Leading causes of morbidity and mortality

Abstract

Background: Communicable diseases can be the leading causes of morbidity and mortality among population affected by major disasters or public health emergencies. Cyclone Nargis which was the worst natural disaster in Myanmar hit the delta area during May 2008. The objective of this study is aimed to assess the situation of communicable diseases under national surveillance in the areas one year before and after the Cyclone Nargis incident.

Methods: Monthly data during 2007 and 2009 from routine reporting system for disease surveillance of the Myanmar Ministry of Health (MMOH) were reviewed. Weekly reporting from Early Warning and Rapid Response (EWAR) were also used to compare with the routine reporting data of MMOH; and the data from some UN agencies, non-governmental organizations (INGOs/NGOs) and Tri-Partite Core Group (TCG) periodic reviews were also extracted for comparisons with Sphere and Inter-Agency Standing Committee (IASC) for global health cluster communicable diseases control indicators. In addition, focus groups regarding community perception on health sector responses to Cyclone Nargis and hospital surveys on public health emergencies preparedness including surveillance capacity were conducted.

Results: Among the communicable diseases, acute respiratory infection (ARI), diarrhea, dysentery and malaria were the most disease burden of the community in terms of both morbidity and morality. During the study period, mortality rate for diarrhea and malaria were decreasing while the mortality rate for ARI appeared to be similar before and after the Nargis incident.

Community members also reported that diarrhea diseases, ARI and pneumonia were common health problems immediately after Cyclone Nargis but later declined. Other diseases under national surveillance were also changed. Tuberculosis control program reached the targets of 70% case detection and 85% treatment success rate in 2007 and 2008. Even though the morbidity for STDs such as genital ulcer rate and male urethral discharge rates were not change over time but the coverage of prevention of mother to child transmission of HIV (PMTCT) services was expanded in the year after Nargis. For the expanded program on immunization (EPI), the coverage of DPT 3rd dose reached the target of around 90%, which was the highest, after Cyclone Nargis; but the measles coverage still did not reach the Sphere target. The sanitary latrine coverage in the Nargis affected area was 72% in 2009 as compared to the national sanitary latrine coverage of around 80%.

Conclusion: In general, health services as well as prevention and control measures provided to the Nargis affected population had reduced the excess morbidity and mortality of the communicable diseases recommended by Sphere. However, the distribution of such health services varied among townships within the affected areas. There is still considerable need for equity in distribution of health services for the public health emergency management.

Background

There are approximately 450 to 800 major emergencies, disasters and crises per year; and these has been shown as increasing trends due to global warming, increase population movement, environmental damage, poverty and inadequate or underfunded public health system [1]. The general effects

of disasters or emergencies include injury, death, infectious diseases outbreak, displacing a large number of people, disruption of essential services, destruction of property and infrastructure, economic loss and psychological effect [2, 3]. The magnitude and causes of excess morbidity and mortality caused by emergencies and disasters may vary according to the underlying demographic and epidemiologic profile of the population [4]. During emergency and disaster situation, communicable diseases can cause high mortality and morbidity because of disruption of health services, poor access to health care, malnutrition and inadequate logistic supply [5, 6]. Disaster-affected people are particularly vulnerable to communicable diseases due to malnutrition, stress, fatigue and unsanitary living conditions [6].

Cyclone Nargis struck the coast of Myanmar on 2 and 3 May, 2008 and causing many deaths, destroying infrastructure, affecting on economic and social activities. It was the most devastating natural disaster in history of Myanmar and the most deadly cyclone in Asia since 1991 with 2. 4 million people were severely affected by Nargis [7]. The common water and food borne diseases in the affected area before Cyclone Nargis were diarrhea diseases including cholera, typhoid, shigellosis, hepatitis A and E and acute watery diarrhea. Dengue and malaria has been the major vector borne diseases endemic in the affected area. Measles, acute respiratory infection (ARI), diphtheria, pertusis and meningococcal diseases were reported as associated with the overcrowding in the area. Others diseases endemic in the region were tuberculosis, snake bites and sexually transmitted infection (STIs) [8].

