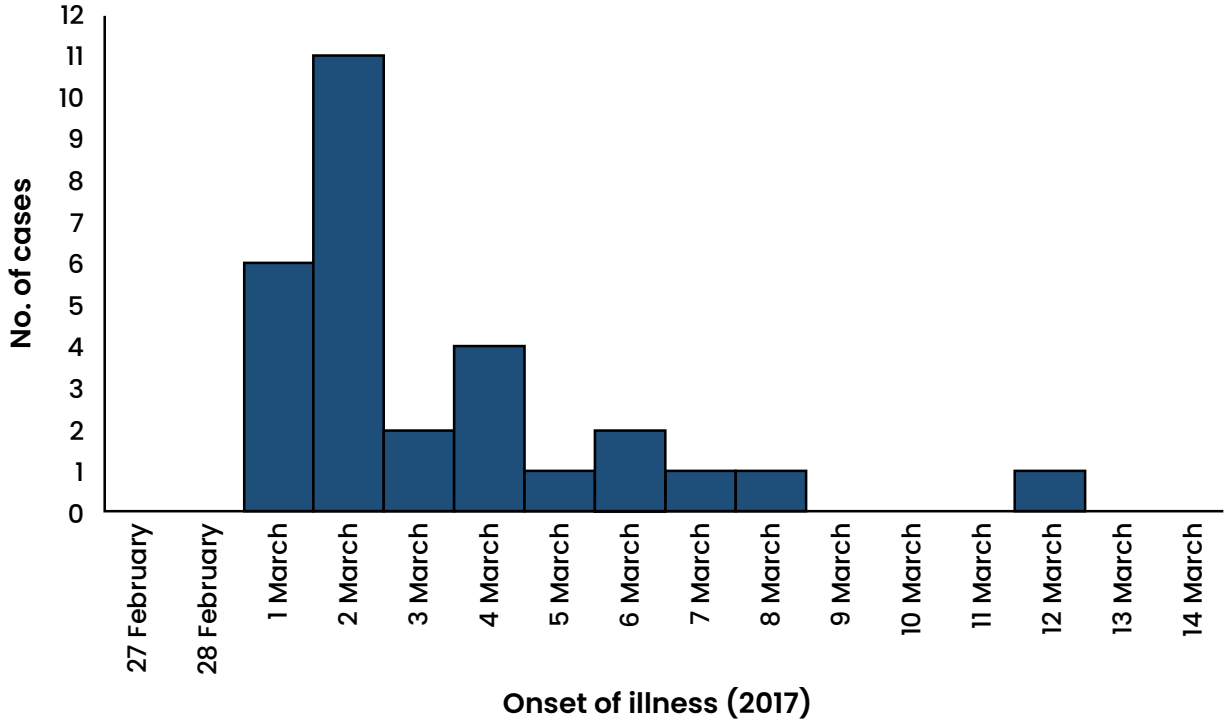
Descriptive analysis

The first symptomatic cases of suspected gastrointestinal anthrax appeared on the evening of 1 March 2017, 12 hours after the meat of the dead carabao was consumed, and peaked on 2 March (**Fig. 1**). Most of the 29 cases identified were male (15/29, 52%), with ages ranging from 6 to 77 years old (median 17 years). The most affected age group was 5–9-year-olds (6/29, 21%). The most common symptoms were abdominal pain (26/29, 90%), fever (16/29, 55%), diarrhoea (14/29, 48%) and difficulty swallowing (9/29, 31%). One case presented with lymphadenopathy and was further referred to the provincial hospital for management. No deaths were reported.

Key informant interviews

According to the Municipal Health Officer, the first case from Cayapa village presented on 6 March 2017 with an itchy and painless skin lesion, headache, malaise, difficulty breathing and neck pain that began on 3 March. The case reported that he participated in butchering a dead carabao on 1 March. An interview with the health

Fig. 1. **Suspected gastrointestinal anthrax cases by onset of illness (*N* = 29), Cayapa village, Abra province, Philippines, 27 February–14 March 2017**



workers who reported the cases revealed that residents had small blisters that looked like an eschar on their hands. Moreover, since the residents had experienced a similar incident of anthrax in the past, most affected residents were self-medicating with over-the-counter medicines as soon as they felt itchiness on their upper extremities.

The animal owner reported that the carabao looked weak when they purchased it on 28 February 2017 from a nearby municipality. The carabao was taken to a dry, harvested rice paddy to graze. The farm was about 1 km away from the community. On the early morning of 1 March, the animal was found dead, appearing slightly bloated. To recoup the value of the animal, the owner decided to sell the meat. Some parts of the carcass were consumed by those who participated in the butchering of the carabao, while the rest was sold to the community. Some was cooked as a meal on the same day and some was cured or sundried for later cooking. According to the owner, anthrax was never entertained as the cause of death.

The interview with representatives from the local Department of Agriculture revealed that there were three additional animal deaths in the village in the period 8–17 March 2017. All were goats that had died of dehydration and had been grazing in the same area where the dead carabao was found. The goat meat was not consumed as the carcasses were burned and buried. It was also reported that anthrax is endemic in the region.

Environmental results

During the ocular inspection, it was noted that most of the farm fields were bare and dry. This was consistent with the site where the implicated carabao had grazed and was found dead.

Laboratory results

The 11 serum specimens collected from cases were negative for any important pathogen, including *B. anthracis*. The five soil samples collected were positive for *Bacillus cereus* through bacterial culture.

