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An approach to building Field Epidemiology Training Programme (FETP) trainees' capacities as educators

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Field Epidemiology Training Programmes (FETPs), which are modelled after the Centers for Disease Control and Prevention's Epidemic Intelligence Service programme, began in 1980 and have produced graduates in more than 70 countries, including 12 in the Western Pacific Region.[1,2] These programmes aim to "build sustainable capacity for detecting and responding to public health threats" and "develop expertise so that disease outbreaks can be detected locally and prevented from spreading".[3] FETPs thus include training in applied epidemiology and public health services. FETP trainees and graduates, however, often have additional responsibilities: mentoring newer trainees, supervising in the field, leading short training courses, facilitating meetings, etc. Programmes therefore must provide trainees with the knowledge and skills to fulfil these responsibilities.

One approach to building trainees' capacities has recently shown promise in two Western Pacific Region FETPs. The approach employs participatory training methods based on adult learning principles[4] and a systematic design based on the Experiential Learning Theory.[5] In contrast to traditional lectures, participatory methods recognize that trainees bring unique experiences and knowledge to a training event that should be shared for the group's benefit. The approach aims to empower participants to define problems from their own experiences, fostering connection to the material in meaningful ways and encouraging participants to collaboratively develop practical solutions that fit their situations. The systematic design (based in the cyclical Experiential Learning Theory) guides participants to articulate their experiences and to reflect on those experiences to understand how they might relate to the topic's abstract concepts. Next, participants generalize those concepts to multiple situations and apply them in simulated or real scenarios relevant to their work, therefore creating a new experience with which to repeat the cycle. Another benefit of this approach is that it engages people with different learning styles and not only those who learn best by lecture. This approach has been used or advocated in fields such as medical education,[6] geography,[7] general higher education,[8] and health behaviour education.[9]

In February 2017, FETP Japan convened a training of trainers (ToT) using and teaching this approach with facilitators and trainees (see **Table 1**). At the conclusion of the ToT, participants evaluated positively both their satisfaction with the event and their change in knowledge; the only negative comments were requests for more time. ToT participants then used the skills and knowledge acquired to redesign the FETP Surveillance Evaluation Project into a series of eight 3-hour workshops based on the new approach. Facilitators believe that trainees in these redesigned workshops have reached a greater depth of understanding of surveillance evaluation, programme evaluation and national surveillance and that the resulting projects have produced improved recommendations for strengthening national surveillance. FETP Japan trainees have used this approach to improve workshop design and facilitation for the annual Rapid Response Training of Surveillance Officers in local public health centres across the country.

In March 2017, FETP Japan led a ToT on this approach in Ulaanbaatar for Mongolian FETP trainees, graduates and supervisors. Pre- and post-test questionnaires showed a 70% increase in knowledge

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Table 1. **Example lesson plan for a three-day training of trainers employed in Japan and Mongolia, 2017, for building the training capacity of Field Epidemiology Training Programme trainees and supervisors**

Session/Topic	Principal Objective(s)	Training Method(s)
Introductions	• Review characteristics of effective trainers. • Self-assess facilitation strengths and identify areas for improvement.	• Found objects icebreaker • Group brainstorm
Characteristics of Effective Trainers	• Recognize techniques for effective verbal and nonverbal communication during a training event. • Practise techniques to demonstrate interest and respect.	• Reflection • Self-assessment
Effective Verbal & Non-verbal Communication	• Develop strategies for managing challenging behaviours learners might display during a workshop.	• Large-group brainstorm • Q&A • Demonstration • Small-group skit
Challenging Behaviours	• Introduce principles of the Experiential Learning Theory. • Discuss how the Theory can help create better trainings.	• Paired role play
Experiential Learning Theory	• Identify Kolb's four learning styles. • Explain the importance of accommodating the full variety of learning styles in training courses.	• Guided imagery • Discussion • Lecture • Individual worksheet
Adult Learning Styles	• Compare advantages and disadvantages of different training methods. • Practise designing and delivering a training method.	• Kinaesthetic activity • Interactive lecture • Small-group skill activity • Large-group worksheet
Training Methods	• Match training methods to learning styles and Learning Theory stages.	• Small-group game • Demonstration • Discussion • Small-group teach-backs*
Training Best Practices	• Identify and describe best practices for planning a workshop.	• Creative demonstration • Discussion
Icebreakers, Energizers, Breaks and Closers	• Employ icebreakers, energizers, breaks, and closing activities to improve participant focus, engagement, comfort, and learning.	• Lecture • Brainstorm
Training Course Evaluation	• Create a useful, feasible, and accurate training course evaluation plan.	• Panel discussion • Large-group discussion • Interactive lecture
Planning an Effective Training Course	• Create a training plan for a relevant public health training course using the 12 steps.	• Small-group game • Small-group research • Small-group project • Gallery walk
Individual Action Plans	• Review self-assessment and develop an action plan for continuing transfer of knowledge and skills into the workplace.	• Paired discussion • Paired worksheet

* Teach-backs are a training method in which training participants teach the content they have learnt back to the trainers in order to confirm apprehension of the concepts.

and attitudes with respect to learning theory and training methods. Additional outcomes included trainees' demonstrated ability to design and facilitate participatory training activities (observed during practice sessions), the systematic redesign of the Mongolian FETP Introductory Course and the systematic development of the Basic Epidemiology and Public Health Surveillance training course for officers in the Mongolian Frontline, who are staff in health, veterinary, inspection, and emergency management sectors working in local surveillance and trained to improve country capacity to detect, respond to and contain public health emergencies more rapidly.[10] Evaluation showed participants' learning needs and performance requirements in both courses were met. Of the 63 rapid risk assessments conducted in Mongolia in 2017–2018 (to date), 43% were led by provincial rapid response teams trained using this approach, representing a 30% increase in the percentage of provincial teams conducting risk assessments compared to previous periods. Facilitators commented that trainees attending the redesigned Introductory Course were better able to concentrate compared to previous cohorts, particularly during theory-heavy sessions, and that trainees who completed the ToT have been more effective in leading and facilitating technical working group meetings across sectors. The most notable example was a series of

multisectorial meetings (April–November 2017) facilitated by Mongolian FETP graduates who had attended the ToT that led to significant adjustments in the legal framework to improve intersectoral coordination and communication during public health emergencies.

In both Japan and Mongolia, the positive effect this approach has had on trainees has been demonstrated in post-ToT evaluations and post-training application of knowledge and skills to redesign training courses and facilitate events. We believe that subsequent events have been more effective than similar events using traditional approaches.

Implementing this approach revealed some challenges: first, the approach requires assessment of participant learning needs and subsequent systematic training design; thus, facilitators must review and redesign curricula for each event. Second, participatory methods can be new and uncomfortable for individuals educated in formal or traditional styles, implying that programmes with longer records and institutional memory may be hesitant to change. Third, systematically evaluating short- and long-term effects of this approach beyond pre- and post-test questionnaires was challenging; therefore, programme administrators should develop careful impact evaluations that begin before training. Finally, the approach requires a facilitator who is skilled and comfortable with participatory methods. It is expected that with each iteration of ToT a new group of skilled facilitators will emerge who can employ these methods and theories in multiple settings, thus creating a positive ripple that will be resource-saving in the long term. To support these facilitators, programmes should periodically evaluate and re-train them.

In summary, FETPs seeking to further build sustainable capacity and expertise for handling public health threats across their countries' health sectors should consider incorporating this approach—combining participatory methods and the Experiential Learning Theory—into routine FETP training schedules. Periodic follow-up assessments with re-training opportunities and concurrent outcome and impact evaluations will further the understanding of its potential cost savings and the sharing of achievements and lessons learnt with other FETPs.

Conflicts of Interest

None.

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A tuberculosis contact investigation involving a large number of contacts tested with interferon-gamma release assay at a nursing school: Kanagawa, Japan, 2012

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In May 2012, a teacher of a nursing school with about 300 staff members and students in Japan was diagnosed with sputum smear-positive pulmonary tuberculosis (TB), leading to an investigation involving nearly 300 contacts. We describe the contacts' closeness to the index TB patient and the likelihood of TB infection and disease.

A case of TB was defined as an individual with positive bacteriological tests or by a physician diagnosis of TB. A latent TB infection (LTBI) case was defined as an individual who had a positive interferon-gamma release assay (IGRA).

A total of 283 persons screened with IGRA were analysed. Eight persons (2.8%, 95% confidence interval [CI]: 1.2–5.4) tested positive by IGRA; one student who had intermediate (less than 10 hours) contact with the index patient was found to have pulmonary TB by chest X-ray. The positivity in IGRA among staff members with very close contact with the index patient (4 of 21, 19%, 95% CI: 5.4–42%) with a statistically significant relative risk of 17 (95% CI: 2.0–140) was high compared with that of the intermediate contacts (1 of 88, 1.1% [95% CI: 0.028–6.2]). There was a statistically significant trend in the risk of TB infection and closeness with the index patient among the staff members and students ($P < 0.00022$).

In congregate settings such as schools, the scope of contact investigation may have to be expanded to detect a TB case among those who had brief contact with the index patient.

In Japan, the tuberculosis (TB) notification rate has declined in the past six decades from 698.4 per 100 000 population in 1951 to 17.7 per 100 000 population in 2011.[1] However, 8000 smear-positive TB cases are still reported annually, and more than 65% of those involve persons aged 65 years or older.[2] TB outbreaks involving hospitals, workplaces and homeless people have also been reported;[3–5] however, only a few involving schools were reported in the past decade.[6,7]

In May 2012, a teacher in her 50s was diagnosed with sputum smear-positive pulmonary tuberculosis (TB). She taught at a nursing school in Kanagawa, Japan that has over 300 staff members and students. At the school, new teachers and students are tested with tuberculin skin testing (TST), followed by interferon-gamma release assay (IGRA), if indicated, and annual chest X-ray (CXR) thereafter. Although the teacher had a cough for several months and had an abnormal finding by CXR a year before, TB had not been suspected since she had a history of asthma and nontuberculous mycobacterial infection. The teacher had close contact with other teachers and students, particularly those in the first and second years. The affiliated hospital demanded all the staff and students be screened for TB, which led to an unusually large-scale contact investigation involving over 300 individuals.

TB contact investigations in Japan rely on IGRA[1,6,8] rather than TST to screen latent TB infection (LTBI). IGRA is more specific and avoids interference caused by Bacillus Calmette–Guérin (BCG) vaccination,[9] which an estimated 90–95% of the population receives.[10] This study aims to describe and compare the contacts' closeness to the index TB patient with the positivity of IGRA among those contacts.

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METHODS

A case of TB was defined as an individual who was confirmed with a positive sputum smear, culture or nucleic acid amplification test (NAAT) or by a physician diagnosis of TB from January 2011 through December 2013. An LTBI case was defined as an individual who had a positive IGRA.

The index patient's period of infectiousness was determined to be from December 2011 through May 2012 based on her history of symptoms.

We conducted a retrospective cohort study, enrolling almost all staff members and nursing students who were considered to have had contact with the index TB patient. The following three groups were excluded from the analysis: 1) staff and students who had a history of TB, 2) students who had a history of IGRA positivity or LTBI treatment at or before entry to the nursing school, and 3) staff who had been working more than three years at the school and had a history of IGRA positivity or LTBI treatment before 2009. For these groups, it was impossible to attribute their IGRA positivity to contact with the index patient in this investigation, and it was unlikely that the previous events were linked to this investigation. Since our focus of this study was to compare the contacts' closeness to the index TB patient with their IGRA results, those who were screened solely by CXR (mostly administrative staff who did not have many contacts with the index patient) were also excluded from the analysis.

