World Health Organization
Western Pacific Region

WPSAR
Western Pacific Surveillance and Response Journal

Volume 10, Number 3, 2019, Pages 1–26
p-ISSN: 2094-7321 e-ISSN: 2094-7313

IN THIS ISSUE

Western Pacific Surveillance and Response

Open access journal with continuous publication

Western Pacific Surveillance and Response (WPSAR) is an open access journal dedicated to the surveillance of and response to public health events. The goal of the journal is to create a platform for timely information sharing both within our region and globally to enhance surveillance and response activities. WPSAR is a continuous publication which means articles will be published online as soon as they have completed the review and editing process. Every three months articles will be batched for a print issue. It is a publication managed by the World Health Organization Regional Office for the Western Pacific.

To contact us:

Western Pacific Surveillance and Response
World Health Organization
Office for the Western Pacific Region
United Nations Avenue
1000 Manila, Philippines
wpsar@who.int
https://ojs.wpro.who.int/

p-ISSN: 2094-7321
e-ISSN: 2094-7313

Risk assessment of Ebola Reston virus in humans in the Philippines

Johnette A Peñas,[a] Mary Elizabeth Miranda,[a] Vikki Carr de los Reyes,[a] Ma. Nemia L Sucaldito[a] and Rio L Magpantay[a]

Correspondence to Johnette A Peñas (email: penasjohnettea@gmail.com)

Objective: There have been five documented outbreaks of Ebola Reston virus (RESTV) in animals epidemiologically linked to the Philippines. This assessment was conducted to determine the risk of RESTV occurring in humans in the Philippines and its potential pathogenicity in humans.

Methods: The World Health Organization *Rapid Risk Assessment of Acute Public Health Events Manual* was used for the assessment. A literature review was done and a risk assessment matrix was used for the risk characterization of the outbreaks in the Philippines. The risk assessment was conducted by the Philippines Field Epidemiology Training Program.

Results: The risk of RESTV occurring in humans in the Philippines and its potential pathogenicity in humans were both assessed as moderate. Animals involved in RESTV outbreaks in the Philippines were non-human primates and domestic pigs. The presence of RESTV in pigs poses a possibility of genetic evolution of the virus. Although RESTV has been identified in humans, there was no death or illness attributed to the infection. The Philippines Inter-agency Committee on Zoonoses oversees collaboration between the animal and human health sectors for the prevention and control of zoonoses. However, there is no surveillance of risk animals or previously affected farms to monitor and facilitate early identification of cases.

Discussion: The moderate risk of RESTV recurring among humans in the Philippines and its potential pathogenicity in humans reinforces the need for early detection, surveillance and continued studies of RESTV pathogenesis and its health consequences. The One Health approach, with the involvement and coordination of public health, veterinary services and the community, is essential in the detection, control and management of zoonosis.

Ebola Reston virus (RESTV) is one of the six virus species of the Ebola virus in the family Filoviridae.[1,2] Although three filoviruses have been identified in animals in Asia,[3,4] RESTV is the only filovirus isolated from Asia that is known to infect humans.[5] There have been five documented RESTV outbreaks in animals epidemiologically linked to the Philippines.[6,7] RESTV was detected in non-human primates (NHPs) in the periods 1989–1990, 1992–1993 and 1996;[6,8] in pigs in 2008–2009;[6,9,10] and again in NHPs in 2015.[7] These NHPs were cynomolgus macaques used for preclinical research, drug development, disease modelling, experimental infections, and biological production, with breeders being collected from wildlife trapping areas mostly in southern Philippines.[6] Four of of the five outbreaks were investigated by the Philippines Field Epidemiology Training Program (FETP).[7–12]

There is concern in the Philippines that RESTV will continue to occur in animals with spillover into humans and could one day become pathogenic to humans.[1,10,12,13] It has been hypothesized that ongoing, undetected RESTV infections and replication in pigs and other animals could result in the emergence of more pathogenic viruses in humans and/or livestock.[13] Therefore, a risk assessment was conducted to determine the risk of further occurrence and potential pathogenicity of RESTV in humans in the Philippines.

METHODS

The World Health Organization (WHO) *Rapid Risk Assessment of Acute Public Health Events Manual*[14] was used for this risk assessment. It included conducting hazard, exposure and context assessments to determine the level of risk. The WHO risk assessment matrix was used to characterize the level of risk based on the combined estimate of likelihood and consequences of the event.

The risk assessment was conducted by the Philippines FETP. The team was comprised of public health specialists in applied epidemiology with expertise in

[a] Department of Health, Philippines.

Submitted: 11 July 2016; Published: 5 July 2019
doi: 10.5365/wpsar.2017.3.004

epidemiology, infectious diseases, risk communication and emergency planning. Several team members were part of the response teams for the RESTV investigations.

To enable an evidence-based risk assessment, literature reviews were conducted on articles with RESTV data. The archives of the Epidemiology Bureau library in the Department of Health (DOH) were searched for all RESTV-related investigations conducted by FETP fellows from 1989 to 2015. A MEDLINE search using PubMed was conducted using the search terms "Ebola" and "Reston" with search dates between 1 November 1989 and 1 November 2016. Only articles containing data on RESTV studies and its occurrence were reviewed. Information on the pathogenicity of RESTV was published in a 2009 WHO meeting report on Ebola Reston pathogenicity in humans.[15] This informal meeting was conducted to provide guidance on responding to queries related to RESTV pathogenicity in humans.

RESULTS

Literature review

Seven RESTV-related investigation reports by FETP fellows were identified.[7–12,16] A MEDLINE search produced 129 scientific and medical abstracts and full-text reports, and 19 were relevant to the risk assessment.[1–6,13,17–31] These 26 reports are all full-text reports; 12 studies were conducted following the five RESTV outbreaks in animals epidemiologically linked to the Philippines and one occurring in China. The remaining 14 reports were serological/molecular studies in humans, monkeys and/or bats (9); genome virus analyses (2); ecologic niche modelling of outbreaks (1); study on filovirus survival ability (1); and a review of RESTV in the Philippines (1).

Hazard assessment

RESTV outbreaks in animals epidemiologically linked to the Philippines

There were five documented RESTV outbreaks in animals epidemiologically linked to the Philippines.[6,7] The first outbreak was in November 1989 in Reston, Virginia, United States of America (USA) when quarantined NHPs from the Philippines became ill and died.[12,22] Epidemiological investigation in the monkey-breeding facilities in the Philippines at that time revealed RESTV-infected animals in the facilities.[11,12] This was the first-ever Ebola virus detected outside of Africa and was the first known natural infection of Ebola virus in NHPs.[6]

From 1992 to 1993, RESTV was detected in an NHP quarantine facility in Sienna, Italy, and infected NHPs were again traced back to the Philippines.[6] In March 1996, imported macaques from the Philippines tested positive for RESTV in another facility in Texas, USA.[8] In October 2008, RESTV RNA was unexpectedly identified in pig tissue samples sent from the Philippines for porcine reproductive and respiratory syndrome (PRRS) strain analysis in the Plum Island Animal Disease Center in Greenport, New York, USA.[9] Joint investigation by the FETP, the Bureau of Animal Industry and international experts revealed that the positive samples came from two commercial pig farms.[10] RESTV was detected in the Philippines in September 2015 in monkeys bound for export.[7] Risk communication was done to allay public fears. It was emphasized that RESTV is the mildest type of Ebola and does not pose the same threat as the Democratic Republic of the Congo Ebola virus in West Africa.[32]

Serological testing in human and animals

Across these five RESTV outbreaks in animals, a total of 1445 humans were tested for RESTV; all had been occupationally exposed to NHPs or pigs or were close contacts of seropositive persons.[6–11] A total of 105 people (7%) were positive; most (100/105, 95%) were pig handlers and abattoir workers from the 2008–2009 investigations after the detection of RESTV in pigs in Pangasinan and Bulacan.[9,10]

The highest number of animals testing positive for RESTV was in the 1989–1990 investigation when 142/179 (79%) NHPs tested in the Philippines were antibody positive and 141/279 (51%) were antigen positive (**Table 1**).[6–12] Two per cent (3/186) of occupationally exposed animal handlers tested positive.[15] This serosurvey was initiated following the report of RESTV-infected macaques in the USA from two major export facilities in the Philippines.[11,12]

Clinical factors

Signs and symptoms manifested by RESTV-positive NHPs were diarrhoea, respiratory symptoms, wounds, bleeding, weakness, gastrointestinal infection, anorexia

Table 1. **Ebola Reston virus laboratory results and signs and symptoms, 1989 to 2015**

Year of outbreak	NHP			Pig			Human		
	Antibody	Antigen/ RNA	Signs and symptoms	Anti-body n=153	Anti-gen/ RNA	Signs and symptoms	Antibody	Signs and symptoms	Population group
1989–1990	142 (79%) [a] [(9)]	141 (51%) [b] [(9)]	Diarrhoea, respiratory symptoms, wounds, bleeding, weakness, loss of appetite [(9)]	-	-	-	3 (3%) [c] [(8)]	No illness [(8)]	Animal handler, veterinarian [(8)]
1992–1993	-	-	-	-	-	-	2 (2%) [d] [(3)]	No Illness [(3)]	Breeding and export facility employees [(3)]
1996	3 (2%) [d] [(5,25)]	131 (47%) [e] [(5,25)] 6 (2%) [f] [(23)]	Signs of gastrointestinal infection, anorexia, paralysis [(23)]	-	-	-	1* (1%) [d] [(5)]	No illness [(5)]	Breeding and export facility employee [(5)]
2008–2009	-	-	-	153 [d] [(7)]	28 [f] [(6)]	Clinical signs resembling PRRSV [(7)]	100 (95%) [d] [(3,6,7)]	No illness [(6,7)]	Abattoir workers and pig handlers [(6,7)]
2015	34 (19%) [g] [(4)]	1 (0%) [f] [(4)]	Anorexia, dehydration, petechial haemorrhage [(4)]	-	-	-	0 (0%) [g] [(4)]	-	Workers at monkey-holding facilities [(4)]
Total	**179**	**279**	-	**153**	**28**	-	**105**	-	-

NHP: non-human primate; PRRSV: porcine reproductive and respiratory syndrome virus.

a Indirect fluorescent antibody assay cut-off of ≥ 1:16.

b Antigen detection by enzyme-linked immunosorbent assay (ELISA).

c Indirect fluorescent antibody test cut-off of ≥ 1:256.

d IgG antibody by ELISA.

e Antigen detection test by enzyme immunosorbent assay (EIA) cut-off of ≥ 1:16.

f Reverse-transcriptase polymerase chain reaction (RT-PCR).

g IgG and IgM antibody by ELISA.

* Same person already IgG positive in 1992–1993.

Note: Not all RESTV-positive non-human primates and pigs are symptomatic.

and paralysis.[6,12,26] Some of the RESTV-positive pigs had clinical signs that resembled PRRS virus infections.[1,9,10,13] However, it was also observed that RESTV can be asymptomatic in NHPs and pigs (**Table 1**).[7,8,18,26,27] Some animals infected with RESTV were shown to be immunocompromised or having a coinfection.[1,24] These coinfections included simian haemorrhagic fever (NHPs, 1989–1990),[6] PRRS (pigs, 2008–2009)[9,10,24] and measles (NHPs, 2015).[7]

In humans, there have been no deaths or illness attributed to RESTV infection; rather, infection results in a very mild illness.[6,8–11] Therefore, RESTV does not pose the same public health threat as the African Ebola virus subtypes.[11,27] As the evidence available relates only to healthy adults, further studies are needed to clarify whether these health effects would be the same for all population groups, such as those with underlying medical conditions, immunocompromised individuals, pregnant women and children.[15] However, these population groups may be less likely to be in contact with infected NHPs, pigs and bats compared to the other groups (healthy, no special condition) as they probably spend more time indoors and are less likely to engage in activities exposing them to the said animals. RESTV in domestic pigs also increases the opportunity of pig-to-human interspecies transmission because of their frequent and close level of contact.[15]

According to the WHO experts consultation on RESTV pathogenicity in humans, the virus is genetically diverse,[15] and slight changes in its genetic sequence could result in a more virulent virus in humans.[21] When there was interspecies transmission (e.g. monkeys to pigs), RESTV was thought to evolve more rapidly.[1,15] In the affected farm in the 2008–2009 RESTV outbreak in pigs, there was a 0.079% genetic diversity of the virus over a one-year period, and simultaneous samplings in

another farm in 2008 found the divergence to be about 4.5%.[18] The presence of RESTV in pigs poses a high potential for genetic evolution since domestic pigs, as compared to NHPs and bats, have frequent contact with humans.[9,10,15] With no surveillance for RESTV in pigs, bats and NHPs in the wild, it is possible that there is undetected ongoing circulation of the virus in animals, providing opportunity for continued genetic evolution with passage, adaptation and its possible natural selection.[13,15] However, there is no research on RESTV virulence factors, and it is difficult to tell based on genetic sequence data which RESTV strain might be pathogenic in humans.[15]