Early Warning and Rapid Response (EWAR) was set up after Cyclone Nargis with involvement of other national and international agencies working in Nargis affected area [9]. EWAR covers 16 common diseases and conditions in the affected area. This study was carried out to examine communicable disease burden and the changes in morbidity and mortality of the diseases under national surveillance in Cyclone Nargis affected area. The study also attempted to assess the effectiveness of control measures of these diseases employing health management information system indicators of the Sphere and Inter-Agency Standing Committee (IASC) for global health cluster communicable diseases indicators [10, 11].

Materials and Methods

Study sites

The focus of data collection in this study included 10 townships in Ayeyarwady and Yangon divisions which were severely affected by Cyclone Nargis. These townships in Ayeyarwady division included Ngapudaw, Labutta, Bogale, Pyapon, Dedaye, Kyaiklat and Mawlamyinegyun townships while those in Yangon division Twantay, Kawnmu and Kungyangon townships. There were about 2. 8 million people living at these townships in 2007 [12].

Secondary data sources

In examining communicable diseases burden and changes in mortality and morbidity of diseases under national surveillance, system data were extracted from the Health Management Information System (HMIS) of the Myanmar Ministry of Health (MMOH). The HMIS is the routine reporting system for 17 diseases under national system in Myanmar, with monthly

reporting from township to central level [12]. The official secondary data during 2007-2009 from the Department of Health, and Department of Health Planning regarding communicable diseases prevention and control programs such as immunization and water-sanitation program were also extracted for assessing the situations of such communicable diseases at the township level. In addition, other related data such as distribution of relief items from EWAR, Myanmar Red Cross Society and Myanmar offices (WHO, UNICEF, Save the Children, Merlin and MSF (Holland)) were also requested for exploring the strength and weakness in the communicable diseases management. Moreover, data from the periodic reviews released by Tri-partite Core Group (TCG) are also used for supplementation of population data [13].

Primary data Sources

The study employed both quantitative and qualitative data collection method. The questionnaire regarding public health emergencies preparedness, particularly on disease surveillance capacity, was developed and sent to hospitals under Department of Health. The questionnaires were sent to 65 hospitals (25% of the total 252 hospitals in coastal Myanmar which includes all 5 states/divisions (i. e., Yangon, Ayeyarwaddy, Mon, Tanintharyi and Rakhine). The questionnaires were responded by hospital directors from those hospitals by means of self administered method. Focus group discussion was used to find out the community perception on health sector response to Cyclone Nargis. The totals of 6 focus groups discussion were carried out in 3 villages among the selected townships in the affected areas. Only issues related to communicable diseases were presented in this

paper. The detailed analyses of hospital preparedness and community perceptions were reported elsewhere.

Ethical Consideration

This study received ethical approvals from Myanmar Ministry of Health and Faculty of Tropical Medicine, Mahidol University.

Results

Disease surveillance in study areas

For disease surveillance, MMOH sets up the coordinating health sectors for disease surveillance, outbreak detection and response. The diseases surveillance data were submitted form local level up to national health information management system (HMIS). After Cyclone Nargis, the MMOH also set up EWAR with rumor verification of the system for disease monitoring and management, particularly for early warning and rapid responses. It was recognized by the MMOH that there are still challenges regarding timeliness of notification and complete data reporting in both HMIS and EWAR. As shown in Table 1, among the 40 out of 65 hospitals that responded the survey, it was found that about 90% of the hospitals have surveillance system for 17 diseases under national surveillance [14]. More than 60% of the response hospitals have syndromic surveillance system but only 27. 5% have microbiological surveillance system, with especially low percentage in primary referral hospitals with less than 10%.

—————Insert Table 1 here————————-

Diarrhea & Dysentery

Among the communicable diseases reported in the HMIS, acute respiratory infection, diarrhoea, dysentery and malaria are the highest diseases burden for the communities within the Nargis affected areas. Morbidity of acute diarrhea in 2007 was 571. 40 per 100, 000 person year and increased up to 755. 80 in 2008 due to Cyclone Nargis while remained and was slightly higher than baseline in 2007 as 610. 56 in 2009. From the EWAR Weekly Report, diarrhea cases after Nargis incident represented 6. 30% of total consultation (4341 cases) in June 2008 (week 23-26) and reduced to 2. 04% (3931 cases) in July 2008 (week 27-31). The number of cases was stable to less than 2. 00% of total consultation during August to December 2008 (926 cases to 1601 cases). In contrast to normal monthly report of severely acute watery diarrhea (suspected cholera) of less than 5 cases, the suspected cholera was reported the highest during June 2008 (21 cases) and serge again a year after Nargis in March 2009 (15 cases). The participants from focus group discussion also revealed that diarrhea diseases, ARI, influenza and pneumonia are prevalence immediately after Cyclone Nargis. One participant mentioned that