The contacts were divided into four groups: very close contacts (the staff who shared the same room with the index patient), close contacts (first- and second-year students who attended the class of the index patient for over 10 hours during the infectious period), intermediate contacts (third-year students who attended the index patient's class for 10 hours or less) and other contacts (remaining staff and students who had almost no contact with the index patient). The very close contacts were tested twice with IGRA in May and July–August 2012; the close, the intermediate and the other contacts were tested once with IGRA in July–August 2012. However, 19 of the other contacts, mostly administrative staff, who did not have contact with the index patient were tested only by CXR in May 2012. All the IGRA-positive contacts were screened by CXR, and people who had abnormal findings were referred to a chest physician for follow-up. Those who were IGRA-positive without any abnormal findings on CXR were treated for LTBI with isoniazid for six to nine months. The one who was diagnosed with pulmonary TB was tested (sputum acid-fast bacilli smear and culture three times and NAAT) and treated with the standard regimen.

Analysis of IGRA positivity, 95% confidence intervals, and other statistical tests were carried out with R software (The R Foundation, Vienna, Austria). A Fisher's exact test was used to calculate the relative risks among the contact groups. The intermediate contact group was used as the reference in calculating the relative risks because they were a large group (about 90 individuals) and were less likely to be exposed to the index patient but unlikely zero positivity. A Cochran-Armitage test was conducted to determine whether there was a trend among the positivity of the groups. A *p*-value less than 0.05 was considered statistically significant.

Ethics

This investigation was conducted in accordance with the Infectious Disease Control Act of 1999 of Japan. We also obtained a waiver of ethical review for the study from the Institutional Review Board of the Research Institute of Tuberculosis because this study was retrospective, it relied on secondary use of the data that had been already collected by the local health offices, and it did not involve confidential information.

RESULTS

A total of 307 persons were enrolled as contacts for screening (**Table 1**) either with IGRA (285 contacts, 93%) or CXR (134 contacts, 44%) or both (115 contacts, 37%). Three first-year students had already tested positive by IGRA and had CXR at entry in early April 2012, and they were excluded from the initial screening. These three students were continuously followed up with CXR every six months. The 19 staff members (6%) who were screened only by CXR were excluded from the analysis. Of the 285 tested by IGRA, one teacher and one student were also excluded since they had histories of TB (about 14 years before) and LTBI treatment, respectively, before the event. Of the 283 (100%) who were analysed, eight (2.8%, 95% confidence interval [CI]: 1.2–5.4) were positive by IGRA (**Table 2**). Of those eight, four staff

Table 1. **Characteristics of the TB contacts of a nursing school and types of screening tests conducted, Kanagawa, Japan, 2011–2013**

		Students				
	Staff	first-year	second-year	third-year	Other	Total
Number	56	81	76	88	6	307
Age (Median, IQR)	46 (10.5)	18 (1)	19 (1)	21 (2)	32 (15)	-
Female (%)	31 (55)	76 (94)	70 (92)	80 (91)	5 (83)	262 (85)
IGRA done	37	78*	76	88	6	285
Chest X-ray taken	44	0	0	88	2	134

IGRA = interferon-gamma release assay

IQR = interquartile range

* Three students had already tested positive by IGRA at entry to the school and were excluded from the analysis.

members and three second-year students tested positive by IGRA in May; one third-year student tested positive in July 2012. The age groups of the IGRA-positive students and the staff members were 20–29 years and 40–49 years, respectively. One third-year IGRA-positive student was found by CXR in August 2012 to have pulmonary TB; the student was smear- and culture-negative (epidemic curve in **Fig. 1**). The student had CXR in April 2012 for the routine check-up and also in May 2012 for contact investigation, and both were considered normal. No other staff member or student developed active pulmonary TB.

The highest prevalence of IGRA test positivity was found in the very close contacts who shared the same office (19% [95% CI: 5.4–42%]), with a statistically significant relative risk of 17.0 (95% CI: 2.0–140), compared with the intermediate contacts group (1.1% [95% CI: 0.028–6.2%]) (**Table 2**). The Cochran-Armitage test revealed that there was a statistically significant trend in the risk of developing TB or LTBI among the ranked groups of staff members and students ($P = 0.00022$).

DISCUSSION

We conducted a TB contact investigation at a nursing school in Japan after a teacher was diagnosed with pulmonary TB. During the investigation, almost the entire staff and student body were screened for TB infection by IGRA, which makes the results of the investigation more accurate than when TST is used in settings with high BCG coverage such as in Japan.[6–8,11,12] The staff who shared an office with the index patient were 17 times more likely to have LTBI than the intermediate contacts consisting of third-year students. Although the staff members were older than the students, IGRA positivity among middle-aged Japanese men and women is not normally as high as 19% (e.g. 3.5% [95% CI: 1.6–6.6%] in the 35–54 year age group).[8] Also, there was a statistically significant trend in the risk of TB infection among the staff members and students ordered by duration of close contact, implying a dose–response relationship seen in previous studies.[13] These findings suggest that this event was a TB outbreak that was propagated from the index patient to staff members and students.

Of note, one of the intermediate contacts was not only infected with TB but also developed TB disease, suggesting contact of even fewer than 10 hours may result in TB infection. Thus, the scope of TB contact investigations may have to be expanded,[14] particularly in school settings.[13]

One weakness of this investigation is the lack of molecular data to confirm that the infective strains were related. Although a third-year student developed TB disease, the sputum culture was negative. However, considering the fact that 13% of all TB cases in Japan are bacteriologically negative,[15] this is not uncommon. The possibility that the student acquired the infection outside of the school is small, considering the low incidence of pulmonary TB in young Japanese (about 3 per 100 000 population in those aged from 15 to 24 years[15]) and the timing of his development of the disease at about eight months after the index patient.

Another limitation is that we were unable to take the baseline IGRA from the contacts except a few who had a large tuberculin reaction at routine entry screening

Table 2. **Numbers of persons with TB disease and with positive IGRA test among staff and students of a nursing school in relation to a TB contact investigation, Kanagawa, Japan, 2011–2013**

	TB disease		Persons with IGRA-positive test, including TB disease			Population
	n	% (95% CI)	n	% (95% CI)	RR† (95% CI)	n
Very close contacts						
Staff shared room with index patient	0	0 (0–16)	4	19 (5.4–42)	17 (2.0–140)	21
Close contacts						
second-year students	0	0 (0–4.7)	3‡	4.0 (0.83–11.2)	3.5 (0.37–33.1)	75‡
first-year students	0	0 (0–4.6)	0**	0 (0–4.6)	n/a	78**
Intermediate contacts						
third-year students	1	1.1 (0.028–6.2)	1	1.1 (0.0028–6.2)	1	88
Other contacts						
Staff in other rooms	0	0 (0–20)	0*	0 (0–20)	n/a	15*
Other students	0	0 (0–46)	0	0 (0–46)	n/a	6
Total	**1**	**0.35 (0.0089–2.0)**	**8**	**2.8 (1.2–5.4)**	**-**	**283**

LTBI = latent tuberculosis infection, CI = confidence interval, n/a = not available, RR = relative risk, TB = tuberculosis

† Compared with third-year students.

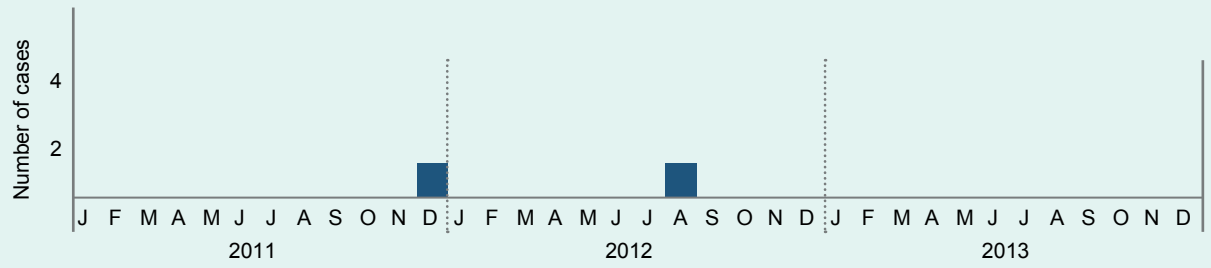
‡ Another student had a positive result; however, he was excluded from analysis because he had a history of LTBI treatment before entry to the school.

* Another staff member had a positive result; however, she was excluded from the analysis because she had a history of TB treatment 14 years before the current event.

** An additional three students had already tested positive for IGRA at entry to the school and were excluded from the analysis.

The Cochran-Armitage test revealed that there was a statistically significant trend in the risk of developing TB or LTBI among the ranked groups of staff members and students ($P = 0.00022$).

Fig. 1. **Epidemiologic curve of TB cases at a nursing school in Kanagawa, Japan, by month of symptom onset or diagnosis (if asymptomatic), 2011–2013**



Before 2011, no staff members or students developed tuberculosis except one teacher who developed pulmonary tuberculosis in 1998.

and were retested with IGRA. However, considering the long duration of symptoms of the index patient, even if the baseline tests had been conducted, some may have already converted at the time.

A final limitation is that this study was based on the observation in a single nursing school. However, we believe the results can be extrapolated to other countries with a medium burden of TB similar to Japan.

In congregate settings, such as schools, administrators should be vigilant against TB to prevent outbreaks. Since it is difficult to distinguish cough caused by TB from cough due to asthma or other illnesses, physicians should take sputum samples for acid-fast bacilli tests from those who have persistent cough more than two weeks to minimize a diagnostic delay. In a country where BCG coverage is high, IGRA, rather than TST, should be used for screening in TB contact investigations. In congregate settings, the scope of contact investigation may have to be expanded to detect TB among those who had brief contact with the index patient.

Conflict of interest

None declared.

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Introduction: In recent years, the incidence of measles has declined in the Lao People's Democratic Republic. However, an outbreak was reported in August 2014 in Houaphanh province, which was the biggest outbreak in the country since 2008. We describe the characteristics of this outbreak and outline critical interventions for the Lao People's Democratic Republic to achieve measles elimination.

Methods: Fever and rash cases in the Khouan and Samtai districts with an onset date from 1 September to 25 October 2014 were investigated. Active case finding and health facility record reviews were carried out. Appropriate samples from the individuals with suspected measles were tested to confirm the diagnosis.

Results: A total of 265 suspected cases including 12 deaths were reported from eight villages in the Khouan and Samtai districts. Forty-five individuals tested positive for measles IgM. Most of the confirmed patients were male (n = 28, 62%), less than 5 years old (n = 23, 51%) and from the Hmong ethnic community (n = 44, 98%). The majority of the people with suspected measles (n = 213, 80%) and all the confirmed ones were unvaccinated. A measles vaccination campaign conducted in the eight affected villages resulted in 76% coverage of the targeted population.

Discussion: Low routine coverage and measles occurrence among unvaccinated individuals indicate underimmunized areas. The geographical and sociodemographic characteristics of this outbreak highlight the need for tailored vaccination strategies to close the immunity gap. A sensitive surveillance system that is able to detect, notify, investigate and guide response measures, including a second measles dose in the routine immunization schedule, will be essential for the Lao People's Democratic Republic to attain its measles elimination status.