Exposure assessment

Geographic distribution

Animal and human infections of RESTV have occurred in five provinces and two cities in the Philippines.[7,8,10,11] Laguna province has had cases in humans and NHPs.[6,8,11] The provinces of Pangasinan and Bulacan have had cases in humans and pigs.[9,10] Nueva Ecija province and Valenzuela City have had cases only in humans,[9,10] and Batangas province and Parañaque City have had cases only in NHPs.[7–12] Some of the infected NHPs in Laguna were caught in the wild on the island of Mindanao.[8] While the geographic origin of RESTV is hypothesized to be South-East Asia and the Philippines,[22] distribution has been shown to be widespread as it also occurs outside Asia.[5,23]

Filoviruses have been identified in Africa, Europe and Asia.[22,23,27,30,37,38] Serological studies in other countries from 1990 to 2011 found RESTV in humans in Germany,[23] pigs and bats in China,[19,24] orangutans in Indonesia[20] and bats in Bangladesh[25] and South Africa.[5]

Modes of transmission

Humans who tested positive in serological studies had daily exposure to pigs or NHPs.[6–11] The mode of transmission of RESTV to humans is most likely through close or direct contact with infected animals' secretions, blood, organs or bodily fluids.[9,10,15] It is uncertain whether RESTV can be transmitted to humans through inhalation of infected respiratory secretions, but it has been described in NHPs. Some studies also found that experimentally infected pigs with RESTV can shed virus from the nasopharynx, suggesting a route of transmission by aerosol or droplet contact. Further investigations are needed for clarification.[13,15,18,21,27,31]

There is no indication of human-to-human transmission of RESTV. In the 1989–1990, 1996 and 2008–2009 investigations, several contacts of RESTV-positive individuals all tested negative.[6] However, human-to-human transmission is potentially possible if an individual were to become viraemic and symptomatic. This has occurred in other filoviruses, and there was a documented three-day viraemia in a human with RESTV infection.[15]

Natural reservoirs of RESTV

Bats have been identified as natural reservoirs of filoviruses, including Ebola and Marburg viruses.[5,13,17,19,25,29,30] In the Philippines, there is evidence of RESTV infections in bats in Quezon City and in the provinces of Bataan, Bulacan and Quezon.[29,30] It is possible that RESTV was transmitted to NHPs and pigs from bats since bats inhabit many areas of the country, including the regions around the affected facilities in Bulacan, Pangasinan and Batangas.[7,9,10,17,30] In a 2010 risk assessment of bat exposure among people in Orani, Bataan, bat meat consumption (93%), presence of bats near house (90%) and handling of bats (77%) were common.[16]

Context assessment

Policy factors

The capacity of the Philippines to detect and respond to the RESTV outbreak is limited but has improved over time. The Philippine National Reference Laboratory for Emerging and Re-emerging Infectious Diseases (NRL-EREID) has the ability to test both human and animal samples for RESTV. Testing for RESTV in humans is done when outbreaks occur in animals. Currently, there are two monkey-holding facilities in the Philippines, and only NHPs for export are tested for filovirus. The Bureau of Animal Industry and the World Organization for Animal Health do not consider RESTV to be a priority or notifiable animal disease.[33,34]

Environmental factors

In the late 1970s there was a marked increase in human population along with logging and deforestation in the Philippines.[18] Deforestation and other landscape transformations result in more direct and indirect human

contact with primates and bats and alter geographic distribution of animals, leading to increased risk of old and new zoonosis.[35]

The total swine population in the Philippines has reached 13.13 million.[36] The pig industry can expose pig handlers and abattoir workers to viruses. In the 2008–2009 RESTV outbreak, the majority of RESTV-positive pig handlers wore only rubber boots as personal protective equipment.[9,10] Despite the 2008–2009 outbreak in pigs, no surveillance has been conducted in the affected farms to determine if transmission stopped after pig depopulation.[10] The risk of contaminated meat entering the food chain is possible. This is a potential route of transmission with an urgent need for risk assessment.[15]

Technical and scientific factors

The first three RESTV outbreaks were initially detected in NHP quarantine facilities in Virginia (USA), Italy and Texas (USA)[6,8,11,12] and were subsequently traced back to one facility in the Philippines.[1,17] In 2008–2009, RESTV was coincidentally detected in pig tissues sent to the USA for PRRS strain analysis.[9,10] In 2015, RESTV was identified in NHPs bound for export; a filovirus test conducted during the 31-day quarantine yielded positive results in nine apparently healthy NHPs.[7] This prevented the exportation of yet another infected NHP from the Philippines. Of the five RESTV outbreaks, only one was detected in the Philippines by the DOH-EREID. Testing of NHPs for export is not sufficient to identify all cases in animals. Animal surveillance and laboratory testing are necessary to capture RESTV cases in animals.

Since previous human cases of RESTV were asymptomatic, possible cases may seek medical care or testing only if another outbreak occurred in animals. Thus, the likelihood that cases are identified is low. The Philippines One Health[37] concept recognizes the need for intersectoral collaboration in public health, social sciences, medicine, veterinary sciences and agriculture to mitigate complex socioecological drivers that contribute to ill health.[35] The Philippines One Health approach addressed RESTV outbreaks in NHPs and pigs; various agencies took part in virus detection, NHP and pig depopulation and bat surveillance. In 2011, The Philippines Inter-agency Committee on Zoonoses was created to establish animal and human health sector collaboration for the prevention and control of zoonoses.[37] The NRL-EREID programme also highlights strategic priorities to prevent and control diseases from becoming public health problems. Priorities include resource management, coordinated networks of facilities and managing information to enhance disease surveillance.[38]

Economic factors

RESTV outbreaks resulted in NHP depopulation and closing of two monkey-holding facilities in 1996 and 2015.[7,26,28] Also, 6210 pigs were culled in 2008 to prevent the spread of the virus to other pigs and to reduce exposure to abattoir workers.[10] These control measures during RESTV outbreaks greatly affected livelihoods and the economy.

Risk characterization

Using the information from the risk assessment, the risk of RESTV occurring in humans in the Philippines was considered moderate, based on that it is likely to occur; however, the consequences would be minor (**Table 2**). The risk of potential pathogenicity in humans was also assessed as moderate. While the consequences of RESTV human pathogenicity could be major if it became highly pathogenic, the very low likelihood makes it unrealistic to consider the resultant overall risk as high as formally dictated by the risk assessment tool. Accepting that the risk assessment tool allows for a certain degree of judgment and flexibility, we thus consider the overall risk as moderate (**Table 3**).

The level of confidence on this risk assessment is low to medium based on the data presented. Information on the hazard, exposure and context assessments was based on different sources, which include first-hand epidemiological investigation reports and peer-reviewed articles; however, there was little information on surveillance, epidemiological and clinical data. These limitations could alter the understanding of RESTV and the risks to humans.

DISCUSSION

In this risk assessment, the risk of RESTV occurring in humans in the Philippines and its potential pathogenicity in humans were both assessed as moderate.

RESTV in humans was deemed likely to occur since RESTV infection has been detected in humans, pigs, bats

Table 2. **Risk analysis matrix for the assessment of risk for RESTV further occurrence**

Likelihood	Consequences				
	Minimal	Minor	Moderate	Major	Severe
Almost certain	Low	Moderate	High	Very high	Very high
Highly likely	Low	Moderate	High	Very high	Very high
Likely	Low	**MODERATE**	High	High	Very high
Unlikely	Low	Low	Moderate	High	High
Very unlikely	Low	Low	Moderate	High	High

Table 3. **Risk analysis matrix for the assessment of risk for RESTV pathogenicity**

Likelihood	Consequences				
	Minimal	Minor	Moderate	Major	Severe
Almost certain	Low	Moderate	High	Very high	Very high
Highly likely	Low	Moderate	High	Very high	Very high
Likely	Low	Moderate	High	High	Very high
Unlikely	Low	Low	Moderate	High	High
Very unlikely	Low	Low	**MODERATE**	High	High

Note: Risk analysis matrix was adapted from WHO [11].

and NHPs from different locations within the Philippines. With pigs as a host of RESTV, the likelihood of further human contact with infected animals is high, and the likelihood of the virus entering the food chain is possible. If RESTV remains non-pathogenic to humans, the consequence will remain minor.

To date, there has been no evidence of RESTV pathogenicity in humans and no deaths or illness among the 105 RESTV-positive humans.[6–12] However, some changes in the genetic sequence of RESTV could result in a virus more virulent in humans, especially if there is interspecies transmission.[15] Should RESTV spread and become pathogenic in humans in the Philippines, the health consequences would escalate. Further evaluation would be needed if it occurred to establish the evolving risks. Response to the event would depend on the RESTV pathogenicity.

Enhanced surveillance is needed, and exposure of humans to animals and environmental sources should be controlled. Strict implementation of quarantine and filovirus testing of all NHPs for export should be continued. Sentinel testing of other NHPs within the Philippines should be considered to detect potentially latent diseases and prevent their introduction into a larger laboratory animal colony. Serological testing of domestic pigs in areas with a history of RESTV should be considered, especially if there are unusual pig deaths. Testing would allow detection of the virus before it enters the food chain, thus limiting the possible emergence of a more pathogenic strain due to replication in livestock.

There are limitations to our risk assessment. Current risk assessment is based on post-hoc reports on incidental findings of the virus through exported animals or tissue samples; therefore, the true epidemiological and clinical profile of infections in animals or humans are unknown. There has been no surveillance or serological surveys of domestic pigs, NHPs or people occupationally exposed to determine if the transmission has stopped or if there is ongoing circulation of the virus. With no ongoing surveillance data, current/baseline infection rates and/or viral genetic evolution are not established. As a result, it is impossible to know the true prevalence of the infection or be alerted for further outbreaks. We used information from the WHO consultation on Ebola Reston pathogenicity in humans, which was conducted after RESTV was detected in pigs (2009), and there have been further incidents since then. Aside from FETP scientific papers,

literature review was limited to MEDLINE. Finally, risk assessments by their nature are somewhat subjective; therefore, other risk assessment approaches may have different outcomes.

Future studies will shed light on RESTV pathogenicity and its consequences on animal and human health. Follow-up and serological studies on RESTV-positive humans should be done. Research studies on RESTV epidemiology, viral genetics, reservoir, potential hosts, clinical disease in humans and animals including incubation period, risk factors for infection, pathogenesis in coinfection and immunocompromised hosts, mechanism and prevention of transmission and public health impact should also be undertaken.

Our assessment showed that the risk of RESTV occurring again in humans in the Philippines is moderate, and the risk of potential pathogenicity in humans is also moderate. The Philippines must not be complacent about the detection of RESTV. Applying and intensifying the One Health approach by doing surveillance, research, risk communication, risk reduction measures, and collaboration involving at-risk communities and human and animal health sectors should be initiated and continued for preparedness and response for potential RESTV outbreaks.

Acknowledgements

We extend our sincere gratitude to the Field Epidemiology Training Program fellows and graduates who were part of the RESTV epidemiologic studies from 1989 to 2015. We also thank staff of the Research Institute for Tropical Medicine, the Bureau of Animal Industry of the Department of Agriculture, the Biodiversity Management Bureau of the Department of Environment and Natural Resources, the Disease Control and Prevention Bureau of the Department of Health, Mr Ramses P Cruz, Dr Melissa Marie R Rondina, Mr Ranillo Rodrigo G Resuello and Mr Eugene Del Mundo for assistance, cooperation and support during investigations; and Mr Gilberto Santos and the Epidemiology Bureau staff for their assistance in providing copies of the needed articles.