" Villagers suffered mostly diarrhea and common cold. Pneumonia was common especially among children. Dengue and malaria were not common among villagers." (35 years old woman)

Despite such increasing disease incidences, mortality rates for diarrhea were reducing during study period, from 0. 68 per 100, 000 person year in 2007 to 0. 40 and 0. 28 in 2008 and 2009 respectively. This finding was also corresponding to the high percentage of treatment with ORT among diarrhea

children (> 95%) in the health facilities and decreasing in severe dehydration among diarrhea children (2. 31% in 2007 to <1% in 2008 and 2009). However, as per TCG periodic report [13], the treatment of ORS among diarrhea patients in community was around 50%. Overall, case fatality rate for diarrhea diseases was reducing during the study period, from 0. 12% in 2007 to 0. 04% in 2009.

Besides diarrhea diseases, dysentery was also one of the leading causes of morbidity among study population; about 350. 90 per 100, 000 person year was reported in 2007 and slightly increased to 475. 40 and 374. 39 during 2008 and 2009 respectively. However, mortality and case fatality rate for dysentery was quite low with nearly 0% during study period.

Acute respiratory tract infection (ARI)

ARI has been reported as the major cause of morbidity and mortality among communicable diseases at study townships. Morbidity of ARI in 2007 was 4041. 91 per 100, 000 person year among under 5 children, highly increased to 599, 621 in 2008 due to Cyclone Nargis, and 4661. 59 in 2009 which was slightly higher than that of at baseline 2007. For morbidity rate among under 5 years old children, as reported by EWAR showed that there were 7. 93% of total consultation (5452 cases) after Nargis in June 2008 (week 23-26), and it dropped to around 5. 00% of total consultation (8842 cases and 5131 cases) in July and August 2008 respectively., and subsequently back to normal stable level at less than 3. 00% during October (3615 cases) to December 2008 (1991 cases). Interestingly, mortality rate for ARI was lower in Nargis year; that is 4. 86, 3. 14, and 4. 11 per 100, 000 person year in 2007, 2008

and 2009 respectively. On the other hand, case fatality rate for ARI has been improving from 0. 12% in 2007 to 0. 09% in 2009.

Malaria and dengue

Vector-borne diseases such as malaria and dengue cases were decreasing significantly in 2009, compared to 2007 and 2008. Malaria morbidity was more 324. 44 and 352. 51 per 100, 000 person year in 2007 and 2008, and then dropped to 227. 18 in 2009. Similarly, percent of malaria inpatient among general clinic attendance has been decreasing during study period, 3. 17% in 2007 to 1. 63% in 2009. In contrast, the mortality percentage among malaria inpatient was increasing, 1. 16% in 2007 to 3. 31% in 2009. It was shown, however, that malaria morbidity and mortality varied among different townships. From the EWAR report, malaria confirmed cases represented about 0. 25% of total consultation (465 cases) in July 2008, then dropped to 0. 10% of total consultation (77 to 237 cases) during August to December 2008.

Dengue hemorrhagic fever cases are 35. 65, 15. 76 and 12. 40 per 100, 000 person year respectively. Confirmed dengue hemorrhagic fever cases were also surge after Nargis during July 2008 which was 273 cases or 0. 14% to total consultations. Normally during other period the numbers of cases ranged from 1 to 95, making the rate of approximately less than 0. 10% of total consultation. Mortality rate and case fatality rate for dengue hemorrhagic fever were decreasing trend during study period.

Tuberculosis, HIV, and other diseases

HMIS data also shows that morbidity and mortality rates for tuberculosis had been decreasing in the study area during the study period (67. 11, 57. 12, and 47. 54 per 100, 000 person year in 2007 to 2009). Morbidity for sexually transmitted infection (STIs) such as genital ulcer rate (> 2 per 100, 000 person year) and male urethral discharge rates (> 1 per 100, 000 person year) had not changed over time and thus it could be assumed that these diseases burden for STIs were the same before and after the Cyclone Nargis. According to EWAR, STIs constituted less than 0. 5% of total consultations during June 2008 to May 2009.