Measles is a highly contagious disease caused by measles virus (genus *Morbillivirus*, family *Paramyxoviridae)* and remains one of the most contagious diseases of humans.[1] Measles is characterized by rash, fever and cough, coryza or conjunctivitis and is usually transmitted from four days before to four days after the onset of rash.[1] The incubation period is normally 10–14 days and complications include otitis media, laryngotracheobronchitis, pneumonia, diarrhoea, encephalitis and secondary bacterial infections.[1] Since 1974, the use of safe and cost-effective measles vaccines has resulted in a marked decrease in measles cases and deaths. Globally, measles-related deaths have declined from about 548 300 in 2000 to an estimated 114 900 in 2014.[2,3] The reduction in measles deaths is a testament to the importance of measles vaccination to global health. However, globally, measles still remains one of the leading causes of death among children under 5 years of age, especially in countries with limited health infrastructure.[4–6]

Both the Global Vaccine Action Plan endorsed by the World Health Assembly in 2012 and the Global Measles and Rubella Strategic Plan 2012–2020 include elimination of measles, rubella and congenital rubella syndrome as one of the main objectives.[7,8] All World

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Health Organization (WHO) regions have established goals to eliminate measles by 2020.[3] In 2005, the WHO Regional Committee for the Western Pacific resolved that the Region should aim to eliminate measles by 2012. Elimination is defined as the absence of endemic measles virus transmission in a defined geographical area more than 12 months in the presence of a well performing surveillance system.[9] In 2012, the Regional Committee reaffirmed its commitment to eliminate measles.[10] The number of measles cases in the Region has decreased from 54 291 in 2009 to 8524 in 2012, and measles incidence decreased by 83% during the same period.[11]

The national policy in the Lao People's Democratic Republic is to provide one dose of measles vaccine to all children at 9 months of age. Since 2011, a combination measles-rubella vaccine has been used to provide additional rubella protection for the children.[12] Since 2000, the Lao People's Democratic Republic has been providing a second opportunity for measles vaccination to children through periodic supplementary immunization activities (SIAs).[13]

Despite reduction in measles incidence since the start of the measles immunization in 1979,[14] several sporadic and widespread measles outbreaks have been reported in the Lao People's Democratic Republic. A measles outbreak was reported in August 2014 in Houaphanh province. The outbreak in Houaphanh province outlined the challenges that lay ahead for the country towards achieving measles elimination. We describe the characteristics of the outbreak with the aim of identifying critical interventions for the Lao People's Democratic Republic to attain the measles elimination status.

METHODS

The WHO-accredited National Center for Laboratory and Epidemiology (NCLE) has been receiving weekly reports of measles cases from all provinces in the Lao People's Democratic Republic since 1994.[14] On 19 September 2014, Khouan District Health Office received reports of fever, cases of rash and red eyes from Khorhai village, Khouan district, Houaphanh province. The patients were treated at the Khouan and Samtai district hospitals. On 24 September 2014, the District Health Office reported the event to the Houaphanh Provincial Health Office, which subsequently reported the cases to NCLE. Rapid response teams conducted investigations of the suspected cases in Khorhai and neighbouring villages within two days of the notification; the suspected patients attending hospitals were investigated by the physicians. Active case finding through house-to-house visits was conducted in all the affected villages to identify and investigate the suspected cases and ensure initial treatment and referral of patients with measles, as needed, to prevent any deaths. The medical records were reviewed at the provincial and district hospitals including the health centres serving the affected geographical areas for a period of nine months preceding the outbreak to identify any missed cases. The standardized case investigation form and line list routinely used by NCLE to record any infectious disease outbreak was adapted to record the information of these fever and rash cases. The data captured in the line list included the characteristics of each of the suspected cases (which conformed to the measles surveillance case definition) such as age, sex, ethnicity, geographical location, date, type and pattern of rash onset, symptoms, travel history, history of contact with individuals with confirmed measles, outcome of the infection and immunization status.

The identified fever and rash cases were classified according to the WHO standard case definition for measles and rubella.[15] A suspected measles case is defined as any person with fever and maculopapular rash (non-vesicular) and cough, coryza or conjunctivitis or any person in whom a clinician suspects measles infection. A laboratory-confirmed measles case is one that meets the above case definition and the presence of measles-specific IgM antibodies is confirmed in a WHO-accredited laboratory.

The vaccination status was reported either by the patient, caregiver or parents present at the time of the investigation. The childhood vaccination card when available was checked to ascertain the reported vaccination status of the cases. Serum samples could not be collected from the suspected cases detected retrospectively during the active case finding or from those who were not in the appropriate time frame for sample collection. To ensure the reliability of the laboratory tests performed to confirm the diagnosis of measles, the optimal time frame of between 7–28 days from the date of rash onset for specimen collection was ensured by the investigation team during the collection of the serum samples.[16] WHO recommends that a single serum sample be obtained from suspected measles cases at the first contact with the health-care system within 28 days after rash onset for adequate measles surveillance;

IgM ELISA detection is most sensitive 4–28 days after the rash onset.[17] The serum samples were sent to NCLE for measles and rubella IgM testing using ELISA (Enzygnost® kits, Siemens, Erlangen, Germany). Viral genotyping was carried out at the Public Health Laboratory Centre, Department of Health, Hong Kong SAR (China).

Affected districts reported all suspected cases to NCLE daily for a 14-day period from 26 September to 10 October 2014.

RESULTS

Geographical distribution of cases

Over a period of eight weeks, 265 suspected cases including 12 deaths (case fatality rate: 4.5%) were reported from four adjoining villages in the Khouan and Samtai districts in Houaphanh province. Of the 265 suspected cases, 45 were laboratory-confirmed. All deaths resulted from pneumonia, and all case-patients had fever and rash. Most of the confirmed cases (n = 34, 76%) and the deaths (n = 9, 75%) were reported from Khouan district. Most of the confirmed cases were reported from Khorhai (n = 15, 33%) and Houiybeuy (n = 11, 24%) villages in the Khouan district, while the rest of the cases were located in six different villages in both districts.

The cases that were suspected but not confirmed (n = 214) were reported mainly from Khorhai village, Khouan district (n = 94, 44%), while the rest of the 51 cases were located in 16 different villages of both districts. The majority of the suspected case-patients in Khouan district belonged to the Hmong ethnic community (n = 211, 80%). All suspected case-patients had fever and rash, 54% (n = 143) had cough and 41% (n = 109) had runny noses at the time of investigation.

Characteristics of confirmed cases

Most of the 45 people with confirmed measles were male (n = 28, 62%), ranging from 6 months to 18 years of age. The median age of patients with confirmed measles was 5 years. The highest proportion of the confirmed patients (n = 23, 51%) were less than 5 years of age followed by those 5–9 years old (n = 17, 38%). Similar age characteristics were also noticed among the suspected case-patients. All infants less than 1 year old with confirmed measles were less than 9 months old.

The majority (n = 44, 98%) of people with confirmed measles were from the Hmong ethnic community, and only one patient (n = 1, 2%) was reported from the Laolum ethnic community. All four confirmed patients from Hinteng village in the Khouan district and Phanhsavanh village in Samtai district had travelled to Khorhai village of the Khouan district, which reported the highest number of confirmed cases.

The epidemiological curve of the outbreak shows a classical pattern of a propagated source of person-to-person transmission (**Fig. 1**).

Clinical characteristics of confirmed cases

All patients with confirmed measles reported fever and rash. The rashes were identified as maculopapular in 87% (n = 39) of the confirmed patients. The other symptoms reported by the confirmed patients were cough (n = 36, 80%), conjunctivitis (n = 36, 80%), runny nose (n = 29, 64%) and diarrhoea (n = 10, 22%). Of the 30 confirmed case-patients who were hospitalized, 29 were admitted to the district hospitals. Most (90%) of the hospitalized patients (both suspected and confirmed patients) were less than 10 years of age. Six (20%) of these hospitalized patients developed pneumonia. There were no reported cases of encephalitis.

Vaccination status

None of the confirmed patients and only one (0.5%) of the suspected case-patients had received any dose of measles-containing vaccine by the time of the investigation. The characteristics of the suspected and confirmed patients are shown in **Table 1**.

Laboratory diagnosis

Serum samples were collected from 51 (19%) of the 265 patients with suspected measles; in addition, nasopharyngeal swabs were collected from only nine suspected patients (3%). Forty-five patients (88%) tested positive by ELISA for measles-specific IgM antibodies; the test results in the remaining six patients were equivocal. All but one sample tested negative for rubella-specific IgM antibodies. The genotype of the detected measles virus identified in this outbreak was H1.

Fig. 1. **Epidemiological curve of measles cases during the outbreak investigation, Houaphanh province, Lao People's Democratic Republic, 1 September–25 October 2014**

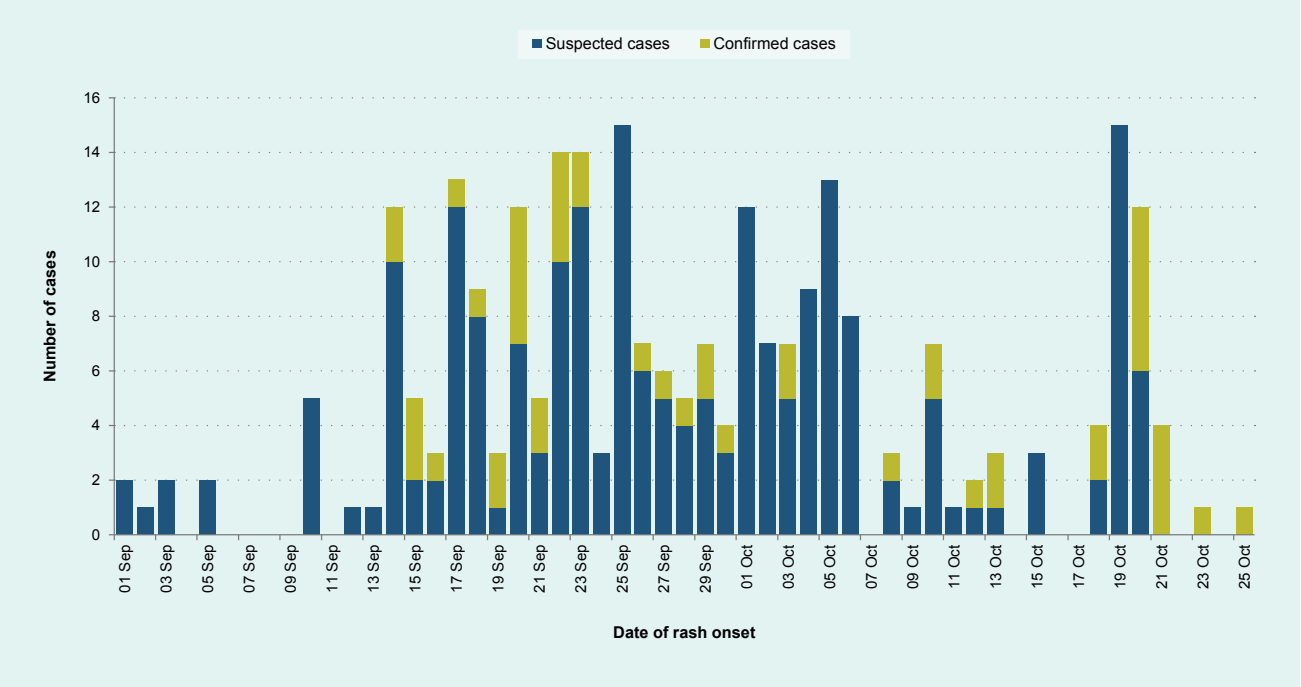

Table 1. **Characteristics of measles patients, Houaphanh province, Lao People's Democratic Republic, 2014**

Characteristics	Suspected but not confirmed (*n* = 214)		Laboratory confirmed (*n* = 45)		Tested "equivocal" (*n* = 6)		Total (*n* = 265)	
	n	%	n	%	n	%	n	%
Sex								
Male	105	49	28	62	2	33	135	51
Female	109	51	17	38	4	67	130	49
Age group (years)								
<1 year	11	5	3	7	0	0	14	5
1–4 years	97	45	20	44	1	17	118	45
5–9 years	80	38	19	43	4	66	103	39
10–14 years	22	10	2	4	1	17	25	9
≥15 years	4	2	1	2	0	0	5	2
Vaccination status								
None	213	99.5	45	100	6	100	264	99.6
Yes	1	0.5	0	0	0	0	1	0.4
Case type								
Suspected but not confirmed							214	80.70
Laboratory confirmed							45	16.98
Laboratory tested but results "equivocal"							6	0.02

Vaccination response in the area

The immunization programme units of the Samtai and Khouan districts carried out outbreak response immunizations targeting individuals between 9 months and 20 years following detection of the confirmed cases. Approximately 19 600 children, irrespective of their previous vaccination status, were vaccinated with one dose of measles-rubella vaccine, achieving an overall 76% coverage in the targeted villages with Samtai district achieving higher coverage (84%) than the Khouan district (63%).