Funding source

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. Barrette RW, Metwally SA, Rowland JM, Xu L, Zaki SR, Nichol ST, et al. Discovery of swine as a host for the Reston ebolavirus. Science. 2009 Jul 10;325(5937):204–6. doi:10.1126/science.1172705 pmid:19590002
2. Viral Hemorrhagic Fevers (VHFs). Atlanta; Centers for Disease Control and Prevention; 2018 (https://www.cdc.gov/vhf/virus-families/filoviridae.html, accessed 17 June 2019).
3. Shi M, Lin XD, Chen X, Tian JH, Chen LJ, Li K, et al. The evolutionary history of vertebrate RNA viruses. Nature. 2018 Apr;556(7700):197-202. doi:10.1038/s41586-018-0012-7 pmid: 29618816
4. Yang XL, Tan CW, Anderson DE, Jiang RD, Li B, Zhang W, et al. Characterization of a filovirus (Měnglà virus) from Rousettus bats in China. Nat Microbiol. 2019 Mar;4(3):543. doi:10.1038/s41564-019-0398-5 pmid:30737494
5. Ogawa H, Miyamoto H, Nakayama E, Yoshida R, Nakamura I, Sawa H, et al. Seroepidemiological prevalence of multiple species of filoviruses in fruit bats (Eidolon helvum) migrating in Africa. J Infect Dis. 2015 Oct 1;212 Suppl 2:S101–8. doi:10.1093/infdis/jiv063 pmid:25786916
6. Miranda ME, Miranda NL. Reston ebolavirus in humans and animals in the Philippines: a review. J Infect Dis. 2011 Nov;204 Suppl 3:S757–60. doi:10.1093/infdis/jir296 pmid:21987747
7. Peñas JA, Rebato ND, Ballera JED, De los Reyes VC, Sucaldito MNL, Magpantay RL. RESTV Investigation in 3 monkey holding facilities in the Philippines. Manila: Epidemiology Bureau, Department of Health; 2015.
8. Miranda ME, Ksiazek TG, Retuya TJ, Khan AS, Sanchez AN, Fulhorst CF, et al. Outbreak of Ebola Reston virus in the Philippines, 1996. Manila: Epidemiology Bureau, Department of Health; 1996.
9. Rosell RS, Feliciano JM, Pabellon JA, Lopez JM, Tayag EA. A long term study on sero-epidemiologic of Ebola Reston virus infection among pig handlers. Manila: Epidemiology Bureau, Department of Health; 2010.
10. Cruz RV, Pabellon JA, Feliciano JM, Lopez JM, Tayag EA. Risk factors of Ebola-Reston virus (ERV) infection among abattoir workers. Manila: Epidemiology Bureau, Department of Health; 2010.
11. Miranda MEG, White ME, Dayrit MM, Hayes CG, Ksiazek TG, Burans JP. A filovirus closely related to Ebola among humans. The Philippines: A seroepidemiologic report. Manila: Epidemiology Bureau, Department of Health; 1991.
12. Hayes CG, Burans JP, Ksiazek T, Del Rosario RA, Miranda MEG, Manaloto CP, et al. Outbreak of fatal illness caused by Ebola virus among captive macaques. The Philippines. Manila: Epidemiology Bureau, Department of Health; 1990.
13. Marsh GA, Haining J, Robinson R, Foord A, Yamada M, Barr JA, et al. Ebola Reston virus infection of pigs: clinical significance and transmission potential. J Infect Dis. 2011 Nov;204 Suppl 3:S804–9. doi:10.1093/infdis/jir300 pmid:21987755
14. Rapid risk assessment of acute public health events. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/70810/1/WHO_HSE_GAR_ARO_2012.1_eng.pdf, accessed 20 January 2016).

15. WHO experts consultation on Ebola Reston pathogenicity in humans. Geneva: World Health Organization; 2009 (http://www.who.int/csr/resources/publications/HSE_EPR_2009_2.pdf, accessed 25 January 2016).

16. Jao JR, Maestro J, Salvador M, Zapanta MJ, Pabellon JA, Mapue MC, et al. Parallel risk assessments of bat exposure among community people. Barangay Tala, Orani, Bataan, Second Bat Study. Manila: Epidemiology Bureau, Department of Health; 2010.

17. Sayama Y, Demetria C, Saito M, Azul RR, Taniguchi S, Fukushi S, et al. A seroepidemiologic study of Reston ebolavirus in swine in the Philippines. BMC Vet Res. 2012 Jun 18;8(1):82. doi:10.1186/1746-6148-8-82 pmid:22709971

18. Carroll SA, Towner JS, Sealy TK, McMullan LK, Khristova ML, Burt FJ, et al. Molecular evolution of viruses of the family *Filoviridae* based on 97 whole-genome sequences. J Virol. 2013 Mar;87(5):2608–16. doi:10.1128/JVI.03118-12 pmid:23255795

19. Yuan J, Zhang Y, Li J, Zhang Y, Wang LF, Shi Z. Serological evidence of ebolavirus infection in bats, China. Virol J. 2012 Oct 13;9(1):236. doi:10.1186/1743-422X-9-236 pmid:23062147

20. Nidom CA, Nakayama E, Nidom RV, Alamudi MY, Daulay S, Dharmayanti IN, et al. Serological evidence of Ebola virus infection in Indonesian orangutans. PLoS One. 2012;7(7):e40740. doi:10.1371/journal.pone.0040740 pmid:22815803

21. Pappalardo M, Juliá M, Howard MJ, Rossman JS, Michaelis M, Wass MN. Conserved differences in protein sequence determine the human pathogenicity of Ebolaviruses. Sci Rep. 2016 Mar 24;6(1):23743. doi:10.1038/srep23743 pmid:27009368

22. Peterson AT, Bauer JT, Mills JN. Ecologic and geographic distribution of filovirus disease. Emerg Infect Dis. 2004 Jan;10(1):40–7. doi:10.3201/eid1001.030125 pmid:15078595

23. Becker S, Feldmann H, Will C, Slenczka W. Evidence for occurrence of filovirus antibodies in humans and imported monkeys: do subclinical filovirus infections occur worldwide? Med Microbiol Immunol (Berl). 1992;181(1):43–55. doi:10.1007/BF00193395 pmid:1579085

24. Pan Y, Zhang W, Cui L, Hua X, Wang M, Zeng Q. Reston virus in domestic pigs in China. Arch Virol. 2014 May;159(5):1129–32. doi:10.1007/s00705-012-1477-6 pmid:22996641

25. Olival KJ, Islam A, Yu M, Anthony SJ, Epstein JH, Khan SA, et al. Ebola virus antibodies in fruit bats, Bangladesh. Emerg Infect Dis. 2013 Feb;19(2):270–3. doi:10.3201/eid1902.120524 pmid:23343532

26. Miranda ME, Yoshikawa Y, Manalo DL, Calaor AB, Miranda NL, Cho F, et al. Chronological and spatial analysis of the 1996 Ebola Reston virus outbreak in a monkey breeding facility in the Philippines. Exp Anim. 2002 Apr;51(2):173–9. doi:10.1538/expanim.51.173 pmid:12012728

27. Rollin PE, Williams RJ, Bressler DS, Pearson S, Cottingham M, Pucak G, et al. Ebola (subtype Reston) virus among quarantined nonhuman primates recently imported from the Philippines to the United States. J Infect Dis. 1999 Feb;179(s1) Suppl 1:S108–14. doi:10.1086/514303 pmid:9988173

28. Miranda ME, Ksiazek TG, Retuya TJ, Khan AS, Sanchez A, Fulhorst CF, et al. Epidemiology of Ebola (subtype Reston) virus in the Philippines, 1996. J Infect Dis. 1999 Feb;179(s1) Suppl 1:S115–9. doi:10.1086/514314 pmid:9988174

29. Taniguchi S, Watanabe S, Masangkay JS, Omatsu T, Ikegami T, Alviola P, et al. Reston Ebolavirus antibodies in bats, the Philippines. Emerg Infect Dis. 2011 Aug;17(8):1559–60. pmid:21801651

30. Jayme SI, Field HE, de Jong C, Olival KJ, Marsh G, Tagtag AM, et al. Molecular evidence of Ebola Reston virus infection in Philippine bats. Virol J. 2015 Jul 17;12(107):107. doi:10.1186/s12985-015-0331-3 pmid:26184657

31. Piercy TJ, Smither SJ, Steward JA, Eastaugh L, Lever MS. The survival of filoviruses in liquids, on solid substrates and in a dynamic aerosol. J Appl Microbiol. 2010 Nov;109(5):1531–9. pmid:20553340

32. DOH assures Ebola Reston in PH 'kind' to humans. Manila: CNN Philippines; 2015 (http://cnnphilippines.com/news/2015/09/10/Ebola-Reston-monkeys-Philippines-DOH.html)

33. Bureau of Animal Industry [Internet]. Manila; Department of Agriculture; 2016 (http://www.bai.da.gov.ph/, accessed 13 January 2016).

34. OIE-listed diseases, infections and infestations in force in 2019. Paris; World Organisation for Animal Health; 2018 (http://www.oie.int/animal-health-in-the-world/oie-listed-diseases-2019/, accessed 28 January 2018).

35. Environment, climate change, social factors and the implications for controlling diseases of poverty. Geneva: World Health Organization (http://www.who.int/tdr/capacity/global_report/2012/chapitre2_web.pdf)

36. Philippines swine population slightly higher. Barcelona: Pig333.com; 2018 (https://www.pig333.com/latest_swine_news/philippines-swine-population-slightly-higher_14491/, accessed 12 March 2019).

37. Amurao SS, Lopez EL, Lagayan MG, Calub NP, Jorca DL. One Health approach: the Philippine experience. Chinese Taipei: The Food and Fertilizer Technology Center; 2018 (http://www.fftc.agnet.org/library.php?func=view&id=20170329160947&type_id=4).

38. Emerging and re-emerging infectious disease program. Manila: Department of Health; 2017 (https://www.doh.gov.ph/emerging-and-re-emerging-infectious-disease-program).

High hepatitis C virus infection among female sex workers in Viet Nam: strong correlation with HIV and injection drug use

Linh-Vi N Le,[a] Siobhan O'Connor,[b] Tram Hong Tran,[c] Lisa Maher,[a] John Kaldor,[a] Keith Sabin,[d] Hoang Vu Tran,[e] Quang Dai Tran,[f] Van Anh Thi Ho[g] and Tuan Anh Nguyen[c]

Correspondence to Linh-Vi N Le (email: leli@who.int)

Objective: The World Health Organization's guidelines on viral hepatitis testing and treatment recommend prioritizing high prevalence groups. Hepatitis C virus (HCV) infection disproportionately affects people who inject drugs and men who have sex with men, but data on female sex workers (FSW) are limited. The study aimed to determine active HCV infection and risk factors associated with HCV exposure among Vietnamese FSW.

Methods: We surveyed 1886 women aged ≥ 18 years from Haiphong, Hanoi and Ho Chi Minh City who had sold sex in the last month. We tested for HCV antibody and HCV core antigen as markers for exposure to HCV and active infection, respectively.

Results: Across these provinces, high prevalence of HCV exposure (8.8–30.4%) and active infection (3.6–22.1%) were observed. Significant associations with HCV exposure were HIV infection (aOR = 23.7; 95% CI: 14.8–37.9), injection drug use (aOR = 23.3; 95% CI: 13.1–41.4), history of compulsory detention (aOR = 2.5; 95% CI: 1.4–4.2) and having more than 10 sex clients in the last month (aOR = 1.9; 95% CI: 1.2–3.2). Among FSW who reported never injecting drugs, HIV infection (aOR = 24.2; 95% CI: 14.8–39.4), a history of non-injection drug use (aOR = 3.3, CI: 1.8–5.7), compulsory detention (aOR = 2.2; 95% CI: 1.2–4.0) and having over 10 sex clients in the last month (aOR = 2.2, 95% CI: 1.3–3.7) were independently associated with HCV exposure.

Discussion: FSW have elevated HCV risks through sex- and drug-related pathways. These findings highlight the need to offer FSW-targeted HCV interventions and ensure their access to HIV prevention and treatment.

Globally, an estimated 71 million people were living with chronic hepatitis C virus (HCV) infection, and 1.75 million were newly infected with HCV in 2015.[1] Approximately 75% of acute HCV infections result in chronic infections. In the absence of treatment, 15–30% of people develop cirrhosis within 20 years with subsequent increased risk of hepatocellular carcinoma and death.[2] The estimated number of new HCV infections exceeds the estimated number of deaths and cures together,[1] warranting rapid scale-up of both preventive and therapeutic interventions for viral hepatitis.

The primary mode of HCV transmission is blood contact, frequently by reuse of injecting equipment or other skin-piercing devices.[3] Accordingly, 23% of new HCV infections occur in people who inject drugs (PWID), and 31% of deaths from chronic HCV infections are attributable to a history of injection drug use.[4] Interventions for prevention have focused on use of sterile equipment for skin-piercing procedures, including making clean equipment available to PWID. Direct-acting antiviral (DAA) medications providing effective cures for HCV infection are yet to become widely available in many low- and middle-income countries.[1] Until there is universal access to DAAs, national viral hepatitis responses may have to prioritize certain populations for testing and treatment; World Health Organization (WHO) guidelines recommend targeting populations with evidence of higher chronic HCV prevalence.[5]

Greater understanding of the viral hepatitis epidemic is needed as global and national responses set strategic

[a] Kirby Institute for Infection and Immunity, UNSW Sydney, Australia.
[b] United States Centers for Disease Control and Prevention, Atlanta, GA, United States of America.
[c] National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam.
[d] UNAIDS, Geneva, Switzerland.
[e] Partners in Health Research, Hanoi, Viet Nam.
[f] General Department of Preventive Medicine, Ministry of Health, Hanoi, Viet Nam.
[g] United States Centers for Disease Control and Prevention, Hanoi, Viet Nam.
Submitted: 29 November 2018; Published: 25 July 2019
doi: 10.5365/wpsar.2019.10.1.002

directions and priorities. Countries of Asia account for one third of global chronic HCV infections.[1] In Viet Nam, mathematic modelling estimated 1 million people to be living with chronic HCV and 24 300 new annual HCV infections, 11% of which are attributed to injection drug use and 60% to blood transfusions or medical services.[6] Recent studies in Viet Nam documented high HCV infection prevalence among PWID, with up to 80% of PWID exposed to the virus.[7,8] More recently, injection drug use also correlated with HCV infection among Vietnamese men who have sex with men (MSM).[9] There is an assumption that female sex workers (FSW) have an elevated risk for blood-borne and sexually transmitted infections, potentially through dual sexual and drug use transmission pathways, but there is limited information on HCV in this population globally, including in Viet Nam. The current study aimed to address the global data gap for knowledge about HCV infection among FSW to inform the viral hepatitis response.