Analytical study

A total of 58 controls were interviewed. Just over half were males (30/58, 52%), with an age range of 3–80 years old (median 19 years). Univariate analysis revealed

Table 1. **Analysis of factors associated with gastrointestinal anthrax (*N* = 87), Cayapa village, Abra province, Philippines, 27 February–14 March 2017**

Factor	Cases (*n* = 29)		Controls (*n* = 58)		Crude odds ratios	Multivariable odds ratios
	No.	%	No.	%	OR (95% CI)	OR (95% CI)
Male	15	52	30	52	1 (0.4–2.7)	0.8 (0.3–2.2)
≥17 years old	13	45	31	53	0.7 (0.3–1.9)	0.3 (0.7–1.0)
Handled raw meat of the dead animal	6	21	8	14	2 (0.4–6.1)	3 (0.6–11.0)
Cooked meat of the dead animal	5	17	8	14	1 (0.3–5.1)	1 (0.2–3.9)
Occupation associated with handling animals	14	48	18	31	2 (0.7–5.7)	3 (0.7–9.4)
Ate ≥5 tbs of meat of the dead animal	18	62	39	67	0.8 (0.3–2.3)	0.7 (0.2–2.2)
Ate uncooked meat of the dead animal	10	34	5	9	6 (1.5–23.1)	6 (1.7–18.4)

CI: confidence interval; OR: odds ratio; Tbs: tablespoons.

that a greater percentage of cases than controls had an occupation associated with handling carabao (48%), ate the uncooked meat of the dead carabao (34%), handled the raw meat (21%), cooked the meat (17%) and helped prepare the meat (3%).

On bivariate analysis, eating the uncooked meat of the dead carabao (odds ratio: 6, 95% CI: 1.5–23.1) was a risk factor for being a case, while multivariable analysis showed that those who consumed the uncooked meat were 6 times more likely to develop signs and symptoms (adjusted odds ratio: 6, 95% CI: 1.7–18.4) than controls (**Table 1**).

DISCUSSION

The epidemic curve indicates a point source outbreak of suspected gastrointestinal anthrax in Cayapa village from 1 to 12 March 2017. The clinical manifestations and epidemiological findings suggested that the event could be attributed to the consumption of the by-products from the implicated dead carabao.

One limitation of our study is that *B. anthracis* was not isolated in either the human specimens or soil samples; therefore, the possibility of other foodborne pathogens as the cause of infection cannot be ruled out. The collection of serum specimens from the cases 3 weeks after administration of antibiotics may have contributed to the non-isolation of the bacteria. *B. anthracis* is highly sensitive to antibiotics. Administering antibiotics for more than 24 hours may result in the pathogen not being isolated from cultures taken from any site.[9] However, using the Bradford Hill criteria as a framework for epidemiological interpretation of the study, we found temporal, strong statistical and cause-and-effect association between exposure to the dead animal's by-products and the occurrence of disease that is consistent with other published epidemiological studies.[10,11]

First, the signs and symptoms presented by the cases, including sore throat, neck pain, difficulty swallowing and lymphadenopathy, are distinctive and less commonly associated with typical foodborne illnesses.[3] Instead, these are commonly observed among cases of gastrointestinal anthrax. A high level of suspicion of *B. anthracis* as the causative agent cannot be disregarded, especially in regions where anthrax is endemic.

Second, there was a statistical association between eating the uncooked meat of the implicated animal and being a case. This was consistent with other studies on gastrointestinal anthrax.[12,13]

Third, there was an appropriate time sequence to establish a temporal relationship between the exposure or consumption of the animal's by-products and the occurrence of disease. All cases had a history of consuming the implicated food before the onset of symptoms. The onset of all cases ranged from 12 hours to 11 days (median 1 day). These fall within the incubation period of gastrointestinal anthrax, which usually ranges between 1 and 7 days but can be as early as <1 day and extend up to 60 days.[14] Also, comparing the incubation period of *B. cereus*, *Staphylococcus aureus* and other common foodborne pathogens with *B. anthracis*, the time sequence is more compatible with the occurrence of gastrointestinal anthrax rather than a typical foodborne illness, which

has a very short incubation period.[13] Similarly, Maddah, Abdollahi & Katebi[15] highlighted the importance of promptly recognizing gastrointestinal anthrax, and that it may be diagnosed based on epidemiological data, such as a history of consuming raw or undercooked livestock products. Bacterial culture or pathologic testing are other ways to diagnose the disease.

The practice of eating and selling the by-products of dead or sick animals has become customary practice in some parts of the Philippines, especially in geographically isolated and disadvantaged areas. This is done to save the value of the dead animal and avoid financial constraints for the owner. However, these practices can lead to a bigger health risk both on the part of the consumer and the producer, as handling and eating sick or dead animals can lead to human infections. Currently, zoonotic diseases are a growing threat to public health and global food security. In March 2014, a highly fatal Henipavirus outbreak was reported in a rural community in the southern province of Sultan Kudarat. Direct exposure, through either contact during slaughtering or eating the meat of the infected animal, was established as the route of infection.[16]

Although annual vaccination of livestock against anthrax is highly recommended, particularly in anthrax-endemic areas, it has not been adopted by many countries, especially low- to middle-income countries like the Philippines, due to the cost of vaccination. Hence, educating the public on how zoonotic diseases affect humans and how they are acquired and transmitted can be the most plausible and convenient preventive measure in dealing with similar outbreaks. The use of personal protective equipment when disposing of animal carcasses should be observed, especially if the cause of death is unknown. Also, the prompt notification of sudden animal deaths or the occurrence of similar symptoms to public officials is highly encouraged so that proper investigation and preventive measures can be undertaken by the appropriate authorities.[6,17,18]

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

The need for ethics approval was waived as this outbreak investigation was conducted as part of normal public health response activities under Republic Act No. 11332. Verbal consent was obtained from all cases and controls (or, in the case or minors, the parents or guardians) who completed the questionnaire and all officials who were interviewed. No personal identifying information was collected.

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