DISCUSSION

The suboptimal vaccination status of the confirmed measles cases in the affected areas indicates pockets of underimmunized populations in the Lao People's Democratic Republic. Since the Lao People's Democratic Republic has adopted the goal of measles elimination as part of a 2005 WHO Regional Committee resolution,[9] the population immunity needs to be sustained above 95% in all districts of the country to prevent measles epidemics.[1]

Measles epidemics have been reported in communities with low vaccination coverage.[18] The coverage of the first dose of measles-rubella vaccine in Khorhai in 2013 was around 50% [reports from National Immunization Programme, unpublished data]. The vaccination coverage for the previous years in Khorhai and in other affected villages could not be assessed as the monthly vaccination records could not be retrieved from the health centres. The administrative coverage of the first dose of measles-containing vaccine (MCV1) of Samtai district was 45%, 49% and 24% for 2011, 2012 and 2013, respectively, while the MCV1 coverage of Khouan district was 52% for 2013 [reports from National Immunization Programme, unpublished data]. Khouan is a newly created administrative district and hence the vaccination coverages for the years 2011 and 2012 are not available. The reported administrative MCV1 coverage of the Houaphanh province was around 59% in 2011, 2012 and 2013 [reports from National Immunization Programme, unpublished data], while the reported coverage for the national level was 69%, 72% and 82% for the corresponding years.[19]

Because MCV1 in the Lao People's Democratic Republic is provided at 9 months of age, the country should consider adding a routine second dose of measles-containing vaccine at age 15–18 months to reduce the rate of accumulation of susceptible children and risk of a future outbreak.[1] Countries aiming for measles elimination should achieve and maintain greater than 95% coverage with two doses in every district of the country.[1]

Because of the delay in reporting by the health centre, almost three weeks after the occurrence of the first case, and the fact that only 19% of the suspected cases had a serum sample, the results of our outbreak investigation may not truly estimate the actual burden of measles in this area.

Houaphanh province is located in the eastern part of the Lao People's Democratic Republic. It has eight administrative districts and is one of the poorest provinces with a total population of around 310 000.[20] The terrain is rugged with dense, mountainous forest forming much of the land mass. The affected villages, including Khorhai village, are situated around 15 km and 30 km from the nearest health centre and the district headquarters, respectively. All eight affected villages are primarily mountainous and have poor road conditions; more than half of the roads are inaccessible during the rainy season, making it difficult for the local health centres to deliver routine vaccination services. These geographic difficulties also make it difficult for these villagers to access the health-care services in the nearest health centres.

Countries with weaker health infrastructure or areas within the countries with moderate or weak functioning health system have used SIAs to deliver measles vaccine to children who were missed by routine vaccination or who are outside the health system. SIAs have been used in the Lao People's Democratic Republic since 2011.[13] The effectiveness of SIAs in reaching the vulnerable population in the Lao People's Democratic Republic should be evaluated. Studies have shown that in situations with low routine immunization coverage, measles vaccination through supplemental immunization using outreach activities helps reduces the accumulation of susceptible people and is cost effective.[21,22] The risk of measles outbreaks is determined by the rate of accumulation of the susceptible population;[1] thus, the National Immunization Programme of the Lao People's Democratic Republic should routinely analyse the available coverage data and immunity gap to monitor the accumulation of susceptible people and plan follow-up SIAs.

Ninety-eight per cent of the patients with measles were reported from the Hmong community, illustrating that an immunity gap exists in this group. The high case fatality seen in this outbreak is comparable to the fatality rate seen in the past outbreaks.[14] The national measles vaccination coverage in the Lao People's Democratic Republic Social Indicator Survey 2011–12 was 55.3% with a wide disparity of vaccination coverage between the ethnic communities, ranging from 35.3% in the Hmong-Mien community to 72.7% in the Lao People's Democratic Republic-Tai community.[23] Data about vaccination coverage in ethnic groups are not routinely collected by the immunization programme and are available only from periodic national coverage surveys.

The outbreak has primarily affected unvaccinated children less than 5 years old who should have received their vaccination doses during routine immunization or during the periodic SIAs conducted in the Lao People's Democratic Republic. A wide-age-range (9 months to 19 years) measles-rubella SIA was conducted in the Lao People's Democratic Republic in 2011,[23] but this outbreak indicates that these cases had missed both the routine and SIA doses. A similar pattern of age-group affected, rate of pneumonia and low vaccination status was observed during a measles outbreak in a district of Balochistan province of Pakistan where the affected population had difficulties in accessing health facilities and had poor routine vaccination coverage.[25]

The H1 genotype identified in this outbreak was also detected in the Lao People's Democratic Republic in 2011–2012 and has been the predominant genotype detected in China between 2009 and 2012.[11,26]

There were several limitations to the investigation of this outbreak. The health-seeking behaviour of the community and their knowledge about measles were not assessed to understand the reasons of low routine coverage in the affected villages. The reported vaccination status of the cases were not verified with the immunization registers at the health centres, and thus recall biases would be inevitable. The existing system of passive notification of measles cases could still be useful for decision-making if the information were promptly shared with the district and provincial levels by the reporting health facilities.[27] The delay in timely reporting resulted in the health system taking 41 days to conduct any SIAs after the detection of the suspected cases in the community. While WHO recommends the use of serum-based IgM ELISA assays to confirm clinically suspected measles/rubella,[1,15,23] there is an inherent limitation in using IgM ELISA for confirmation of measles when the serum samples are collected within four days of rash onset. However, this may not have been relevant in an outbreak setting as individual diagnosis is not critical.[17] In this outbreak, 22% of the serum samples were collected within four days of rash onset; however, all samples tested either positive or equivocal for measles IgM by ELISA. The sample collection for measles diagnosis should be further improved by collecting urine or nasopharyngeal samples to confirm the outbreaks and document measles elimination by virus genotyping.[17,28] Lastly, the line list prepared in this outbreak did not indicate the method of case detection; hence, the differentiation of the cases identified during active case finding or in routine surveillance was not possible.

This outbreak in Houaphanh province was the biggest measles outbreak in the Lao People's Democratic Republic since 2008. The outbreak highlights the vulnerability of the ethnic and other geographically dispersed communities in the country to any vaccine-preventable diseases. To achieve measles elimination, the National Immunization Programme should consider investing in ways to identify and target high-risk populations and use community-specific strategies to close immunity gaps. This includes regular outreach activities and the introduction of a second dose of measles vaccine in the national immunization schedule. In order to achieve elimination, it is crucial that a sensitive surveillance system that can detect, notify and ensure timely investigation of suspected cases, classify them as confirmed or discarded and guide appropriate response measures to prevent further transmission in the Lao People's Democratic Republic.

Conflicts of interest

None declared.

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Viral load suppression and acquired HIV drug resistance in adults receiving antiretroviral therapy in Viet Nam: results from a nationally representative survey

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Objective: The purpose of this survey was to estimate the prevalence of viral load (VL) suppression and emergence of HIV drug resistance (HIVDR) among individuals receiving antiretroviral therapy (ART) for 36 months or longer in Viet Nam using a nationally representative sampling method.

Methods: The survey was conducted between May and August 2014 using a two-stage cluster design. Sixteen ART clinics were selected using probability proportional to proxy size sampling, and patients receiving ART for at least 36 months were consecutively enrolled. Epidemiological information and blood specimens were collected for HIV-1 VL and HIVDR testing; HIVDR was defined by the Stanford University HIVDR algorithm.

Results: Overall, 365 eligible individuals were recruited with a mean age of 38.2 years; 68.4% were men. The mean time on ART was 75.5 months (95% confidence interval [CI]: 69.0–81.9 months), and 93.7% of the patients were receiving non-nucleoside reverse transcriptase inhibitor-based regimens. Of the 365 individuals, 345 (94.7%, 95% CI: 64.1–99.4%) had VL below 1000 copies/mL and 19 (4.6%, 95% CI: 2.8-–7.5) had HIVDR mutations.

Discussion: Our nationally representative survey found a high level of VL suppression and a low prevalence of HIVDR among individuals who received ART for at least 36 months in Viet Nam. Continued surveillance for HIVDR is important for evaluating and improving HIV programs.

There were an estimated 250 000 people living with HIV in Viet Nam in 2016.[1] The HIV epidemic in Viet Nam remains concentrated primarily among people who inject drugs (PWID), female sex workers (FSW) and men who have sex with men (MSM). According to HIV sentinel surveillance, the HIV prevalence was 11.0% in PWID, 2.7% in FSW and 8.2% in MSM in 2016.[2]

Antiretroviral therapy (ART) was first introduced in Viet Nam in the mid-1990s and has been rapidly scaled up since 2005, with a total of 115 927 people receiving ART at the end of 2016.[2,3] However, the prevalence of viral load (VL) suppression and HIV drug resistance (HIVDR) patterns at the national scale were unknown. There have been several HIVDR surveys undertaken in Viet Nam in the past decade. However, no study provided a nationally representative estimate of VL suppression and acquired HIV drug resistance (ADR).

Prior to 2011, the World Health Organization (WHO) recommended the prospective cohort studies of patients in conveniently selected sentinel sites to assess the emergence of ADR.[4] However, considerable financial

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and human resources are required for the recruitment and maintenance of a prospective cohort. Moreover, due to the nature of the survey design, the delay between the initiation of the survey and the dissemination of the results was longer than 24 months, preventing the use of this information for timely public health action. To address these implementation challenges and to ensure findings fully reflect the situation in the national programme, WHO developed a new survey method using a cross-sectional approach to estimate the level of VL suppression and ADR using a nationally representative sample of people receiving ART in the country.[5] The survey can be implemented quickly and the results are nationally representative; thus, it has greater potential to inform the public health response in timely manner.

In 2014, Viet Nam became one of the first countries in the world to conduct an ADR survey using the new WHO guidance. The study aimed to determine the prevalence of VL suppression and HIVDR among individuals who had been receiving ART for ≥36 months in Viet Nam.

METHODS

Study design and sampling

In line with WHO guidance, this cross-sectional survey used a two-stage cluster design.[5] In the first stage, 201 clinics that had provided ART for at least three years by the end of 2013 composed the sampling frame. Clinic-level information on the number of patients starting ART and on ART for at least 36 months was not available; however, Viet Nam had reliable site-level data on the number of patients on ART. We used probability proportional to proxy size (PPPS) sampling in which the probability that a clinic was sampled is proportional to the size of the proxy patient population. The selected clinics were sampled through systematic PPPS sampling.[5] The number of persons receiving ART at the end of 2013 at each clinic was used as the proxy size of patients on ART at each clinic.

In the second stage, a sample of eligible patients was consecutively recruited from each of the selected clinics. The sample size for 16 representative clinics without stratification was calculated following the formula for a Wald-type confidence interval as recommended in WHO guidance.[5] To estimate the required sample size, the following assumptions were made: VL suppression prevalence of 70% for those receiving ART for ≥36 months, expected amplification failure rate at 15%,[5] expected proportion of individuals sampled still receiving first-line ART at 95% and expected proportion of individuals sampled on first-line ART receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens at 100%. Based on these assumptions and a desired confidence interval of ±7%, it was estimated that a sample size of 368 persons was required, resulting in the enrolment of 23 eligible persons at each of the 16 selected clinics.