METHODS

Data collection

Viral hepatitis investigation was added to the 2013 round of the routine Integrated Biological and Behavioural Surveillance (IBBS) conducted by the Viet Nam National Institute of Hygiene and Epidemiology (NIHE) and the United States Centers for Disease Control and Prevention (US CDC). We conducted separate cross-sectional surveys among street-based sex workers (SSW) and venue-based sex workers (VSW) from Hanoi, Haiphong and Ho Chi Minh City (HCMC) using time-location sampling from June to October 2013. The survey consisted of interviews and HCV serological testing. Women aged ≥ 18 years who sold sex in the last month (n = 1886) were eligible to be recruited. The sample sizes were calculated to detect 20% anti-HCV prevalence and expected prevalence based on the 2009 IBBS surveys[10] with 95% confidence level, 2–5% targeted confidence interval width, and adjustment for design effect. For each province and population, we generated a sampling frame of locations where FSW were known to be present. Locations for the SSW sampling frame were streets, parks and other openly public spaces; venues for the VSW sample were entertainment or service establishments.

The number of sex workers present at each location was enumerated through field visits. Locations were randomly selected with probability proportional to size. At each selected cluster, invitational coupons were provided to potential participants to enroll in the study conducted at health clinics. Sample sizes were reached for all populations.

Women who fulfilled the eligibility criteria and provided written voluntary informed consent underwent individual face-to-face interviews conducted by trained interviewers. A structured questionnaire used in previous IBBS rounds was used to collect information on sociodemographic characteristics, sex work history, condom use behaviours, alcohol and drug use risks, sex partner drug use risks, incarceration history and access to health services. A series of questions were asked about different types of illicit drugs, including lifetime and recent drug use, injection drug use and sharing of needles and syringes. Certified laboratory technicians collected venous blood by venipuncture. No personal identifying information was collected. The study protocol and data collection instruments were reviewed and approved by the Ethics Review Board of NIHE and the Internal Review Board of the US CDC.

Laboratory tests

The participants' serum was tested using the Abbott ARCHITECT® automated immunologic assay platform and commercially available ARCHITECT assay kits for HCV antibody (anti-HCV) and HCV core antigen (HCVcoreAg), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatitis B core antibodies (anti-HBc) (Abbott Laboratories, USA). Specimens were initially screened for anti-HCV and HBsAg and with subsequent testing of reactive specimens for HCVcoreAg and HBeAg, respectively. Each run included standardized ARCHITECT® controls.

Blood specimens were tested for HIV per national guidelines: screening for HIV antibody using Genscreen Ultra HIV Ag/Ab (Bio-Rad, USA) with confirmation of positive tests by Determine HIV-1/2 (Alere, Japan) and Murex HIV Ag/Ab Combination (DiaSorin, United Kingdom of Great Britain and Northern Ireland) testing. The National Reference Laboratory at NIHE conducted external quality assurance on a randomly selected 10% of HIV-negative and 5% of HIV-positive screening samples.

Statistical analyses

Summary statistics were calculated by province and subpopulations. Sampling weights were applied to adjust for sampling probabilities in prevalence estimation. All statistical analyses were performed using STATA version 14,[11] with adjustments for correlation between and within clusters.

HCV infection status was classified as HCV exposure (anti-HCV-positive), active HCV infection (anti-HCV-positive and HCVcoreAg-positive) or no evidence of HCV exposure (anti-HCV-negative). For hepatitis B virus (HBV), classifications were past or active HBV infection (HBsAg-positive or anti-HBc-positive), active HBV infection (HBsAg-positive) and HBeAg-active HBV infection (HBsAg-positive and HBeAg-positive).

Univariable and multivariable analyses were conducted to determine factors associated with HCV exposure. We used Pearson's $\chi 2$ statistic to test the association between selected demographics and risk characteristics and HCV exposure. Random effects logistic regression were used to account for intracluster correlation. Independent variables associated with HCV infection at $P < 0.20$ were entered into the multivariable logistic regression model and retained in the reduced model if association was $P < 0.05$ for the Wald statistic. Age and marital status were retained in the reduced model as a priori confounders. The variable "type of sex work" was defined based on participants' responses to where they mainly negotiated sex rather than using recruitment venues. We calculated the population attributable risk (PAR) to show potential impact of injection drug use on infection prevalence. Records that were missing outcome variables were excluded.

RESULTS

Sample characteristics and risk behaviours

Table 1 presents sociodemographic and behavioural indicators by province and subpopulation of FSW. Across the subpopulations and provinces, the mean ages ranged from 28.9 to 35.4 years, and durations of sex work ranged from 4.9 to 7.4 years with SSW being older and working in the sex industry for a longer period of time than VSW. Formal education beyond the sixth grade was attained by a large majority (> 85%) of FSW in Hanoi and Haiphong and by lower proportions in HCMC. The median total monthly income was higher for VSW (US$ 430–480) than SSW (US$ 290–380). A history of drug use was high across all subpopulations, ranging from 8.3% to 31.8%. A history of injection drug use reached 24.2% among Haiphong SSW and ranged from 3.0% to 8.2% among other subpopulations.

In the multivariable analysis (**Table 2**), over two fifths reported negotiating sex mainly on the street or in other public areas, and three quarters had sold sex to over 10 clients in the past month. Consistent condom use, defined as condom use for every vaginal or anal sex act with clients in the past month, was reported by 71.7%. Eight per cent of FSW had ever injected drugs, and 10.2% had been involuntarily detained in a rehabilitation centre.

Prevalence of infection

HCV, HBV and HIV prevalence are presented in **Table 1**. Twenty-four specimens for the HCMC SSW population and one specimen for the Hanoi VSW were missing HBV and HCV results. Exposure to HCV infection was highest among Haiphong SSW (30.4%) and lowest among HCMC VSW (8.8%). In the remaining provinces and subpopulations, HCV exposure ranged from 12.4% to 15.6%. The prevalence of active HCV infection was highest among Haiphong SSW (22.1%) and lowest among HCMC VSW (3.6%) and ranged from 5.6% to 9.4% in the remaining provinces and subpopulations.

Across the provinces and subpopulations, HBV exposure ranged from 55.9% to 84.1%, whereas active HBV infections ranged from 5.6% to 11.1%. HBeAg-positive HBV infection ranged from 1.4% to 4.0%. There were no active HBV and HCV coinfections.

HIV prevalence patterns were similar to HCV, with the highest observed among Haiphong SSW (31.9%) and lowest among HCMC VSW (8.2%). Coinfection with HCV and HIV ranged from 1.6% among HCMC SSW to 13.7% among Haiphong SSW.

Predictors of HCV exposure

In univariable analyses (**Table 2**), sociodemographic factors associated with anti-HCV prevalence included older age and being separated, divorced or widowed. Occupational characteristics showing significant crude

Table 1. **Demographic characteristics and HIV, HBV and HCV prevalence among female sex workers in three urban provinces of Viet Nam, 2013**

Indicators	Street-based sex workers (*n* = 918)			Venue-based sex workers (*n* = 968)		
	Hanoi	Haiphong	Ho Chi Minh City	Hanoi	Haiphong	Ho Chi Minh City
	***N* = 299**	***N* = 204**	***N* = 415**	***N* = 300**	***N* = 304**	***N* = 364**
Age (mean years) (s.d.)	32.7 (6.9) *n* = 299	34.6 (5.5) *n* = 204	35.4 (10.2) *n* = 413	29.0 (5.9) *n* = 300	28.9 (5.9) *n* = 304	29.0 (7.0) *n* = 363
Education (%)	*n* = 299	*n* = 204	*n* = 415	*n* = 300	*n* = 304	*n* = 363
Primary or no formal schooling (≤ 5)	14.4	14.2	50.2	8.0	4.6	29.2
Secondary school (6–9)	50.2	56.9	38.8	45.3	59.2	49.6
High school (10–12)	34.4	25.5	10.8	41.3	33.6	19.3
College/University (13+)	1.0	3.4	0.2	5.3	2.6	1.9
Years in sex work (mean) (s.d.)	7.3 (4.4) *n* = 293	7.0 (4.9) *n* = 169	7.4 (6.7) *n* = 402	6.0 (4.4) *n* = 290	4.9 (4.2) *n* = 260	5.1 (4.7) *n* = 357
Median total monthly income (million VND*) (IQR)	8.0 (6.0–10.0) *n* = 299	6.0 (5.0–7.2) *n* = 203	6.0 (4.0–9.0) *n* = 386	10.0 (8.0–12.0) *n* = 300	10.0 (8.0–15.0) *n* = 303	9.0 (6.0–12.0) *n* = 345
Consistent condom use with clients in past month (%) (95% CI)	82.3 (76.2, 87.1) *n* = 299	76.5 (65.6, 84.7) *n* = 204	60.2 (53.4, 66.7) *n* = 415	75.7 (68.4, 81.7) *n* = 300	87.2 (81.6, 91.2) *n* = 304	57.1 (51.0, 63.1) *n* = 364
Consumed at least one alcoholic drink daily in past month (%) (95% CI)	4.0 (1.9, 8.2) *n* = 299	1.5 (0.5, 4.0) *n* = 204	3.9 (2.5, 5.9) *n* = 415	13.3 (9.1, 19.2) *n* = 300	1.0 (0.3, 3.0) *n* = 304	41.5 (33.3, 50.1) *n* = 364
Ever used illicit drugs (%) (95% CI)	13.8 (9.8, 17.7) *n* = 298	31.8 (25.3, 38.4) *n* = 198	18.2 (13.6, 22.8) *n* = 413	8.3 (5.0, 13.7) *n* = 300	20.8 (15.8, 26.8) *n* = 289	9.6 (6.5, 14.0) *n* = 363
Ever injected any illicit drug (%) (95% CI)	6.4 (3.8, 10.6) *n* = 298	24.2 (16.1, 34.9) *n* = 198	8.2 (5.7, 11.7) *n* = 415	5.3 (2.9, 9.5) *n* = 300	7.6 (4.1, 13.8) *n* = 289	3.0 (1.5, 6.1) *n* = 363
Had a sex partner that injected drugs in past month (%) (95% CI)	17.7 (14.1, 22.1) *n* = 299	20.6 (14.0, 29.2) *n* = 204	15.7 (12.2, 19.9) *n* = 415	12.0 (8.3, 17.0) *n* = 300	11.5 (7.7, 16.9) *n* = 304	8.3 (5.5, 12.2) *n* = 363
Past and current HCV infection (%) (95% CI)	14.8 (8.9, 23.4) *n* = 298	30.4 (23.0, 38.9) *n* = 204	15.6 (11.0, 21.7) *n* = 392	13.5 (8.2, 21.2) *n* = 299	12.4 (8.5, 17.7) *n* = 304	8.8 (5.6, 13.6) *n* = 364
Active HCV infection (%) (95% CI)	8.4 (4.6, 14.9) *n* = 298	22.1 (15.8, 30.0) *n* = 204	9.4 (6.7, 13.1) *n* = 392	5.6 (3.4, 9.2) *n* = 299	8.2 (5.4, 12.4) *n* = 304	3.6 (2.0, 6.2) *n* = 364
Past and current HBV infection (%) (95% CI)	57.4 (51.4, 63.2) *n* = 298	55.9 (48.5, 63.0) *n* = 204	59.2 (53.9, 64.4) *n* = 392	75.0 (69.4, 79.8) *n* = 299	84.1 (78.8, 88.2) *n* = 304	55.8 (49.2, 62.3) *n* = 364
Active HBV infection (%) (95% CI)	8.4 (5.7, 12.1) *n* = 298	7.4 (4.5, 11.9) *n* = 204	8.8 (6.1, 12.5) *n* = 392	8.9 (6.2, 12.6) *n* = 299	11.1 (7.5, 16.0) *n* = 304	5.6 (3.1, 9.8) *n* = 364
HBeAg+ active HBV infection (%) (95% CI)	4.0 (2.3, 7.0) *n* = 298	3.4 (1.6, 7.1) *n* = 204	3.1 (1.6, 5.8) *n* = 392	2.5 (1.3, 4.9) *n* = 299	1.4 (0.6, 3.4) *n* = 304	3.0 (1.5, 5.8) *n* = 364
HIV infection (%) (95% CI)	10.4 (6.2, 16.9) *n* = 298	31.9 (22.5, 42.9) *n* = 204	13.5 (10.1, 17.9) *n* = 415	16.0 (11.1, 22.5) *n* = 300	10.5 (6.6, 16.4) *n* = 304	8.2 (5.3, 12.6) *n* = 364
Active HCV and HIV infections (%) (95% CI)	5.4 (2.7, 10.5) *n* = 298	13.7 (7.9, 22.9) *n* = 204	6.4 (4.2, 9.6 *n* = 392	5.4 (3.2, 8.9) *n* = 299	5.3 (3.1, 8.8) *n* = 304	1.6 (0.6, 4.2) *n* = 364
Past and current HCV infection among FSW who were HIV-negative and reported never having injected drugs (%) (95% CI)	6.0 (3.2, 11.0) *n* = 252	14.2 (8.8, 22.0) *n* = 113	4.0 (2.4, 6.7) *n* = 323	6.2 (3.0, 12.4) *n* = 242	4.9 (2.9, 8.1) *n* = 113	1.2 (0.5, 3.2) *n* = 327

CI = confidence interval, HBV = hepatitis B virus, HCV = hepatitis C virus, FSW = female sex workers, IQR = interquartile range, s.d. = standard deviation, VND = Vietnamese dong.