Interestingly, as part of the surveillance, mortality rates for snake bite had not changed much during 2007 to 2009 but case fatality rates for snake bite and meningitis were quite high in the study area. It was also found that vaccine preventable diseases such as diphtheria, pertusis, neonatal tetanus and measles were not the major causes of morbidity and mortality among the under 5 children during study period. Morbidity for viral hepatitis and typhoid constituted <10 per 100, 000 person year during the study period.

—————Insert Figure 1 here————————————-

—————Insert Table 2 here——————————-

Health services utilization

Based on the data in HMIS, the general clinic attendance was 15. 13, 23. 18 and 21. 33% in 2007, 2008 and 2009 respectively; this reveals that general clinic attendance had been increasing significantly since 2008 compared to 2007. However, percentage of average visit per patient attending clinic and

referral hospitals did not change much during 2007 to 2009. The data from EWAR which includes statistics from international NGOs indicated that there was a total of 754, 852 consultations in 15 townships at Nargis affected area one year after Nargis incident, from June 2008 to May 2009. It was also estimated that the total consultation per person was about 0. 3, and there was a total consultation of more than 300, 000 to mobile clinics sent by MMOH. As shown in Figure 2, monthly general clinic attendance did increase during May 2008 to July 2008 which was 3 months after Cyclone Nargis, and subsequently attendance slowly decrease start from August 2008. During 2009, monthly attendance appears to be stable with not much variation in months.

In assessing accessibility to health facilities, it was found that there was not significantly change during 2008 to 2010 for the presence of health personnel at health facilities at most of the time. In contrast, drugs availability at health facilities for most of the time has been dramatically increased from 76% to 92%. On the other hand, average number of clinic visit by household head count has decreased from 1. 9 in July 2009 to 0. 5 in 2010; this falls short when comparing to the international standard target of 2. 0-4. 0 (as set by Sphere).

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—————Insert Figure 2 here————————-

Prevention and control measures

During May 2008 to April 2009, there were a total of 50, 000 pamphlets, 2, 945 posters, 12, 000 booklets about diarrhea diseases and childhood

infections distributed to the Nargis affected areas by National Health Programs and other organizations. Interestingly, most of the participants in focus group discussion pointed that they were not interested in health education and went to health education only for receiving relieve items.

" Health education was given on dengue, malaria, diarrhea diseases, and other communicable diseases. Most of the villagers did not go because they were busy with activities such as building shelter." (57 years old farmer)

It is found that rapid diagnostic test and artemesinin combination therapy (ACT) were available in about 70% of rural and sub rural health centers. The national health programs and other organizations distributed a total of 191, 718 ACT strip and 282, 532 insecticide long lasting nets (ILLN) during May 2008 to April 2009. Availability of information education and communication (IECs) materials for dengue in health centers was high, with more than two-third of the health center have IECs materials for dengue. On the other hands, IECs material for malaria was present in about 50% of health centers. The vector-borne diseases control program distributed 37, 000 pamphlets on vector-borne diseases during May 2008 to April 2009. Particularly in a malaria high endemic area, Ngapudaw, the training program for malaria case management was carried out for 80 hospital staffs. Insecticide residual spray had also been carried out in high endemic area with population coverage of 40, 122. Mass larviciding activities were carried out with population coverage of 347, 231 in study area for dengue control. It was found that distribution of malaria drug was well covered as one health personnel mentioned that " During Cyclone Nargis, a lot of malaria drugs supply was given to my health

center but malaria is not prevalence in my area. I was afraid of malaria drugs to be expired."

Tuberculosis control program reached the targets of 70% case detection and 85% treatment success rate before Nargis incident since 2007. However, the case detection in the Nargis affected area of 70% was slightly lower than the national average of 77%. It was found that the case detection was quite different among townships, in some townships is lower than 50%. During May 2008 to April 2009, the national health program distributed 2000 pamphlets, 1000 posters and 8800 booklets on education for tuberculosis to the study area.