Participant recruitment

Individuals with HIV aged 18 years or older who had been on ART for at least 36 months at the time of the clinic visit were eligible for inclusion. WHO guidance suggests conducting the survey at two treatment time points (12 ± 3 months and ≥48 months after initiation);[5] however, Viet Nam started planning the survey in late 2013, before the WHO guidance was finalized. We used the inclusion criteria listed in the draft recommendation, which was to survey adults who had received ART for ≥36 months.

To estimate the size of the clinic population and allow adjustments during the analysis, survey sites recorded all eligible patients who attended the clinic during the first three months of the study. At each clinic, eligible patients were enrolled consecutively until 23 patients were enrolled or until the maximum enrolment period of three months had passed, whichever came earlier. Following patient consent, blood specimens were drawn for VL measurement and genotyping. On the day of specimen collection, clinical data were also collected from the patient's medical record by ART clinic staff, including age, sex, date of ART start and ART regimen and CD4 counts before ART initiation and the most recent results before enrolment.

Specimen shipment and laboratory testing

Plasma specimens were tested for VL and HIVDR in two laboratories designated by WHO as national HIVDR laboratories: the National Institute for Hygiene and Epidemiology (NIHE), which tested specimens from eight outpatient clinics in the north of the country, and the Pasteur Institute in Ho Chi Minh City (PI HCMC), which tested specimens from eight outpatient clinics in the south of the country.

HIV-1 RNA viral quantification was conducted using the automated Abbott real-time HIV-1 assay (in NIHE) and the automated Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 assay (in PI HCMC) with detection limits of 20 copies/mL. HIVDR genotypic test was conducted on the pol gene with the ABI 3130XL system using the Big-Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystem, California, USA). HIVDR was interpreted using the HIValg Program on the Stanford University HIV Drug Resistance Database website.[6] HIVDR was defined as low-level, intermediate or high-level resistance to one or more of the following drugs: nevirapine (NVP), efavirenz (EFV), any nucleotide reverse transcriptase inhibitors NtRTI, atazanavir (ATV), darunavir (DRV) or lopinavir (LPV). NNRTI resistance was defined as resistance to NVP or EFV, NRTI resistance was defined as resistance to any NtRTI, including abacavir (ABC), zidovudine (ZDV), emtricitabine (FTC), lamivudine (3TC), tenofovir (TDF), stavudine (D4T) and didanosine (DDI). Protease inhibitor (PI) resistance was defined as resistance to ATV, DRV or LPV. Estimates were weighted for study design.

Data entry and statistical analysis

Data were entered using Epi Data 3.0 (EpiData Software, Odense, Denmark) and statistical analysis was performed using STATA version 11 (STATA Corp., Texas, USA). Standard descriptive statistics were calculated for categorical and continuous variables. Data analysis for prevalence of VL suppression was conducted in STATA using the survey (svy) suite of commands. Data were weighted by clinic size (i.e. the number of eligible patients screened at a clinic during the three months after the survey start date, the number of patients with VL suppression and the number of individuals with sequences genotyped).[5] A 95% confidence interval was calculated using a standard Wald formula or by a logit transformation. The FASTA files were submitted to the Stanford University HIV Drug Resistance Database for interpretation.[7] A detailed description of the technical data analysis has been described elsewhere.[5]

Ethics and permissions

The study protocol was reviewed and approved by the Institutional Review Board of Hanoi University of Public Health, Hanoi, Viet Nam (Approval no: 210/2014/YTCC-HD3).

RESULTS

Characteristics of study participants

During the enrolment period, a total of 6920 patients were screened at 16 sampled clinics, from which 368 eligible patients were recruited. Three patients were excluded because the duration of ART was less than 36 months; therefore, 365 persons were included in the final analysis. Their baseline characteristics are summarized in **Table 1**. The study-design-weighted mean age was 38.2 years (95% confidence interval [CI]: 37.0–39.4) and 68.4% were males. At the time of study enrolment, 93.7% of the participants were on a first-line NNRTI-based regimen, 77.8% (273/351) had advanced HIV infection (CD4 < 100 cells/ml) and the mean duration on ART was 75.5 months (95% CI: 69.0–81.9). Of the 365 patients, 55.9% (204) were on a ZDV-containing regimen, 54% (197) on a NVP-containing regimen, 40.3% (147) on an EFV-containing regimen and 8.4% (140) on a TDF-containing regimen. The adjusted proportions are presented in **Table 1**.

Viral load suppression

Among the 365 participants with VL testing, 345 (95.1%) achieved VL suppression (defined as VL <1000 copies/mL). The prevalence of VL suppression among individuals on first-line ART was 94.8% (95% CI: 92.1-96.6%) (**Table 2**).

HIV drug resistance

The study-design-weighted prevalence of any HIV drug resistance among patients on ART was 4.6% (95% CI: 0.28–0.75) and among persons with VL >1000 copies/ml was 94.7% (95% CI: 64.1–99.4%) (**Table 3**). Of the 20 (14.5%) persons with a detectable VL, 19 carried a virus with mutations associated with HIVDR (five persons with VL between 1000 and 5000 copies/mL and 14 persons with VL >5000 copies/mL).

All the detected mutations were associated with resistance to reverse transcriptase inhibitors, and no major mutations associated with resistance to PI were found (**Fig. 1**). In the 19 cases with drug resistance mutations, one case (5.3%) had mutations associated with only NRTI resistance, another one (5.3%) had mutations associated with only NNRTI resistance, and the remaining 17 cases (89.4%) had mutations associated with both NRTI and

Table 1. **Characteristics of individuals on current ART regimen for at least 36 months (*n* = 365)**

	n	Proportion[a] % (95% CI)
Gender		
Women	118	31.6 (25.9–37.9)
Men	247	68.4 (62.1–74.1)
Mean[b] age (95% CI), years		38.2 (37.0–39.4)
≤ 25 years	1	< 0.5
> 25 years	364	99.6 (97.1–100)
Individuals on first-line ART	345	93.8 (88.3–96.8)
Individuals on NNRTI-based first-line ART	344	93.7 (88.3–96.8)
Individuals on PI-based second-line ART	20	6.2 (3.2–11.6)
Current ART		
TDF + XTC + EFV	93	25.6 (18.5–34.3)
TDF + XTC + NVP	47	12.3 (7.7–19.1)
TDF-based regimen	158	43.3 (33.4–53.8)
ZDV + XTC + EFV	54	13.7 (9.6–19.2)
ZDV + XTC + NVP	148	41.4 (32.9–50.5)
ZDV-based regimen	204	55.4 (45.1–65.3)
EFV-based regimen	147	39.3 (32.3–46.8)
NVP-based regimen	197	54.5 (47.5–61.3)
PI-based regimen (all LPV based)	20	6.2 (3.2–11.6)
Other	3	0.8 (0.2–2.9)
Mean[b] time on ART (95% CI), months		75.5 (69.0–81.9)

[a] Study-design-weighted proportion and 95% confidence interval

[b] Study-design-weighted mean and 95% confidence interval

ART = antiretroviral therapy, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TDF = tenofovir, XTC= either lamivudine or emtricitabine, EFV = efavirenz, NVP = nevirapine, ZDV = zidovudine.

Table 2. **Prevalence of VL suppression (<1000 copies/mL) for individuals on ART for at least 36 months**

	n	Prevalence[a] % (95% CI)
VL suppression among individuals on ART	345	95.1 (92.3–96.9)
VL suppression among individuals on first-line ART	325	94.8 (92.1–96.6)
VL suppression among individuals on NNRTI-based first-line ART	325	94.9 (92.1–96.7)
VL suppression among individuals on second-line ART	20	100%
VL suppression among individuals on LVP-based regimen	20	100%
VL suppression among individuals on ZDV-based regimen	192	94.7 (90.6–97.0)
VL failure among individuals on ZDV-based regimen	12	5.3 (3.0–9.4)
VL suppression among women on ART	112	95.7 (89.8–98.2)
VL suppression among men on ART	233	94.9 (90.1–97.4)
VL suppression among individuals on ART aged ≤25 years	-	-
VL suppression among individuals on ART aged >25 years	344	95.1 (92.3–96.9)

[a] Estimates were weighted for study design (see methods section).

VL = viral load.

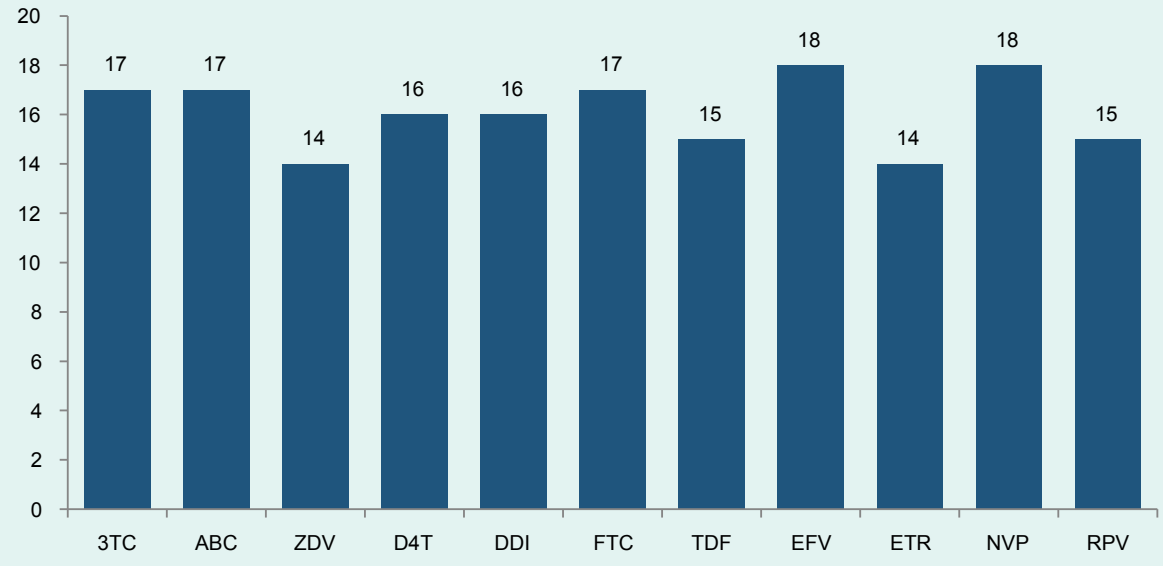
Table 3. **Prevalence of HIVDR among individuals on ART for at least 36 months**

	n/N	Prevalence[a] % (95% CI)
HIVDR among individuals on ART with VL ≥1000 copies/mL		
Any	19/20	94.8 (64.4–99.5)
NNRTI	18/20	87.0 (53.6–97.5)
NRTI	18/20	87.7 (55.4–97.6)
PI	0/20	-
NNRTI+NRTI	17/20	79.9 (46.6–94.8)
HIVDR among individuals on first-line ART with VL ≥1000 copies/mL		
Any	19/20	94.8 (64.4–99.5)
NNRTI	18/20	87.0 (53.6–97.5)
NRTI	18/20	87.7 (55.4–97.6)
PI	0/20	-
NNRTI+NRTI	17/20	79.9 (46.6–94.8)
HIVDR among individuals on NNRTI first-line with VL ≥1000 copies/mL		
Any	18/19	94.7 (64.1–99.4)
NNRTI	17/19	86.8 (53.3–97.5)
NRTI	17/19	87.5 (55.1–97.6)
PI	0/19	-
NNRTI+NRTI	16/19	79.7 (46.1–94.7)
HIVDR among individuals on ART		
Any	19/365	4.6 (2.8–7.5)
NNRTI	18/365	4.2 (2.4–7.4)
NRTI	18/365	4.3 (2.4–7.4)
PI	0/365	-
NNRTI+NRTI	17/365	3.9 (2.0–7.3)

[a] Estimates were weighted for study design (see method section). Any HIVDR is defined as low-level, intermediate or high-level resistance (according to the Stanford HIVdb) with respect to one or more of the following drugs: NVP, EFV, any N(t)RTI, ATV, DRV or LPV; NNRTI resistance is defined as resistance to NVP or EFV; NRTI resistance is defined as resistance to any N(t)RTI; and PI resistance is defined as resistance to ATV, DRV or LPV. Estimates were weighted for study design (see methods section).