* Exchange rate at time of study = 21 0000 Vietnamese dong: US$ 1.

Table 2. **Association between HCV exposure and selected characteristics of female sex workers in three urban provinces of Viet Nam, 2013**

Variable	%	Crude association		Adjusted association*	
		OR	95% CI	aOR	95% CI
Sociodemographic					
Age (years)	(*n* = 1858)	-	-	-	-
18–24	20.7	1.00	-	1.00	-
25–29	22.3	1.75	1.08, 2.81	1.13	0.59, 2.14
30–34	25.9	2.94	1.80, 4.81	1.28	0.67, 2.45
35+	31.1	2.12	1.29, 3.46	0.98	0.50, 1.94
Obtained grade 6 or higher education (%)	77.8 (*n* = 1860)	1.14	0.82, 1.60	-	-
Marital status	(*n* = 1804)	-	-	-	-
Never been married	33.7	1.00	-	1.00	-
Married	12.6	1.02	0.63, 1.64	0.59	0.29, 1.19
Separated/divorced	46.6	1.44	1.03, 2.02	1.34	0.81, 2.22
Widowed	7.1	2.32	1.33, 4.04	1.59	0.74, 3.39
Occupational characteristics and sexual behaviours					
Age at first sex (per year increase)	(*n* = 1769)	0.94	0.89, 0.99	-	-
Years in sex work (per year increase)	(*n* = 1749)	1.03	1.02, 1.06	-	-
Total monthly income (VND, using IQR categories)	(*n* = 1811)	-	-	-	-
< 5 million	-	1.00	-	-	-
5 to < 7 million	-	0.75	0.50, 1.12	-	-
7 to < 8.5 million	-	0.71	0.45, 1.12	-	-
≥ 8.5 million	-	0.75	0.51, 1.10	-	-
Negotiate sex mainly on street or in other public areas	43.1 (*n* = 1860)	1.90	1.33, 2.73	-	-
Ever sold sex in other provinces	7.3 (*n* = 1860)	1.66	1.06, 2.59	-	-
Had over 10 sex clients in past month	74.7 (*n* = 1861)	2.33	1.55, 3.49	1.94	1.17, 3.21
Consistent condom use with clients in past month	71.7 (*n* = 1861)	1.01	0.74, 1.36	-	-
Alcohol and drug use behaviours					
Daily alcohol consumption in past month	12.0 (*n* = 1861)	0.68	0.41, 1.13	-	-
Injection drug use (lifetime)	8.1 (*n* = 1836)	30.73	18.94, 49.87	23.32	13.13, 41.44
Sex partners' drug use behaviour					
Sex partners injected drugs in past month	(*n* = 1860)	-	-	-	-
No	61.2	1.00	-	-	-
Yes	13.9	2.75	1.90, 3.97	-	-
Unknown	24.9	2.14	1.53, 3.01	-	-
Incarceration history					
Ever detained in rehabilitation centre for sex workers	10.2 (*n* = 1853)	3.80	2.64, 5.49	2.46	1.44, 4.21
STI					
Experienced genital pain or ulcers in past 12 months	54.5 (*n* = 1861)	1.29	0.97, 1.71	-	-
Blood-borne infections					
HBV	65.1 (*n* = 1861)	0.82	0.63, 1.07	-	-
HIV	13.6 (*n* = 1861)	18.47	13.27, 25.71	23.67	14.79, 37.88
Province	(*n* = 1861)	-	-	-	-
Hanoi	-	1.32	0.84, 2.12	-	-
Hai Phong	-	1.95	1.34, 2.86	-	-
Ho Chi Minh City	-	1.00	-	-	-

* *n* = 1828. Variables in multivariate model are adjusted for age and marital status.

associations were longer duration of sex work, negotiating sex mainly on the streets, selling sex in more than one province, having over 10 clients in the last month and ever having been confined in compulsory detention centres for sex workers. The sexual and drug use risk behaviours crudely associated with HCV exposure were ever using injection drugs and having a sex partner who had injected drugs in the last month or whose drug use status was unknown to the FSW. HIV infection was a strong predictor of HCV infection exposure.

When adjusted for age and marital status in multivariable analysis, HIV seropositivity and injection drug use were the strongest predictors of HCV exposure (**Table 2**). FSW who tested HIV-positive had 23.7 (95% CI: 14.8–37.9) times greater odds of having been exposed to HCV than those who tested HIV-negative. Compared to FSW who had never injected drugs, those who had ever injected drugs had 23.3 (95% CI: 13.1–41.4) times the odds of HCV infection exposure. The PAR for ever having injected drugs was 64.3% (95% CI: 49.4–76.5). Other independent predictors for HCV exposure were having over 10 sex clients in the last month and a history of compulsory detention.

HIV seropositivity is also the strongest predictor of HCV exposure in the subpopulation of FSW who self-reported never having injected drugs (**Table 3**). Other factors significantly associated with HCV were lifetime non-injection drug use, compulsory detention and having over 10 sex clients in the last month.

DISCUSSION

We found high prevalence of HCV exposure (8.8–30.4%) and active HCV infection (3.6–22.1%) among FSW across all study provinces and subpopulations, an important finding with implications for HCV prevention and treatment. The small body of studies of HCV among FSW has documented exposure but not current infection. Studies have shown lower anti-HCV prevalence ranging from 2.6% in India to 12% in China, Taiwan.[12,13] In contrast, a more recent study in Canada found higher anti-HCV seropositivity (42.5%) among FSW.[14]

This is the first study in Viet Nam to examine risk factors for HCV exposure among FSW. Injection drug use was the key driver of HCV infection among FSW as it is among MSM and PWID in Viet Nam.[8,9] Although only 8% of FSW reported injection drug use, almost two thirds of HCV exposures were attributable to injection drug use. Notably, HCV exposure was also high among FSW without a history of injection drug use. Non-injection drug use was a significant factor for HCV exposure among FSW. We previously found similar correlations with HIV infection among FSW, in that HIV risk increased with the use of non-injection drugs, specifically amphetamine-type stimulants, which was high in HCMC and Hanoi.[10] In the context of these findings, it is important that Viet Nam's HCV interventions address FSW vulnerabilities for infection. FSW and other women who inject drugs face gender-specific health risks that lead to increased levels of injection risk behaviour, yet among PWID, women are often overlooked by harm reduction programmes.[15] Compulsory detention was a predictor of HCV exposure among FSW, potentially due to HCV exposure at the detention centres, or FSW engaged in higher-risk activities that exposed them to HCV and led to incarceration. Given that there is evidence of high HCV incidence in detained populations across the world,[16] the 2012 closure of detention centres for FSW in Viet Nam is an important policy change that can reduce the risk of HCV infection, along with HIV infection, among FSW.

The positive association of HCV exposure with having a greater number of clients indicates that FSW are vulnerable to infection through sexual risks. Although sexual intercourse has relatively low efficiency in transmitting HCV, a history of multiple sex partners may increase the probability of having sex with an infectious partner during the acute phase of infection,[3] and the use of stimulants potentially elevates risky sexual contact.[17] FSW in this study reported low levels of consistent condom use, exposing them to HIV and potentially frequent sexually transmitted infections, which increases risk for HCV infection.[18,19]

Even taking into account a history of injection drug use, HIV was independently associated with HCV, which is consistent with evidence establishing the role of viral STI in the transmission of HIV.[20] Since HCV and HIV share a parenteral route of transmission, the WHO-recommended approach to HIV prevention involving a comprehensive package that includes both harm reduction and condom interventions[21] also applies to HCV prevention programmes. Given high HCV and HIV coinfection among FSW, Viet Nam could leverage the resources and infrastructure available for HIV services

Table 3. **Association between HCV exposure and selected characteristics of female sex workers who reported never having injected drugs in three urban cities of Viet Nam, 2013**

Variable	%	Crude association		Adjusted association*	
		OR	95% CI	aOR	95% CI
Sociodemographic					
Age (years)	(*n* = 1684)	-	-	-	-
18–24	21.4	1.00	-	1.00	-
25–29	22.2	1.98	1.09, 3.58	1.53	0.74, 3.16
30–34	25.0	3.24	1.73, 6.07	1.61	0.76, 3.41
35+	31.3	2.72	1.50, 4.94	1.63	0.76, 3.52
Obtained grade 6 or higher education (%)	(*n* = 1686) 77.2	1.17	0.76, 1.82	-	-
Marital status	(*n* = 1686)	-	-	-	-
Never been married	34.0	1.00	-	1.00	-
Married	12.3	0.94	0.52, 1.68	0.53	0.24, 1.18
Separated/divorced	46.5	1.52	1.01, 2.29	1.23	0.71, 2.14
Widowed	7.1	2.86	1.56, 5.24	1.35	0.61, 2.98
Occupational characteristics and sexual behaviours					
Age at first sex (per year increase)	(*n* = 1604)	0.97	0.91, 1.03	-	-
Years in sex work (per year increase)	(*n* = 1592)	1.03	1.00, 1.06	-	-
Total monthly income (VND, using IQR categories)	(*n* = 1643)			-	-
< 5 million	-	1.00	-	-	-
5 to < 7 million	-	0.71	0.43, 1.16	-	-
7 to < 8.5 million	-	0.68	0.39, 1.17	-	-
≥ 8.5 million	-	0.72	0.47, 1.10	-	-
Negotiate sex mainly on street or in other public areas	(*n* = 1686) 41.1	1.70	1.14, 2.55	-	-
Ever sold sex in other provinces	(*n* = 686) 7.1	2.04	1.23, 3.38	-	-
Had over 10 sex clients in past month	(*n* = 1686) 73.1	2.17	1.36, 3.48	2.16	1.25, 3.72
Consistent condom use with clients in past month	(*n* = 1686) 71.4	0.99	0.69, 1.41	-	-
Alcohol and drug use behaviours					
Daily alcohol consumption in past month	(*n* = 1686) 12.7	0.85	0.49, 1.48	-	-
Non-injection drug use (lifetime)	(*n* = 1686) 8.9	3.10	2.01, 4.79	3.25	1.84, 5.73
Sex partners' drug use behaviour					
Sex partners injected drugs in past month	(*n* = 1686)	-	-	-	-
No	64.9	1.00	-	-	-
Yes	11.9	1.51	0.90, 2.54	-	-
Unknown	23.2	1.86	1.30, 2.68	-	-
Incarceration history					
Ever detained in rehabilitation centre for sex workers	(*n* = 1682) 8.02	2.63	1.64, 4.21	2.19	1.19, 4.02
STI					
Experienced genital pain or ulcers in past 12 months	(*n* = 1686) 53.3	1.12	0.81, 1.56	-	-
Blood-borne infections					
HBV	(*n* = 1686) 65.4	0.82	0.60, 1.11	-	-
HIV	(*n* = 1686) 10.9	20.31	13.98, 29.49	24.16	14.81, 39.41
Province	(*n* = 1484)	-	-	-	-
Hanoi	-	1.32	0.84, 2.12	-	-
Hai Phong	-	1.95	1.34, 2.86	-	-
Ho Chi Minh City	-	1.00	-	-	-

* *n* = 1828. Variables in multivariate model are adjusted for age and marital status.

to deliver HCV testing and treatment services to FSW and other key populations. HIV coinfection reduces the likelihood of spontaneous clearance of HCV infection and accelerates the progression of liver disease.[22]

HBV infection prevalence among FSW did not differ from that in the general population, estimated at 9.1%,[6] a finding that is consistent with the primarily perinatal and childhood transmission of HBV in Asia.[23] Prevalence of HBeAg-active HBV infections among FSW was also similar to prevalence previously detected among Vietnamese women of child-bearing age.[24] HBeAg positivity usually indicates viral replication and therefore high levels of infectiousness. Yet in genotypes B and C, which are most common in Viet Nam,[25] high viral replication can occur without the presence of HBeAg due to mutations in the precore and basal core promoter regions. The mutations suppress HBeAg synthesis while enhancing viral genome replication.[26,27] Nevertheless, as the Vietnamese Ministry of Health expands treatment, targeted provision of routine HBV testing and treatment for active HBV infection would benefit FSW and other populations where stigma and discrimination impedes access to services. For example, high antenatal screening uptake would be difficult to achieve with few sex workers presenting to health-care services.[28]

Increasing HCV prevalence from north to south had been expected given the older injection drug use epidemic in HCMC in the south of Viet Nam.[29] Instead, HCV infection was higher in the two northern provinces than in HCMC, a pattern observed also among MSM in Viet Nam.[9] The higher prevalence of reported injection drug use among SSW and VSW in Haiphong may explain the higher HCV infection in the north, but it contrasts with lower reported injection drug use among MSM in the north than in the south.[9] Further phylogenetic research may help to explain these infection patterns.