Coverage of prevention of mother to child transmission of HIV (PMTCT) services increased from 2 townships in 2007 to 7 townships in 2009. Performance of PMTCT services such as percentage of treatment taken by HIV (+) pregnant mother (61% in 2007 to 80% in 2009) and percentage of new born HIV (+) have been improved overtime (14% in 2007 to <5% in 2009). In terms of HIV IECs material, it was found that less than 50% of regional health centers had HIV IECs material (14). Majority of the organizations distributed condoms for prevention of STIs; the total male condoms distributed by National Health Programs and other organizations were 430, 390. However, it was still less than the target of 1 condom/person/month set up by Sphere. There were also 24, 500 pamphlets, 400 posters and 8, 000 booklets about STD/HIV distributed to the affected area during May 2008 to April 2009.

In terms of expanded program immunization (EPI) coverage, it was found that the coverage reached highest in 2008 after Cyclone Nargis; the DPT 3rd dose reached the target of around 90%. However, measles coverage was lower, around 84% during the study period. The EPI IECs materials were presented in around two-third of health facilities in the survey done by UNICEF during December 2008 [14]. One health personnel also confirmed in focus group discussion that immunization services were successful after Cyclone Nargis.

The sanitary latrine coverage was increased after Cyclone Nargis in 2009 compared to 2007 both in urban and rural area. The sanitary latrine coverage for population was 72. 36 in 2009. However, the sanitary latrine coverage on 2009 was still low in certain rural area, i. e., in Ngapudaw, Labutta and Bogale townships. During May 2008 to April 2009, the total of 316, 891 pamphlets and 200, 415 posters were distributed to disaster affected area by several organizations. The TCG survey reported that the population receiving improved drinking water has been increasing from 66% in December 2008 to 72% in July 2010, but there was approximately 43% for improved sanitation facilities which was contradict with MMOH surveillance data of 70%. The national health Programs also rehabilitated 4235 ponds, 1028 wells in study area. A total of 236 ponds, 760 shallow wells and over 200 deep tubes well were also constructed in study areas. Participants from focus groups discussion mentioned that sanitary latrine constructions by villagers were associated with the supply of both latrine pan and construction cost. " Latrine pans were distributed. However, I could not construct latrine because I had no money." (25 years old man) and " In our

village, most of the villagers were constructed sanitary latrine because the organization (—–) provided not only gave latrine pans but also provided the construction cost." (18 years old student)

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Discussion

MMOH had established HMIS for routine reporting disease surveillance system and the system has been fully functioning in almost all levels of hospitals. However, the hospitals especially in the secondary referral level should consider strengthen the microbiological surveillance because of weakness in laboratory capacity at such hospitals. Microbiological surveillance is important for early detection of public health emergencies especially communicable diseases outbreak. Currently, the there are only about 20-30% of hospitals that have microbiological surveillance system, compared to 64. 5% of hospitals in China in preparation for public health emergencies [18].

World Health Organization recommended that major diseases/syndromes that should be included in emergency surveillance are bloody diarrhea, acute watery diarrhea and suspected cholera, acute respiratory tract infection (ARI), measles, meningitis, HIV/AIDS, sexually transmitted infections, tuberculosis, and neonatal tetanus [6]. Setting up of EWAR with participation of national and international organizations working in public health emergency response is best practice for public health emergency management and should be maintained in future public health emergency

management. It was found in this study that surveillance system is also compatible with the diseases impact in the affected area but there are rooms to improvement for areas such as recording and calculation of actual proportion such as timeliness for surveillance and sensitivity for outbreak detection [12]. However, it is also recommended the necessity of setting up the database for logistic and drugs supply for health sector with involvement of other organizations working in public health emergencies [17].

The national surveillance data coincided with the EWAR reports suggested that morbidity of communicable diseases highly increased for about 3 months after Cyclone Nargis. Diarrhea diseases, ARI and malaria have been reported as major communicable diseases, in this area. The diseases increased significantly during the months after Cyclone Nargis which was similar to other disaster incidents elsewhere in which the diseases that could cause major morbidity and mortality in emergencies including ARI, diarrheal diseases, measles and, malaria in endemic area, epidemic meningococcal disease, dengue, tuberculosis, tetanus, pneumonia, relapsing fever, yellow fever, and typhus [6, 16]. With early diagnosis and prompt treatment with trained staff by using standard protocols at all health facilities, the management of communicable diseases would help solve the situation [5]. Thus, it might be due to the good predisposition of drugs for common diseases in risk areas and the strengthened preparation for disaster management by both governmental programs, international organizations and NGOs. The morbidity and mortality of common communicable diseases seem to be in better situations after the Nargis incident.