ART = antiretroviral therapy, VL = viral load, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitors, PI = protease inhibitor.

Fig. 1. **Frequency of mutations conferring resistance to NRTIs**



3TC = lamivudine, ABC = abacavir, ZDV = zidovudine, D4T = stavudine, DDI = didanosine, FTC = emtricitabine, TDF = tenofovir, EFV = efavirenz, ETR = etravirine; NVP = nevirapine, RPV = rilpivirine.

NNRTI resistance. In cases with drug-resistance mutations to both NRTI and NNRTI, the mean viral load was 45 556 copies/mL (95% CI: 16 603–74 509).

Among the 20 patients with a detectable VL, the most common NNRTI mutations were Y181C (10/20, 50%), K103N (7/20, 35%), V106I (7/20, 35%) and G190A (7/20, 35%). For NRTI resistance, the most common resistance mutations were M184V (16/20, 80%); V75M (5/20, 25%); and thymidine analogue mutations (TAMs), consisting of T215F/I/Y (12/20, 60%), K219E/Q (9/20, 45%), K70R (9/20, 45%), D67N (8/20, 40%), M41L (7/20, 35%) and L210W (4/20, 20%). There were 45% (9/20) of patients harbouring viruses with three or more TAMs. Of the 20 patients failing ART, 75% (15) had mutations that predict resistance to tenofovir, while 85% (17) and 70% (14) had mutations that predict resistance to either lamivudine (3TC) or emtricitabine (FTC) and ZDV, respectively (**Fig. 1**). Prevalence of NNRTI resistance ranged from 70% (14/20) for etravirine (ETR) to 90% (18/20) for EFV and/or NVP (**Fig. 1**).

Association between CD4 count and HIVDR mutations

Table 4 shows the results of bivariate analysis and multivariate analysis assessing the relationship between CD4 counts with the presence of HIVDR mutations. Bivariate analysis showed that CD4 counts <100 cells/mm3 or between 100 and 350 cells/μl were associated with HIVDR mutations. In multivariate analysis, these two conditions were independently associated with the presence of HIVDR mutations: adjusted odds ratio (aOR) = 98.3 (95% CI: 10.9–888.2) for CD4 <100 cells/mm^3 and aOR = 11.4 (95% CI: 2.51–51.9) for CD4 between 100 and 350 cells/μl.

DISCUSSION

This study was the first survey of ADR in Viet Nam following the WHO guidance for ADR surveillance released in 2014,[5] and Viet Nam was one of the first countries in the world to adopt the new WHO ADR survey protocol.[8] The new WHO protocol is aimed at obtaining nationally representative estimates of VL suppression and ADR using a cross-sectional design in contrast to the previous prospective cohort method that focused on sentinel ART clinics.[4] Our survey proved that the new cross-sectional WHO approach is feasible to implement in Viet Nam and is able to generate important information that could be used to optimize ART programmes.

In our survey, the level of VL suppression was one of the highest and the ADR level the lowest among the four countries that have reported the results of an ADR survey using the new WHO protocol.[8]

In the past decade, various surveys of HIVDR were conducted in Viet Nam that reported levels of transmitted HIV drug resistance (TDR), pre-treatment HIV drug resistance (PDR) and ADR. In a study among 70 newly diagnosed HIV-positive clients aged 18–24 years in Hanoi in 2006, the prevalence of TDR was at a low level (<5% to all drugs),[9] while a moderate resistance prevalence (5–15%) of TDR to NNRTIs was observed among similar clients (aged 18–21 years at voluntary counselling and testing sites) in Ho Chi Minh City in 2007–2008.[10] A five-year study (2008–2012) among 1426 ART-naïve patients in a single hospital in southern Viet Nam indicated that the annual prevalence of TDR remained low to moderate (2.4–5.48%).[11] A prospective cohort study of ADR conducted between 2009 and 2012 at four treatment clinics (two clinics in Ho Chi Minh City and two clinics in northern Viet Nam) showed that PDR to the drugs used in the first-line ART regimen was 2.7% (95% CI: 1.6–4.4%) (13/490 participants).[12] This study also showed 91.3% (CI 95%: 87.0–97.9%) of patients achieved VL suppression at 12 months after ART initiation, 2.9% of patients had developed an HIVDR to NNRTIs or NRTIs at 12 months after ART initiation and no patients had developed detectable PI resistance.[13] A cross-sectional study at three clinics in Ho Chi Minh City in 2009–2011 reported the level of ADR among those receiving ART for 12 ± 2 months and 24 ± 2 months were 22/296 patients (7.4%) and 25/300 patients (8.3%), respectively.[14]

These previous studies in Viet Nam did not use a nationally representative sample and thus were limited by potential site selection bias. At the same time, these results suggest that HIVDR has been at a low level in Viet Nam, and the results of the present survey are in line with these previous findings. However, it should also be noted that TDR[10] and ADR[14] surveys conducted in Ho Chi Minh City report somewhat higher (moderate) levels of HIVDR compared to the rest of the country. While it is important to generate nationally representative estimates, future studies may also require stratification of sampling to understand potential geographical differences.

Table 4. **Correlates of HIVDR mutation (any mutation)**

Variables	N	Any mutation	Crude OR (95% CI)	P-values	Adjusted OR (95% CI)[a]	P-values
Provinces						
Hanoi	70	4 (5.7%)	0.776 (0.199–3.019)	0.714		
Other provinces in the north	111	7 (6.3%)	0.862 (0.262–2.829)	0.806		
Ho Chi Minh City	115	3 (2.6%)	0.343 (0.079–1.482)	0.152		
Other provinces in the south	69	5 (7.2%)	1			
Administration level						
District level	184	8 (4.3%)	0.702 (0.276–1.789)	0.459		
National or provincial level	181	11 (6.1%)	1			
Years, median (IQR)		37 (33–42)				
Age group						
Under 35 years old	148	8 (5.4%)	1.07 (0.42–2.728)	0.887	1	
From 35 years old and above	217	11 (5.1%)	1		1.334 (0.393–4.526)	0.644
Sex						
Male	274	13 (5.3%)	1.037 (0.384–2.8)	0.943	0.363 (0.8–1.643)	0.188
Female	118	6 (5.1%)	1		1	
Months from ART to sampling		65 (57–85)				
ART duration						
From 36 months to less than 60 months	108	7 (6.5%)	1.571 (0.512–4.817)	0.429	1	
From 60 months to less than 84 months	115	6 (5.2%)	1.248 (0.391–3.977)	0.708	1.383 (0.359–5.324)	0.63
From 84 months and above	142	6 (4.2%)	1		0.818 (0.189–3.55)	0.789
Self-reported mode of infection						
Injection drug use	141	9 (6.4%)	1.455 (0.562–3.762)	0.440	1.538 (0.420–5.631)	0.516
Heterosexual	201	9 (4.5%)	1		1	
MSM	1	0 (0.0%)	-			
WHO stage before ART initiation						
1	46	1 (2.2%)	1			
2	50	2 (4.0%)	1.875 (0.164–21.397)	0.613	1.538 (0.106–22.245)	0.752
3	152	3 (2.0%)	0.906 (0.092–8.926)	0.933	1.18 (0.106–13.094)	0.893
4	108	13 (12.0%)	6.158 (0.781–48.54)	0.084	7.265 (0.746–70.748)	0.088
History of ARV exposure before ART start						
Yes	24	1 (4.2%)	0.807 (0.102–6.36)	0.839		
No	313	16 (5.1%)	1			
TB treatment history after registration at OPC						
Yes	58	2 (3.4%)	0.578 (0.13–2.571)	0.471		
No	292	17 (5.8%)	1			
CD4 count before ART, median (IQR) (cells/mm3)		124 (43–179)				
Most recent CD4 count, median (IQR) (cells/mm3)		254 (115–320)				
CD4 count before ART start (cells/mm3)						
<100	166	8 (4.8%)	0.686 (0.268–1.752)	0.431		
100–350	160	11 (6.9%)	1			
>350	25	0	-			
Most recent CD4 count (cells/mm3)						
<100	8	4 (50.0%)	77.3 (12.9–465)	0.000	98.304 (10.88–888.183)	<0.001
100–350	119	12 (10.1%)	8.67 (2.40–31.4)	0.001	11.413 (2.509–51.921)	0.002
>350	235	3 (1.3%)	1		1	

[a] Adjusted for age group, sex, ART duration, self-reported mode of HIV infection, pre-ART WHO clinical stage, history of ARV exposure before ART start and the most current CD4 count.

IQR = interquartile range, TB = tuberculosis, ARV = antiretroviral, OPC = HIV outpatient clinic, ART = antiretroviral therapy, MSM = men who have sex with men, OR = odds ratio, CI = confidence interval

The present survey also showed that over 95% of people with HIV who are receiving ART for more than three years have suppressed VL (<1000 copies/ml). This study result is also in line with other studies showing that Viet Nam's programmes are achieving a high level of VL suppression (<1000 copies/ml) at 12 months as reported from cohort studies[13,15] and a cross-sectional survey.[16]

Our study found a strong association between VL and drug-resistance mutations among patients receiving ART for at least 36 months. HIVDR mutations to NNRTI were detected in 19 out of 20 (95%) patients with VL >1000 copies/ml supporting the notion that a prompt switch to second line therapies is needed in people with detectable virus despite treatment. Because HIVDR is associated with a low level of adherence (more importantly with NNRTI resistance emergence)[17] in settings with low levels of NNRTI resistance on ART,[8] strategies to improve ART adherence are critical to prevent widespread reliance on alternate treatment regimens.

In the above-mentioned study among Vietnamese adults initiating first-line ART, the percentages of patients with virologic failure (VL >1000 copies/ml) were 11.5% (95% CI: 7.8–15.1) at 10–14 months and 10.3% (95% CI: 6.9–13.8) at 22–24 months. The percentages of patients with detectable VL that had drug-resistance mutations were 75.9% at 10–14 months and 86.2% at 22–24 months.[14] It is possible the presence of drug-resistance mutations is correlated with time on ART.[18] Following the WHO recommendation to conduct the ADR survey at two time points would enable comparisons of the level of VL suppression and patterns of HIVDR between patients found to be failing ART in the short- and long-term.

The 2010 pre-treatment HIVDR study found that the major drug-resistance mutations to the available first-line ARTs were K103N, Y181C, Y188C, G190A (NNRTI resistance), V75M and M184V (NRTI resistance).[12] Due to the limitations of cross-sectional design, it was not possible in our current study to determine whether the HIVDR mutations stemmed from insufficient drug pressure during ART treatment or had pre-existed from transmitted resistance before ART initiation.

The mutation pattern in our study was similar to the results of an ADR survey at three clinics in Ho Chi Minh City in 2009–2010. Among the 22 patients with HIVDR mutations at 12 months, resistance to NRTIs, NNRTIs and to both classes were reported as 4.5%, 9% and 90%, respectively. At 24 months following ART initiation, there were 25 cases with HIVDR mutations: 96% were resistant to both NRTIs and NNRTIs, 0% were resistant to NRTIs alone and 4% were resistant to NNRTIs alone.[14]

In conclusion, this is the first survey to describe nationally representative levels of VL suppression and ADR in adults receiving ART for at least 36 months in Viet Nam. The survey found high levels of VL suppression, low levels of ADR among people on ART and high levels of HIVDR among people failing ART, suggesting that Viet Nam had successfully managed its programme quality to maintain ADR at a low level at the time the survey was conducted in 2014.

Conflict of Interest

The authors declare that they have no competing interests.