Our study has limitations, including potential misclassification of injection drug use status in that there is greater willingness to report non-injection drug use. This would lead to an overestimation of the association of HCV infection with non-injection drug use. However, our findings of additional sexual and non-injection drug use risks are consistent with studies reporting associations between HCV exposure and non-injection crack use in Canada and with increased number of sex clients and duration of sex work in China.[14,30] Another limitation was that 35 of the 271 anti-HCV-positive samples tested for HCV core antigen returned reactive results in the grey zone, which indicates possible but not confirmed active HCV infection. Almost all grey zone reactive results were from Hanoi. Inclusion of grey zone reactive results would have shown 4% and 5% higher viraemic HCV infection among Hanoi SSW and VSW, respectively. Furthermore, as a limitation of the cross-sectional survey design, the analysis could not assess temporal relationships between risk behaviour with HCV acquisition. Being able to monitor infections and risks across time would help to better target interventions, including understanding the extent to which incarceration contributed to HCV transmission.

The 2013 Vietnamese IBBS round represents the first routine integration of HCV core antigen into national viral hepatitis surveillance, of which we are aware. In contrast to most population or risk group–based estimates of HCV infection, the inclusion of HCV core antigen testing provided data on active HCV infection. HCV core antigen testing is sensitive and specific and is a reasonable alternative to HCV nucleic acid testing, providing similar accuracy without the additional logistic requirements and cost of nucleic acid testing.[31] Assay-based, population-based estimates of both active HCV infection and past HCV exposure are needed to forecast national prevention and diagnostic and treatment needs. In the absence of such data, estimates have been derived from external estimates through mathematic modelling of the relationship between the prevalence of active infection and exposure. As DAAs become increasingly accessible, targeting testing and treatment services to populations at higher risk of HCV infection will be the most effective way to reduce the chronic HCV morbidity and prevent further transmission.

The study showed high past and active HCV infection prevalence and HCV/HIV coinfection among Vietnamese FSW, a vulnerable population historically characterized by low HIV service uptake. Results have the potential to inform national responses designed to address dual sexual and drug-related risks for HCV infection among FSW while highlighting the need to ensure FSW access to HIV prevention and treatment services.

Acknowledgements

The authors are indebted to the study participants and would like to thank the directors and research staff of the

Provincial AIDS Haiphong, Hanoi and Ho Chi Minh City. We are grateful to Abbott Laboratories for donating assays for anti-HCV and HBV serology and to the Department of Viral Hepatitis at the United States Centers for Disease Control and Prevention for providing the HCV core antigen assays. We acknowledge also the dedicated efforts of the IBBS research and laboratory team members from NIHE and Family Health International. Lisa Maher and John Kaldor are supported by the award of Australian National Health and Medical Research Fellowships. The Kirby Institute is affiliated with the Faculty of Medicine, University of New South Wales.

Funding

The research has been supported by the President's Emergency Plan for AIDS Relief through the United States Centers for Disease Control and Prevention under the terms of 5U2GGH000116.

Conflicts of interest

All authors declared no conflict of interest.

References

1. Global hepatitis report 2017. Geneva: World Health Organization; 2017 (https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/).
2. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013 Sep;10(9):553–62. doi:10.1038/nrgastro.2013.107 pmid:23817321
3. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol. 2007 May 7;13(17):2436–41. doi:10.3748/wjg.v13.i17.2436 pmid:17552026
4. Degenhardt L, Charlson F, Stanaway J, Larney S, Alexander LT, Hickman M, et al. Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016 Dec;16(12):1385–98. doi:10.1016/S1473-3099(16)30325-5 pmid:27665254
5. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 (https://www.who.int/hepatitis/publications/guidelines-hepatitis-c-b-testing/en/).
6. Vietnam General Department of Preventive Medicine, Center for Disease Analysis, World Health Organization. Estimates and projection of disease burden and investment case for hepatitis B and C in Viet Nam. Hanoi: Ministry of Health; 2017.
7. Duong HT, Jarlais DD, Khuat OHT, Arasteh K, Feelemyer J, Khue PM, et al.; Drive Study Group. Risk behaviors for HIV and HCV infection among people who inject drugs in Hai Phong, Viet Nam, 2014. AIDS Behav. 2018 Jul;22(7):2161–71. doi:10.1007/s10461-017-1814-6 pmid:28612212
8. Nadol P, O'Connor S, Duong H, Le LV, Thang PH, Tram TH, et al. Findings from integrated behavioral and biologic survey among males who inject drugs (MWID) - Vietnam, 2009-2010: evidence of the need for an integrated response to HIV, hepatitis B virus, and hepatitis C virus. PLoS One. 2015 Feb 18;10(2):e0118304. doi:10.1371/journal.pone.0118304 pmid:25692469
9. Nadol P, O'Connor S, Duong H, Mixson-Hayden T, Tram TH, Xia GL, et al. High hepatitis C virus (HCV) prevalence among men who have sex with men (MSM) in Vietnam and associated risk factors: 2010 Vietnam Integrated Behavioural and Biologic Cross-Sectional Survey. Sex Transm Infect. 2016 Nov;92(7):542–9. doi:10.1136/sextrans-2015-052518 pmid:27044267
10. Le LV, Nguyen TA, Tran HV, Gupta N, Duong TC, Tran HT, et al. Correlates of HIV infection among female sex workers in Vietnam: injection drug use remains a key risk factor. Drug Alcohol Depend. 2015 May 1;150:46–53. doi:10.1016/j.drugalcdep.2015.02.006 pmid:25765480
11. StataCorp. Stata Statistical Software: Release 14. College Station (TX): StataCorp LP; 2014.
12. Sandesh K, Varghese T, Harikumar R, Beena P, Sasidharan VP, Bindu CS, et al. Prevalence of hepatitis B and C in the normal population and high risk groups in north Kerala. Trop Gastroenterol. 2006 Apr-Jun;27(2):80–3. pmid:17089617
13. Wu JC, Lin HC, Jeng FS, Ma GY, Lee SD, Sheng WY. Prevalence, infectivity, and risk factor analysis of hepatitis C virus infection in prostitutes. J Med Virol. 1993 Apr;39(4):312–7. doi:10.1002/jmv.1890390410 pmid:8492103
14. Goldenberg SM, Montaner J, Braschel M, Socias E, Guillemi S, Shannon K. Dual sexual and drug-related predictors of hepatitis C incidence among sex workers in a Canadian setting: gaps and opportunities for scale-up of hepatitis C virus prevention, treatment, and care. Int J Infect Dis. 2017 Feb;55:31–7. doi:10.1016/j.ijid.2016.12.019 pmid:28027990
15. Iversen J, Page K, Madden A, Maher L. HIV, HCV, and health-related harms among women who inject drugs: implications for prevention and treatment. J Acquir Immune Defic Syndr. 2015 Jun 1;69 Suppl 2:S176–81. doi:10.1097/QAI.0000000000000659 pmid:25978485
16. Larney S, Kopinski H, Beckwith CG, Zaller ND, Jarlais DD, Hagan H, et al. Incidence and prevalence of hepatitis C in prisons and other closed settings: results of a systematic review and meta-analysis. Hepatology. 2013 Oct;58(4):1215–24. doi:10.1002/hep.26387 pmid:23504650
17. Maher L, Phlong P, Mooney-Somers J, Keo S, Stein E, Couture MC, et al. Amphetamine-type stimulant use and HIV/STI risk behaviour among young female sex workers in Phnom Penh, Cambodia. Int J Drug Policy. 2011 May;22(3):203–9. doi:10.1016/j.drugpo.2011.01.003 pmid:21316935
18. Thomas DL, Zenilman JM, Alter HJ, Shih JW, Galai N, Carella AV, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore–an analysis of 309 sex partnerships. J Infect Dis. 1995 Apr;171(4):768–75. doi:10.1093/infdis/171.4.768 pmid:7535827
19. Marx MA, Murugavel KG, Tarwater PM, SriKrishnan AK, Thomas DL, Solomon S, et al. Association of hepatitis C virus infection with sexual exposure in southern India. Clin Infect Dis. 2003 Aug 15;37(4):514–20. doi:10.1086/376639 pmid:12905135
20. Ward H, Rönn M. Contribution of sexually transmitted infections to the sexual transmission of HIV. Curr Opin HIV AIDS. 2010 Jul;5(4):305–10. doi:10.1097/COH.0b013e32833a8844 pmid:20543605
21. Implementing comprehensive HIV/STI programmes with sex workers: practical approaches from collaborative interventions. Geneva: World Health Organization; 2013 (https://www.who.int/hiv/pub/sti/sex_worker_implementation/en/).
22. Sulkowski MS. Management of hepatic complications in HIV-infected persons. J Infect Dis. 2008 May 15;197(s3) Suppl 3:S279–93. doi:10.1086/533414 pmid:18447614

23. Hipgrave DB, Nguyen TV, Vu MH, Hoang TL, Do TD, Tran NT, et al. Hepatitis B infection in rural Vietnam and the implications for a national program of infant immunization. Am J Trop Med Hyg. 2003 Sep;69(3):288–94. doi:10.4269/ajtmh.2003.69.288 pmid:14628946

24. Nguyen VT, McLaws ML, Dore GJ. Highly endemic hepatitis B infection in rural Vietnam. J Gastroenterol Hepatol. 2007 Dec;22(12):2093–100. doi:10.1111/j.1440-1746.2007.05010.x pmid:17645465

25. Truong BX, Seo Y, Yano Y, Ho PT, Phuong TM, Long DV, et al. Genotype and variations in core promoter and pre-core regions are related to progression of disease in HBV-infected patients from Northern Vietnam. Int J Mol Med. 2007 Feb;19(2):293–9. pmid:17203204

26. Parekh S, Zoulim F, Ahn SH, Tsai A, Li J, Kawai S, et al. Genome replication, virion secretion, and e antigen expression of naturally occurring hepatitis B virus core promoter mutants. J Virol. 2003 Jun;77(12):6601–12. doi:10.1128/JVI.77.12.6601-6612.2003 pmid:12767980

27. Lin CL, Kao JH. Risk stratification for hepatitis B virus related hepatocellular carcinoma. J Gastroenterol Hepatol. 2013 Jan;28(1):10–7. doi:10.1111/jgh.12010 pmid:23094699

28. Pinkham S, Malinowska-Sempruch K. Women, harm reduction and HIV. Reprod Health Matters. 2008 May;16(31):168–81. doi:10.1016/S0968-8080(08)31345-7 pmid:18513618

29. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int. 2011 Jul;31 Suppl 2:61–80. doi:10.1111/j.1478-3231.2011.02540.x pmid:21651703

30. Zhang GQ, Chen SD, Lian JH. [Seroepidemiological study of HBV and HCV infection in sexually promiscuous groups]. Zhonghua Liu Xing Bing Xue Za Zhi. 1995 Aug;16(4):213–6. (in Chinese) pmid:7585900

31. Freiman JM, Tran TM, Schumacher SG, White LF, Ongarello S, Cohn J, et al. Hepatitis C core antigen testing for diagnosis of hepatitus C virus infection: a systematic review and meta-analysis. Ann Intern Med. 2016 Sep 6;165(5):345–55. doi:10.7326/M16-0065 pmid:27322622

Public health event communication under the International Health Regulations (2005) in the Western Pacific Region, September 2006-January 2017

Li Xi,[a] Li Ailan[a]

Correspondence to Li Ailan (email: lia@who.int)

Highlights

- The International Health Regulations, or IHR (2005), establishes timely communication between the World Health Organization (WHO) and Member States to manage acute public health events and protect health security. Experiences of the WHO IHR contact point for the Western Pacific Region demonstrated the communication mechanism has achieved its functions in the Region.
- Investment in IHR communication as part of the *Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies* (APSED III) during peaceful times between public health emergencies builds capacity, confidence and trust in information sharing during emergencies.
- IHR communication is integral to the national, regional and global epidemic intelligence and risk assessments system.
- Regular simulation exercises (for example, IHR Exercise Crystal) play an important role in testing and strengthening IHR communication.
- IHR communication continues to be vital for Member States and WHO Country Offices to advise on health security.