In 2009, acute diarrhea diseases in the affected area have been compatible with the national average of morbidity and mortality of 667 and 0. 65 per 100, 000 person year respectively. Case fatality rate for diarrhea diseases such as typhoid, dysentery etc. was less than 1% and it achieved the standards set by communicable diseases management in public health emergencies [10]. This finding coincided with the observable fact of high percentage of treatment with ORT among diarrhea children in the health facilities, decreasing in severe dehydration among diarrhea children, and effective case management for diarrhea diseases as well as early diagnosis. The morbidity and mortality of ARI which was the most communicable disease burden revealed increasing trends in the study. Both ARI and diarrhea are still a public health burden and require effective prevention and control programs in this coastal area.

In contrast, mortality and morbidity for vector-borne diseases, particularly malaria and dengue, reveal decreasing trends during 2007 to 2009, except high peak in months of Nargis incident. Malaria morbidity and mortality rates in study area were lower compared to national rate of 1075 and 1. 84 per 100, 000 person year respectively. Overall, major vector-borne diseases control in the study area has been functioning well. However, it was noted by healthcare providers that supply of drugs should be based on risk assessment of malaria in that area.

The situation of other diseases also shows improving trends. Tuberculosis program reached the targets of case detection and treatment success rates but varied in different townships. More efforts are needed in townships that did not reached the national targets. Despite the fact that morbidity rates of

sexual transmitted diseases did not change much, but the PMTCT coverage was improved. It was noted by healthcare providers though that PMTCT services should be secured at all townships by national health programs with financial and technical support. This involves many stakeholders that manage PMTCT services in the country.

Immunization plus program with nutrition services has shown effective practice for public health emergencies management and it should be maintained or even improved not only for future emergency incidents. It was suggested that if measles vaccination coverage rates are lower than 90%, it should be given priority to prevent an outbreak of measles in emergency situations [5, 6]. Measles immunization coverage in the study area was at 84% but it was still considered not reaching the target of 95% coverage set up by Sphere [10]. On contrary, DPT 3rd dose coverage was about 90% reaching the target of national health program but was again less than the IASC indicators of 95% coverage [11]. In all, it was found that all immunizations coverage is slightly lower after Nargis incident in 2009 compared to 2008. Sustainability of immunization services should be considered as part of the routine national health program with involvement of donor agencies and township health department.

Community awareness program should be strengthened because community awareness on early treatment and proper case management are important in reducing the impact of communicable diseases [6]. It is found that almost all of the organizations distributed several IEC materials regarding communicable diseases; however, most of the participants in the focus group discussion reported not interested in health education programs. The

evaluation of effectiveness of health education programs should be then carried out to assess future public health emergency management.

Utilization rate of health services such as general clinic attendance has been improving during the study period but it is still quite low in consideration with the target achievement of 50% target. Clinic attendance rates of some townships were less than 15% while TCG survey also reported that health services utilizations did not reach the Sphere target of 4 visits/person/year. It is necessary to research on factors influencing the utilization of health services. Sanitary latrine coverage in townships at the affected areas was still slightly lower than the national sanitary latrine coverage of around 80%. It was also found that distribution of water and sanitation items were quite varied among communities. Water and sanitation program should be strengthened in townships which are below the national average by cooperation among stakeholders.

Conclusion

Overall, health sectors have achieved the Sphere targets of management of communicable diseases in the coastal townships. The excess mortality and morbidity of the communicable diseases was reduced in the Nargis affected area by means of health services given by Department of Health, MMOH and other several organizations including NGOs and international NGOs. However, communicable diseases are still the high burden in these townships and health sectors including all stakeholders should strengthen the health services. Lesson learned in terms of strengths and weakness for communicable diseases prevention control during Cyclone Nargis could be

applied for setting up policy and plan for preparation and management of public health emergency in Myanmar.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NWM, JK, PS were involved in the conceptualization and design of the study. NWM prepared research instruments and other study logistics, collected data in Myanmar. SLN and TTM assisted in study management and data support in Myanmar. KC, PS, AKM, PP provided conceptual framework and technical support for the study. NWM and JK performed analyses and drafted the manuscript. All authors read and approved the final manuscript.

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We