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An investigation of a measles outbreak in Japan and Taiwan, China, March–May 2018

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Objective: To investigate a measles outbreak that spread to Japan and Taiwan, China during March–May 2018, exploring the characteristics of the super-spreading event.

Methods: A contact investigation of the index case and reconstruction of the epidemiological dynamics of measles transmission were conducted. Employing a mathematical model, the effective reproduction number was estimated for each generation of cases.

Results and discussion: A single index case gave rise to a total of 38 secondary cases, 33 in Japan and five in Taiwan, China. Subsequent chains of transmission were observed in highly vaccinated populations in both Japan and Taiwan, China. The effective reproduction number of the second generation was >1 for both Japan and Taiwan, China. In Japan, the reproduction number was estimated to be <1 during the third generation. Vaccination of susceptible individuals is essential to prevent secondary and tertiary transmission events.

Measles is caused by the measles virus, a single-stranded negative-sense enveloped RNA virus. It is a vaccine-preventable disease, subject to control and elimination via surveillance and vaccination programmes.[1,2] Since the year 2000, a two-dose schedule for measles vaccination has been recommended by Global Measles Mortality Reduction and Regional Elimination: Strategic Plan,[2] organized by the World Health Organization (WHO), United Nations Children's Fund and the United States Centers for Disease Control and Prevention, and substantial progress has been made towards measles elimination in countries that belong to the WHO Western Pacific Region.[3,4] Nevertheless, the virus has continued to circulate, causing multiple outbreaks in member countries and surrounding areas.[3–5] Since 2017, there has been a surge of global measles cases, especially in European countries,[6] and the chance of experiencing an outbreak in the Western Pacific Region has continued to be to be high.

Even in highly vaccinated countries such as Japan,[7] imported cases can produce clusters with multiple chains of transmission.[8] Interrupting these chains requires supplementary vaccination among adults, especially those who are unvaccinated or have received only one vaccination.[5,9] If susceptible groups of people remain unvaccinated, countries are at risk of experiencing outbreaks with additional introductions of imported cases. On 23 March 2018, the Japanese Government was notified of an imported case of measles in Okinawa prefecture, the southernmost prefecture of Japan, arising from a Taiwan Chinese traveller.[10] An outbreak of measles occurred in Okinawa, arising from the contact with the index case; moreover, there have been chains of transmission arising from the same index case in Taiwan, China.[11]

The present study aims to investigate a cross-border outbreak of measles that spread to Japan and Taiwan, China and describe the dynamics of disease transmission in this outbreak.

METHODS

Case definition and epidemiological data collection

A measles case was defined by the presence of (1) a generalized rash, (2) fever, and (3) other typical symptoms including cough, coryza and conjunctivitis

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and by laboratory confirmation of measles infection. Laboratory-confirmed measles is defined as the detection of measles-specific immunoglobulin M (IgM) antibodies in patient serum[12] or detection of virus by nested real-time polymerase chain reaction (PCR). Modified measles is defined by the presence of at least one of the three signs or symptoms described above plus laboratory confirmation of measles infection. In general, modified measles is a milder form of the disease with a longer incubation period (14–20 days) and a lack of premonitory symptoms, Koplik spots or a generalized rash.[13] The rash, when it occurs, can be localized to a foot or hand. Modified measles is less infectious than typical measles infection, but those with modified measles can spread the infection to others and still require watchful observation.[14]

The present study is based on governmental reports of the outbreak investigations in Japan and Taiwan, China.[10,15] We retrospectively scanned all real-time reports of the outbreak, including those from local prefectures that were affected: Okinawa, Aichi, Kanagawa and Tokyo in Japan.[16–19] We then reconstructed the transmission dynamics of the measles outbreak that arose from the index case. Dates of illness onset and laboratory confirmation, age, sex, country or area of residence and vaccination history of cases were retrieved, allowing us to characterize the epidemic as a function of these variables. The index case's entry and exit dates, to and from Japan and Taiwan, China, and a detailed history of potential contacts were retrieved from publicly available information.[15,16] Using this information, we characterized the descriptive epidemiological features of the epidemic.

Effective reproduction number

Effective reproduction number (R_n), interpreted as the average number of secondary cases generated by a single primary case in generation n, is an objective epidemiological measure to quantify disease spread between generations. An R_n value >1 reflects an increase in the number of cases, while an R_n value <1 ensures that the number of cases is decreasing. The temporal distribution of R_n values could thus reflect an outbreak brought under control; therefore, the measure can be used for assessing the effectiveness of public health interventions and/or for designing disease control policy in the future, such as restricting human movements during the course of an epidemic or raising awareness among the general public.

Because the mean generation time of measles infection is relatively long compared to its variance (mean: 11.7 days and variance: 9.0 days^2),[20] we estimated a generation-specific R_n in the present study. We first reconstructed the transmission network using publicly available information. Subsequently, we calculated the generation-dependent number of cases by either referring to the contact history or imposing an assumption that the interval between generations was constant at 11 days. To assign cases into a particular generation, first we relied on the known contact history (the link to a primary case) that was available in the case reports. We confirmed that the peaks of the generation-specific epidemic curve were about 11 days apart from each other, and then we separated cases into different generations by referring to contact-tracing results. If the transmission tree was not known, we took the mid-point between peaks as the cut-off date separating two generations. As part of the sensitivity analysis, we also calculated the number of cases in each generation, including +/– 1 day of the imposed cut-off date. Given the number of cases in the nth generation, c_n, the expected number of cases in the $(n+1)$th generation was modelled as $\mathrm{E}(\mathrm{c}_{n+1}) = R_n \mathrm{c}_n$, where R_n represents the effective reproduction number of the nth generation which represents the average number of secondary cases generated by a single primary case. We assumed that the observed number of generation-dependent cases followed a Poisson distribution:

$$\Pr(X = \mathrm{c}_{n+1}; R_n) = \frac{\mathrm{E}(\mathrm{c}_{n+1};R_n)^{\mathrm{c}_{n+1}} \exp(-\mathrm{E}(\mathrm{c}_{n+1};R_n))}{\mathrm{c}_{n+1}!}$$

Maximum likelihood estimation was employed to appropriately quantify the uncertainty (confidence intervals) of parameters. Alternatively, we could have identified a point estimate of the R_n by counting the number of cases in each generation and taking the ratio of the number of cases in adjacent generations. Using the second equation as the likelihood function, the maximum likelihood estimate of parameters was calculated to obtain parameter estimates of the R_n, and the 95% confidence interval (CI) was computed by using the profile likelihood method.

Data availability

In addition to provided data sources,[15–19] the collected information of cases is shared on an open online repository.[21]

Ethics

This study was based on publicly disclosed information as part of an outbreak investigation and did not require ethical review.

RESULTS

Index case and contacts

The cross-border outbreak has been linked to an adult man from Taiwan, China who visited Thailand from 1 to 4 March 2018. On 14 March, the index case developed fever and cough. On 17 March, he flew from Taiwan, China to Okinawa on a commercial flight, infecting two flight attendants and two passengers who were unvaccinated, and then travelled to Naha city, the capital of Okinawa. The index case developed a rash on 19 March, leading him to seek care at the local medical service. He was hospitalized on the date of clinical diagnosis on 19 March. On 26 March, he returned to Taiwan, China on a commercial flight. **Fig. 1** shows the epidemic curves for Japan and Taiwan, China. In Japan, at least eight cases were definitively linked to the index case (**Fig. 2**). Many unlinked cases also developed symptoms within a time period consistent with the transmission chain from the index case. In total, the transmission from the index case resulted in producing 123 local cases in Japan and 13 local cases in Taiwan, China.

Ten case patients in Taiwan, China were exposed to measles on an aircraft or at airport-associated facilities. One case in Taiwan, China acquired an infection in the workplace, and the history of transmission among the other two cases remained unknown. In Japan, 10 cases were infected at an unknown (undisclosed) Facility A in Okinawa prefecture, 17 cases were nosocomial, 13 cases acquired infection in households, 10 cases at their workplace and three were infected in schools. Out of the total 124 cases that include the index case, the route of transmission was unknown for 71 cases.

Due to a large number of transmission events that were very closely traced, the index case is considered to have acted as the primary case of the super-spreading event. The index case visited a densely populated area in Japan (Kokusai Street in Naha city of Okinawa prefecture). In Aichi prefecture, Japan, Nagoya Daini Red Cross Hospital was an important foci of secondary transmissions. In that hospital, a patient who had returned from a trip to Okinawa sought medical attention and unintentionally exposed hospital staff who possessed only low levels of antibodies.

A total of 33 cases in Okinawa prefecture were diagnosed as having modified measles. The transmission potential of modified measles in the current outbreak was estimated elsewhere.[14]

Temporal dynamics in Japan

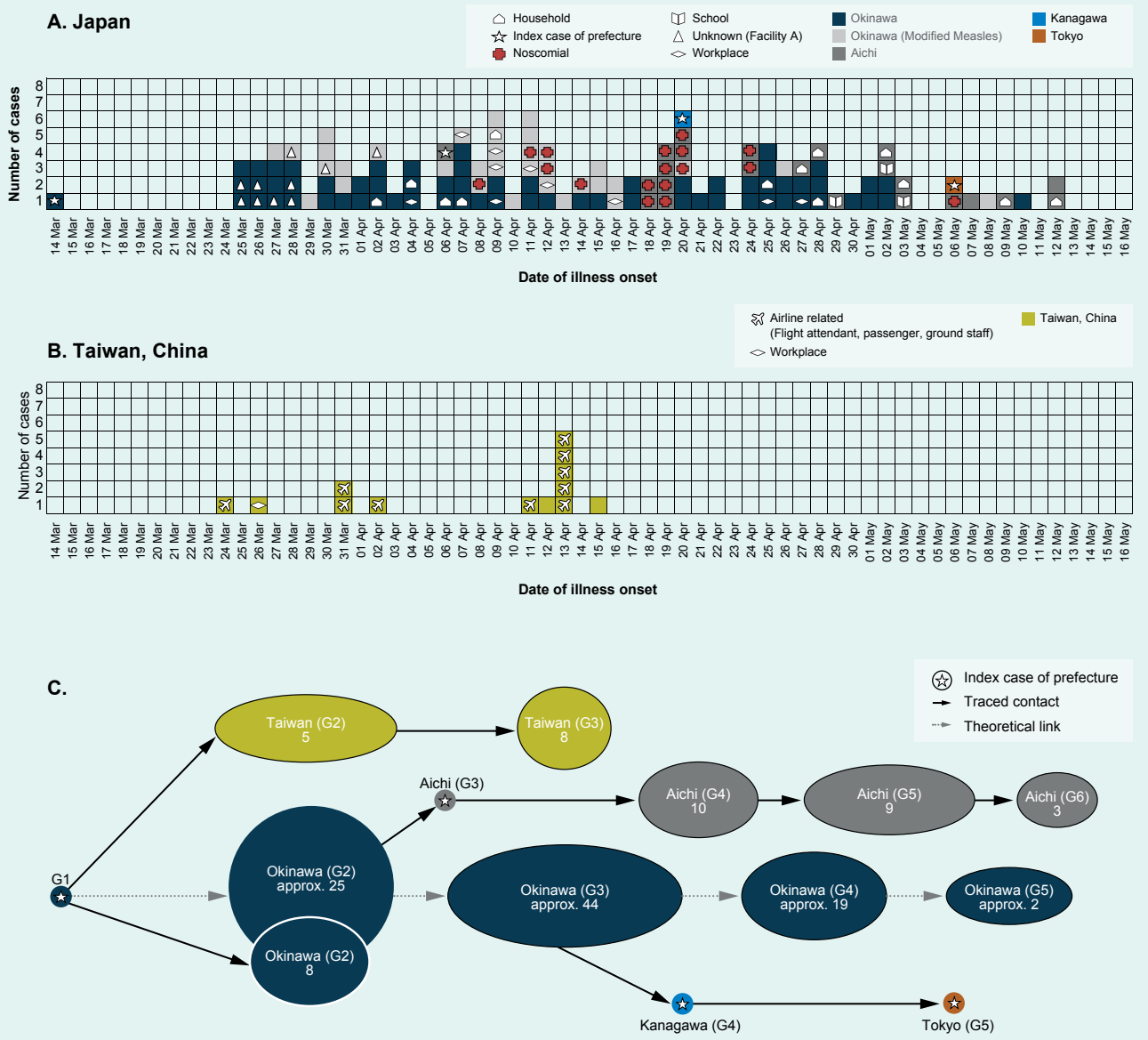
The first peak of illness was observed on 30 March, and a subsequent peak occurred on 9 April (**Fig. 1A**). Referring to the contact-tracing results of known links and observing the greater variance of illness onset dates in tertiary cases as compared to secondary cases, we determined that there were 30 cases in the fourth generation. Despite intensive follow-up of contacts, 12 cases in the fifth generation and three cases in the sixth generation were observed.