The revised International Health Regulations (IHR) (2005), entered into force in June 2007, is a legally binding international agreement on 196 States Parties, including all 194 Member States of World Health Organization (WHO).[1] In the Western Pacific Region, National IHR Focal Points (NFPs) have been established in 27 Member States, which are States Parties to the IHR. Communication between WHO and countries through the NFPs is the cornerstone of timely detection of public health risks and effective response to health emergencies. Countries are required to notify WHO of all events that may constitute a public health emergency of international concern (PHEIC) through their NFPs. Strengthening the functions of NFPs is one of the strategic actions to enhance public health emergency preparedness through the implementation of the *Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies* (APSED III).[2]

IHR event communication refers to official communication between NFPs and WHO IHR contact points (CPs) at regional and global levels, as well as communication between NFPs in different countries, and between the NFP and relevant departments or agencies within the country to notify public health events; share and verify information; determine whether an event constitutes a PHEIC; and coordinate emergency responses.[1] Email has been the main mechanism of communication between WHO CPs and NFPs. In addition to email communication, WHO has developed a password-protected website, the Event Information Site (EIS), to facilitate information sharing with all NFPs. Events posted on EIS, which are often potential PHEICs or public hazards with international impact, are accessible to all NFPs.[3]

IHR Exercise Crystal, a simulation exercise organized by the WHO Western Pacific Regional Office (WPRO) to test and strengthen event communication between the IHR CP of WPRO (WPRO IHR CP) and NFPs in the Region, has been conducted in the Western Pacific Region annually since 2008,[4] except that in 2009 NFPs communicated frequently with the WPRO IHR CP during

[a] WHO Health Emergencies Programme, WHO Regional Office for the Western Pacific, Manila, Philippines
Submitted: 22 January 2019; Published: 27 September 2019
doi: 10.5365/wpsar.2019.10.1.006

the PHEIC of pandemic influenza A(H1N1). The role of IHR Exercise Crystal in testing and strengthening the communication functions is well recognized in the 10-year evaluation of APSED and meetings of the Technical Advisory Group on APSED.[5,6]

This regional analysis presents an evaluation of the extent and function of IHR event communication in the WHO Western Pacific Region as informed by email records of the WPRO IHR CP and experiences from IHR Exercises Crystal. Specifically, we classified each event under one IHR article related to communications from States Parties to WHO and analysed the number and types of events communicated under the relevant IHR articles: Article 6 Notification; Article 8 Consultation; Article 9 Other reports; Article 10 Verification; Article 44 Collaboration and assistance.[1] We also summarized the types of events posted on EIS and the scopes, objectives and results of IHR Exercise Crystal from 2008 to 2016.

IHR COMMUNICATION

Email was the main mechanism of communication between the WPRO IHR CP and NFPs. In rare cases, documents were faxed to WPRO, and the WPRO IHR CP received email notices when faxes arrived. Telephone calls were infrequent and were always accompanied by an email.

Emails were retrieved from the archives of the mailbox of the WPRO IHR CP. The emails covered communications from September 2006, when the mailbox was put into use, to January 2017 at the time of analysis. The contents of emails received from NFPs and external partners or from other regional WHO IHR CPs were reviewed to determine the disease or public health hazard reported, the IHR article under which the event was communicated, the countries involved and the time of the communication. In case of novel influenza viruses, the notification of the first case in a Member State is counted as one event, while the subsequent reports of additional cases were considered as updates to the event. Event information disseminated by the International Food Safety Authorities Network (INFOSAN), in which NFPs were copied, were not included in the analysis. Email exchanges among WHO staff other than those between the designated WHO IHR CPs were not included; these were considered to be internal business processes after events were communicated to WHO.

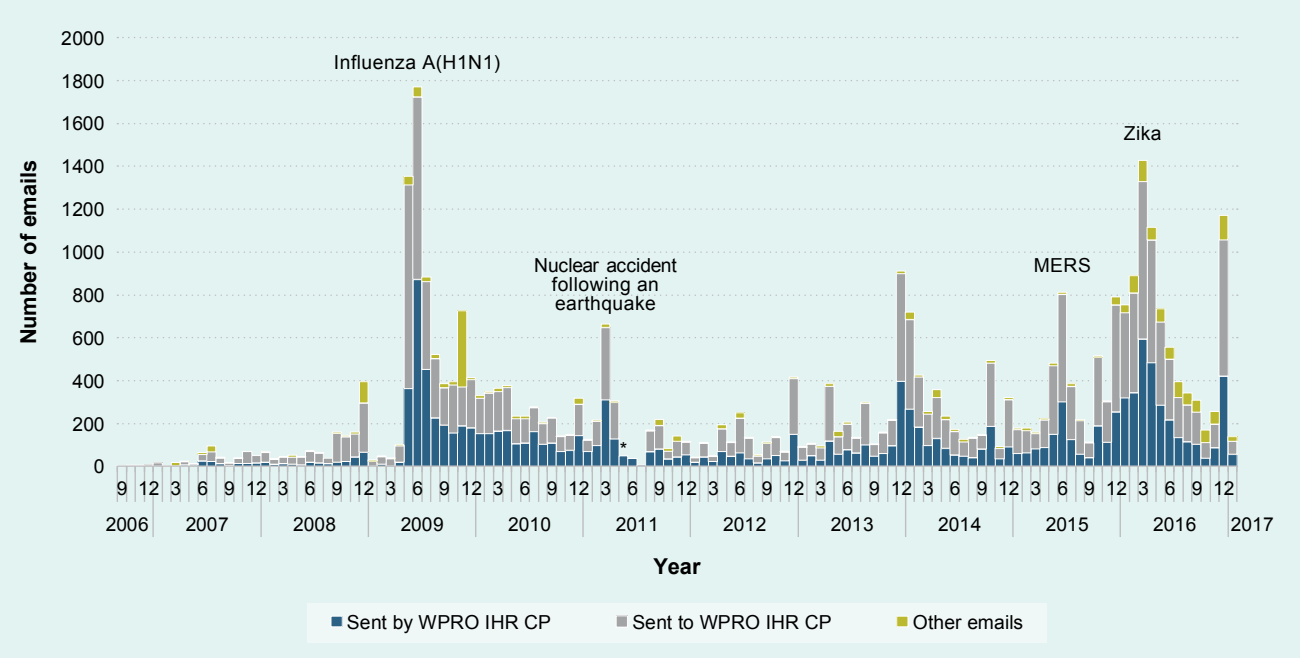
After removing duplicates, a total of 34 438 emails were recovered from the archives of WPRO IHR mailbox from 11 September 2006 to 12 January 2017, of which 2944 (8.5%) were IHR exercise messages. Emails received from 1 May to 25 August 2011 could not be recovered due to archiving issues. Among the 34 438 retrieved emails, 13 252 (38%) were sent from the WPRO IHR CP; and 18 922 (55%) were sent to the WPRO IHR CP, including 5523 emails that copied the WPRO IHR CP. The other 2264 emails (7%) included fax notices, surveillance reports that did not list the recipients and emails sent to a very large group of recipients for which we could not determine if WPRO was on the direct or copying lines as the lines were truncated when data were imported into an Access database. **Fig. 1** shows the number of emails by month.

Of the 21 186 emails received by the WPRO IHR CP, 5809 (27.4%) were from Member States in the Western Pacific Region, 508 (2.4%) were from Member States and areas outside the Western Pacific Region, 2881 (13.6%) were from WHO IHR CPs in WHO headquarters or other WHO regional offices, 10 582 (49.9%) were from WHO staff other than WHO IHR CPs, 612 (2.9%) were from INFOSAN and 41 (0.2%) were from international partner organizations (**Fig. 2**). The remaining 753 (3.6%) included autoreplies, subscriptions to event alerts and system-generated emails. All 27 NFPs in the Western Pacific Region communicated with the WPRO IHR CP. Thirty-four Member States and areas[§] of the WHO Western Pacific Region, including those that are not States Parties to the IHR, communicated with the WPRO IHR CP. Thirty-five countries outside the Western Pacific Region communicated with the WPRO IHR CP.

Notification (IHR Article 6, Article 9)

A total of 89 notifications of potential PHEIC under Article 6 were received from Member States and areas of the Western Pacific Region as of 12 January 2017 (France and the United States of America made notifications on behalf of their territories in the Pacific). All States Parties in the Western Pacific Region, except for Tuvalu, made at least one notification of a potential PHEIC to the WPRO IHR CP during this period. Thirty-three diseases and one nuclear accident following an earthquake were reported to the WPRO IHR CP. Forty-three (48%) notifications were about novel influenza viruses, including 32 notifications on pandemic H1N1, four on H5N1,

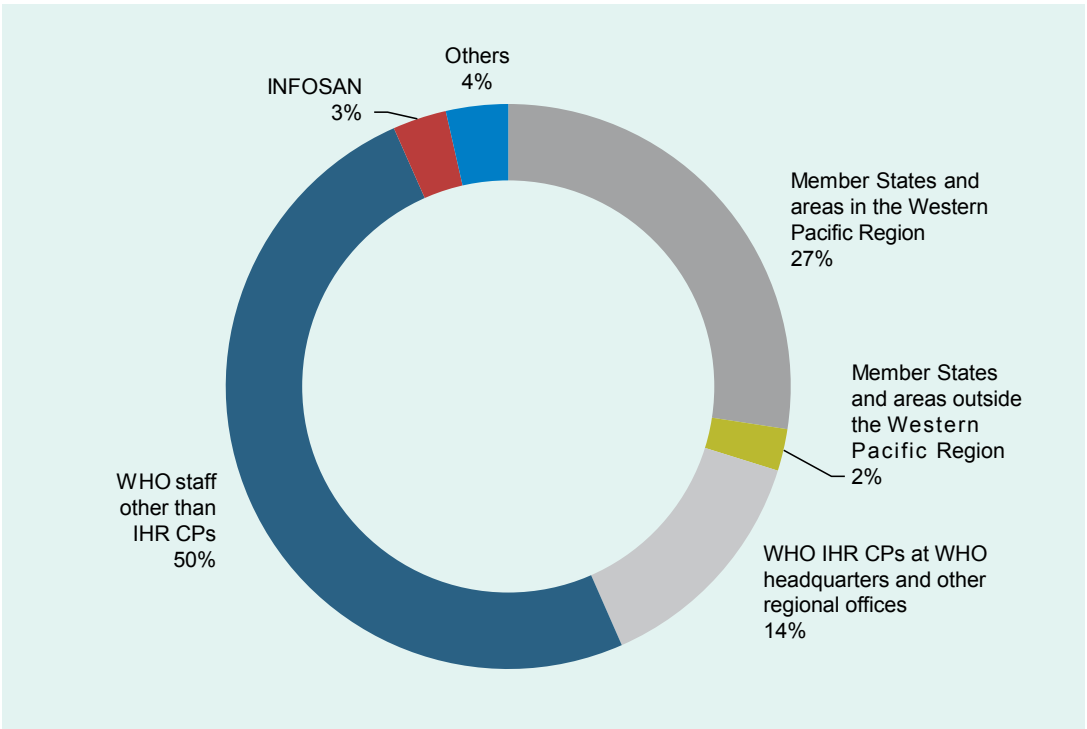
Fig. 1. **Number of emails by months in the mailbox of the WPRO IHR CP, September 2006–January 2017**



CP: contact point; IHR: International Health Regulations; MERS: Middle East respiratory syndrome; WPRO: Western Pacific Regional Office.

* Emails received from 1 May 2011 to 25 August 2011 could not be recovered because of archiving issues.

Fig. 2. **Number of emails received by the WPRO IHR CP by sender categories, September 2006–January 2017**



CP: contact point; IHR: International Health Regulations; INFOSAN: International Food Safety Authorities Network; WPRO: Western Pacific Regional Office.

two on H7N9, two on H9N2 and one each for H10N8, H3N2, and H5N6. Eleven notifications were about Zika virus disease, including microcephaly and Guillain–Barré syndrome associated with Zika virus disease.

In addition to notifications under Article 6, five notifications cited Article 9, which asks States Parties to inform WHO of a public health risk identified outside their territory that may cause international disease spread. These notifications included cases of Zika virus disease and cholera imported from other countries, a norovirus outbreak during an international gathering, and a close contact of a Middle East respiratory syndrome (MERS) case who travelled internationally.