During the third generation, one case patient moved to Aichi prefecture, contributing to 10 subsequent cases in the following generation. **Table 1** shows the composition of cases. The vaccination coverage of case patients aged 9 years old or younger was 33.3%, indicating that they were predominately unvaccinated individuals. Cases in this outbreak were primarily young adults aged 20–39 years (n = 70 (56.5%)) (**Table 1**). Cases who had received at least one dose of measles vaccine accounted for 33.1%.

Temporal dynamics in Taiwan, China

Fig. 1B shows the epidemic curve in Taiwan, China. The index case from the outbreak in Japan also started chains of transmission in Taiwan, China. Before travelling to Okinawa, the index case caused a secondary case in a workplace contact. Subsequently, during his flight from Taiwan, China to Japan, two flight attendants and two other passengers were infected (**Fig. 1C**). A secondary transmission event was seen on the index case's flight to Japan, while no one was identified as infected on his way back to Taiwan, China (**Fig. 2**). Subsequently, linked to the third and fourth cases, a total of eight tertiary cases were confirmed.

Fig. 1. **Transmission dynamics of measles in Japan and Taiwan, China March–May 2018**

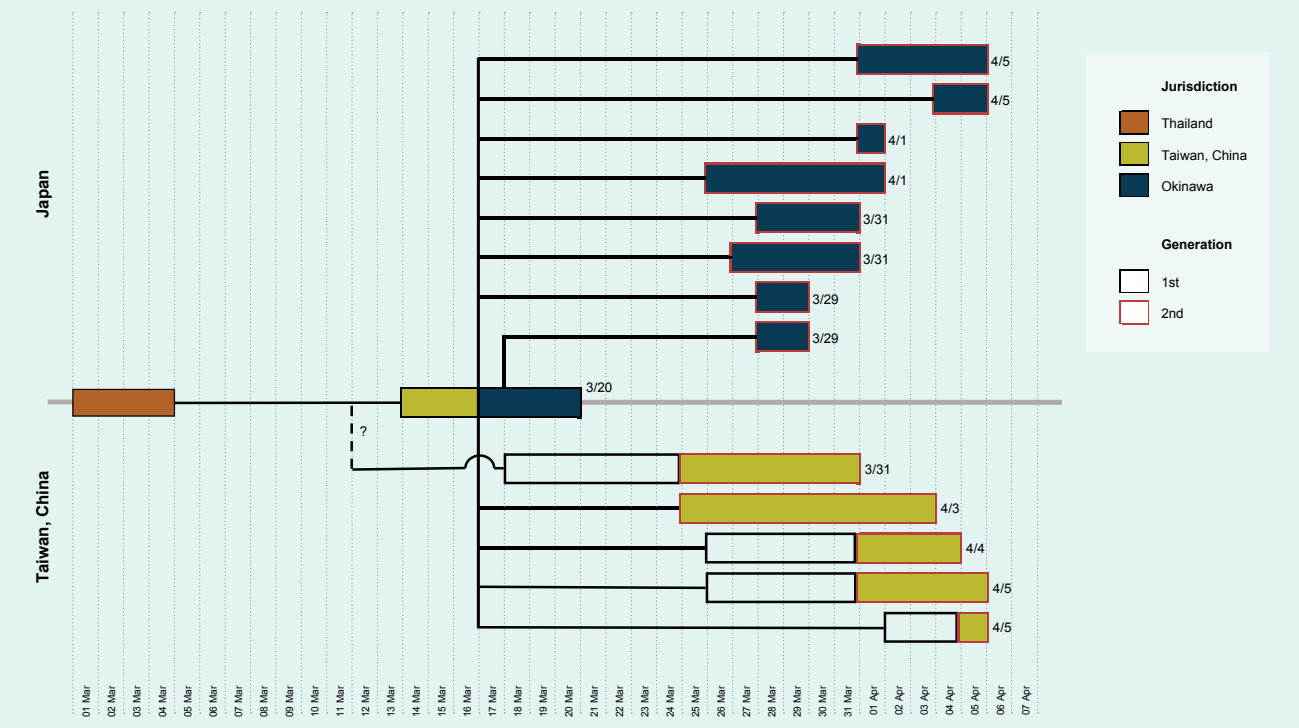


A. Characteristics of measles transmission in Japan given an imported case, March–May 2018. Daily onset of reported measles cases were characterized over time after the onset of illness of the index case on 14 March. Those colored in black (and grey), brown, green and yellow represents measles cases notified respectively in Okinawa, Aichi, Kanagawa, and Tokyo, Japan. Cases from the Okinawa colored in grey were modified measles. Five cases were not accompanied by explicit date of illness onset; dates of illness onset were assumed as the date of confirmation minus five days.

B. Characteristics of an imported measles case in Taiwan, China, March–May, 2018. The symptoms of the initial case appeared after arriving to Okinawa, and therefore, this case is not described in B. The squares coloured in green represents cases notified in Taiwan, China.

C. Transmission network of the Japan and Taiwan, China outbreak of measles, March–May, 2018. The brown box shows the travel period of index case in Thailand, while the following box on the same line represents the illness onset and confirmation of index case. The star indicates the initial case of measles identified in each prefecture of Japan. Numbers in the ellipse represent the number of cases. The bold arrows represent a known link. The dotted arrows represent a theoretical link, assuming that the mean serial interval is 11 days. Note that the horizontal time axes are aligned through panels A, B and C.

Fig. 2. **Transmission tree of measles associated with the index case in Japan and Taiwan, China, March–May 2018**



Transmission tree of measles in Japan and Taiwan, China associated with the index case. Vertical lines represent calendar day. Each box corresponds to a diagnosed case, starting from the date of illness onset to notification. Partially unfilled boxes for four cases in Taiwan, China represent an uncertainty of the date of illness onset (i.e. possible range of the date of illness onset). Thick lines represent the link of transmission based on contact-tracing practice. At least eight cases in Japan were linked to the index case.

Table. 1. **Age, sex and vaccination history of measles cases in Japan and Taiwan, China, March–May, 2018**

		Japan Number (%)	Ever vaccinated*	Taiwan, China Number (%)
Age (years)	0–9	21 (16.9)	33.3%	-
	10–19	16 (12.9)	43.8%	
	20–29	30 (24.2)	36.7%	7 (53.8)
	30–39	40 (32.3)	37.5%	5 (38.5)
	40–49	13 (10.5)	7.7%	1 (7.7)
	50 and older	4 (3.2)	0.0%	-
Sex	Female	58 (46.8)	37.9%	6 (46.2)
	Male	66 (53.2)	33.3%	7 (53.8)
Measles vaccine received	1+ doses	41 (33.1)	-	-
	0 doses	23 (18.5)	-	-
	Unknown	60 (48.4)	-	13 (100)

* Ever vaccinated indicates the percentage of individuals who have received at least one dose of measles vaccine.

Estimates of reproduction number

For the first generation, the R_n in Japan was estimated to be 33.0 (95% CI: 23.0–45.6). In the second generation, the estimate dropped to 1.3 (95% CI: 1.0–1.7); subsequently, the R_n of the third, fourth and fifth generations took the value below unity, estimated at 0.7 (95% CI: 0.5–1.0), 0.4 (95% CI: 0.2–0.6) and 0.2 (95% CI: 0.0–0.6), respectively. Even when we varied the cut-off date by +/– 1 day, the R_n of the first generation was as large as 37.0 and 28.0, respectively. In Taiwan, China, the reproduction number of the first generation was estimated to be 5.0 (95% CI: 1.8–10.7). In the second generation, the R_n declined to 1.6 (95% CI: 0.7–3.0). Subsequently, cases ceased in Taiwan, China, and thus, the R_n of the third generation was zero.

DISCUSSION

The present study explored epidemiological features of the cross-border outbreak of measles that spread to Japan and Taiwan, China in the WHO Western Pacific Region, where great progress has been made towards measles elimination in recent years.[3] As of July 2018, Japan was among eight countries and areas in the Western Pacific Region that had achieved elimination of measles (in addition to Australia, Brunei Darussalam, Cambodia, Hong Kong SAR [China], Macao SAR [China], New Zealand and the Republic of Korea). A single index case contributed to super-spreading events, leading us to observe clusters of cases in both Japan and Taiwan, China. Given the large number of secondary cases, the chance of observing third and subsequent generations of cases was high even in these highly vaccinated populations. In Japan, the Rn was <1 only from the third generation, leading the incidence to wane over time. Due to the large outbreak size, a substantial number of contacts were followed, resulting in a resource-demanding outbreak.

Two major conclusions can be drawn from our investigation. First, the outbreak was traced back to a single index case. Potential contributing factors to high individual infectivity include a biological cause, such as an individual who exhales a substantial amount of viruses. In this outbreak, we did not identify a particular risk factor other than contact with the index patient, and the transmission was not restricted to health-care settings. The clinical diagnosis of the index case was swiftly made on the same day of the onset of rash, and many contact events that took place before the onset of rash contributed to secondary transmissions.

Second, given the large number of secondary cases, the clusters of cases did not end up with only one generation of cases even in these highly vaccinated populations. A substantial number of tertiary transmission events were observed. It must be noted that the R_n of the second generation was estimated to be >1 for both Japan and Taiwan, China. Especially in Japan, the R_n was <1 only from the third generation. This event led public health officials to trace a substantial number of contacts in both Japan and Taiwan, China, including more than 3500 contacts in Taiwan, China alone.

Considering the potential for continued chains of transmission from secondary cases, our study endorses the need to implement supplementary immunization programmes.[5,9] Three categories of individuals could be susceptible to measles infection and should be targeted for immunization during supplemental campaigns: (1) unvaccinated individuals, especially children; (2) individuals who have received only one dose of measles-containing vaccine; and (3) individuals whose vaccination history is unknown.

The study had several limitations. First, the outbreak in Japan involved a substantial number of modified measles cases whose illness did not meet the definition of a measles case. There could potentially be undiagnosed, modified cases. Second, we used epidemic curves to separate cases into different generations. While we referred to the contact-tracing results, more precise estimation using a sophisticated mathematical modeling approach has yet to be conducted. Third, our study relied on published reports based on the outbreak investigation; more detailed descriptions and discussions over these outbreaks, such as phylogenetic analysis to validate contact-tracing results and detailed laboratory-testing results (e.g. viral load of cases), have yet to be reported.

This study describes an outbreak of measles that originated from a single index case and estimates the R_n. A super-spreading event occurred even with a swift diagnosis upon rash onset. Considering the difficulty with control in this outbreak, our study endorses the importance of vaccinating international travellers, not only those visiting endemic countries but any travellers visiting geographic areas at risk of transmission. To avoid

unnecessary chains of transmission, our findings also indicate the importance of continuing and strengthening routine immunization.

Conflict of interest:

None.

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