Information sharing and consultation with WPRO (IHR Article 8)

Five countries consulted with the WPRO IHR CP about 14 events that either did not require notification as a potential PHEIC or did not have enough information to determine if PHEIC criteria had been met. None of these events was declared as a PHEIC. In addition, 12 NFPs shared information with the WPRO IHR CP about 27 diseases or disasters that might have international impact but did not constitute a PHEIC.

Verification (IHR Article 10)

The WPRO IHR CP made 13 requests for verification of events known to WHO from sources other than notifications and consultations. Of these, eight events (62%) had evidence of response from NFPs within 24 hours.

Inter-country collaboration and assistance (IHR Article 44)

The IHR has been widely used by NFPs for communication between countries. The WPRO IHR CP facilitated or was copied in communication between NFPs in 273 events. In 237 events, NFPs initiated the communication to provide information to other NFPs, including contact tracing in 71 events, follow-up for patient management in 10 events, reporting travellers or foreign nationals under public health observation/investigation in 17 events and sharing information of imported or exported cases of communicable diseases in 135 events. The most frequently reported diseases were tuberculosis (53 events), measles (29 events), chlamydia (16 events), Legionnaire's disease (15 events), MERS (14 events), Zika virus disease (12 events) and Ebola virus disease (10 events for sharing notice of travellers under monitoring with low risk exposure and two events for contact tracing). Due to the pandemic nature of H1N1, communications following initial notifications in each country related to contact tracing of H1N1 cases and antiviral resistance were not counted as separate from initial notification.

In 36 instances, NFPs made requests for information from another NFP. These communications usually took place when NFPs wanted to verify media reports of diseases in another country or ask questions following an EIS posting.

Information sharing through EIS

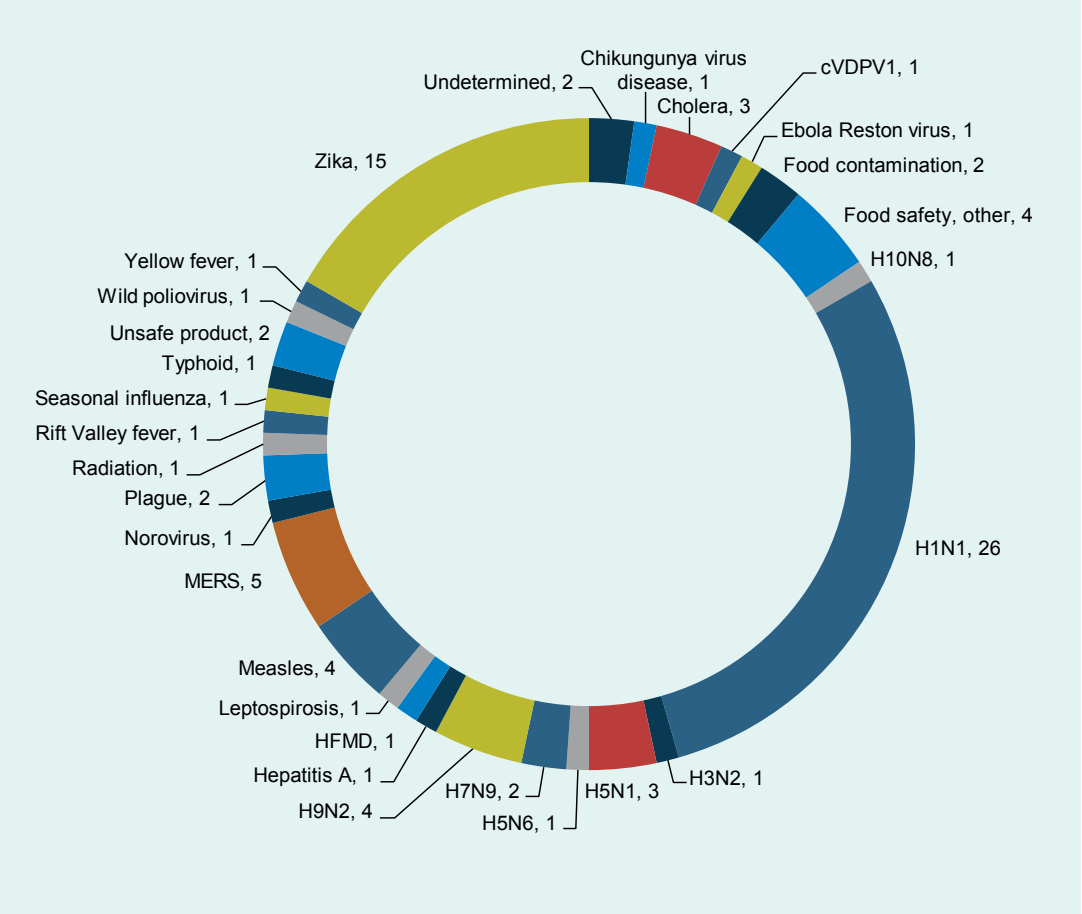
Events that are potential PHEICs or other health hazards with international impact are posted on EIS following notifications or other communications under the IHR. NFPs of all States Parties can view the event information on the password-protected website. A total of 90 postings from 24 countries or areas in the Western Pacific Region were shared on EIS as of January 2017. Thirty-nine (43%) of the postings were about influenza. **Fig 3** shows the type of public health events from the Western Pacific Region posted on EIS between 2007 and 2016.

Avian influenza A(H7N9) in China had the highest number of updates for a single event in the Western Pacific Region. The virus was first laboratory-confirmed in China on 31 March 2013 and notified to WHO on 1 April 2013. The first posting on EIS was published on 1 April 2013 and was accessible to all NFPs. The additional cases were reported daily during the first season of the epidemic, and weekly or monthly in the subsequent seasons. The reporting frequency increased during the seasons when the number of H7N9 cases increased. Between 1 April 2013 and 12 January 2017, 166 updates of H7N9 were posted on EIS. Sixty-two out of 177 updates were posted on the same day. The median time from reporting to EIS posting was 1.62 days.

Requesting information from WHO

Forty-two requests for further information were sent from NFPs to the WPRO IHR CP, often following media reports or EIS postings of events in another country.

Fig. 3. **Types and counts of public health events posted on the Event Information Site from the Western Pacific Region, 2007–January 2017**



cVDPV1: circulating vaccine-derived poliovirus type 1; HFMD: hand, foot and mouth disease ; MERS: Middle East respiratory syndrome.

IHR EXERCISE CRYSTAL

IHR Exercise Crystal has been held annually from 2008 to 2016, with the exception of 2009 when the real-world event of pandemic influenza A(H1N1) tested IHR communication between countries and WHO. The scope of IHR Exercise Crystal has been evolving with increased complexity (**Table 1**). The main objectives of IHR Exercise Crystal have been consistent over the years: to strengthen the accessibility of NFP contact details, event notification process and information sharing through developing postings for EIS. Additional objectives have been added with more functions tested (**Table 2**).

All 27 countries in the Region were invited to participate in IHR Exercise Crystal, except in 2014, when 11 countries were invited to participate in a joint IHR-INFOSAN exercise. In 2016, eight territories and areas in the Region were invited in addition to the 27 countries (**Fig. 4**). The accessibility of NFPs by email increased steadily over 2008–2016. In 2008, 70% (19 out of 27) of NFPs were accessible by emails. This percentage increased to over 95% since 2011. The other ways of communication, including fax, telephone, teleconference and text messaging were tested in some years with varying results. The number of NFPs who completed the expected tasks increased over the years. In 2015, 21 NFPs made notifications during the allotted exercise time, an increase from five NFPs in 2011. In 2015, 20 NFPs completed the draft EIS posting in the allotted exercise time compared to eight NFPs in 2011.

Feedback was collected from NFPs following the exercises. NFPs have commented that the scopes were appropriate and the objectives were achieved; the exercises "enhanced collaboration with partners and promoted teamwork"; and the exercises "strengthened IHR event-related communication" between NFPs and WHO. NFPs recommended that the exercise be continued.

Table 1. **Scopes of IHR Exercise Crystal, 2008–2016**

Year	Event
2008	Verification of an outbreak of unknown etiology occurring in the participating country.
2010	Notification of a Public Health Emergency of International Concern (PHEIC) and share the information on Event Information Site (EIS).
2011	Notification of a potential PHEIC (severe acute respiratory infection of unknown etiology) and share the information on EIS.
2012	Notification of a potential PHEIC (influenza-like illness) and share the information on EIS.
2013	Notification of a potential PHEIC (severe acute respiratory infection of unknown etiology) and share the information on EIS.
2014*	Joint exercise between NFPs and INFOSAN emergency contact points on notification and information sharing of an outbreak of Verocytotoxin-producing *Escherichia coli* infection caused by an internationally distributed food product.
2015	Notification of a novel avian influenza virus and consulting and conferring with WHO about potential impacts on travel and trade.
2016	Notification of a disease of unknown etiology, communication with national disaster management and providing information for IHR Emergency Committee.

* An Ebola simulation exercise was conducted in addition to the regular IHR Exercise Crystal.

Table 2. **Objectives of IHR Exercise Crystal, 2008–2016**

Objectives	2008	2010	2011	2012	2013	2014	2015	2016
Validate the accessibility of NFPs using registered contact details	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IHR notification process	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Draft a posting to share information through the IHR Event Information Site	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Test the use of teleconferencing	No	Yes	Yes	Yes	No	No	Yes	Yes
Additional objectives (see footnotes)	a	b			c	d	e	f

a. Validate IHR verification process; test the WHO guide on IHR communication and Duty Officer System.

b. Test the WHO guide on IHR communication and Duty Officer System.

c. Improve the engagement of WHO country offices in facilitating communication.

d. Validate the accessibility of INFOSAN emergency contact points; facilitate communication and collaboration between them during a foodborne disease emergency event.

e. Practise and evaluate the NFP understanding and use of the IHR principles and obligations regarding travel restrictions and border measures.

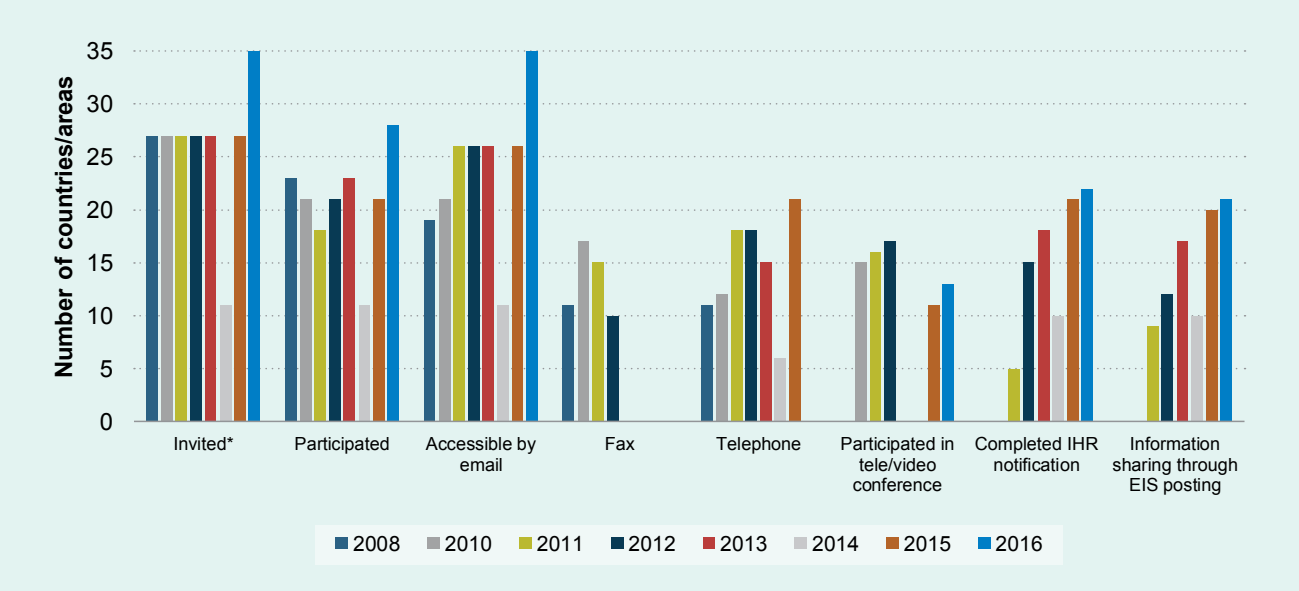
f. Examine protocols when working with non-health actors, particularly national disaster management agencies; familiarize participants with the IHR Emergency Committee.

In October 2014, in response to the global Ebola virus disease (EVD) epidemic, an Ebola simulation exercise and an Ebola preparedness survey were conducted in addition to the regular IHR Exercise Crystal.[7] Twenty-three countries participated in the exercise that simulated the scenario of an imported case of EVD. The majority of the countries were able to complete the expected actions, including sharing national EVD guidelines and response plans, providing technical advice on contact tracing, case management and patient transportation and drafting a press release. The exercise identified specimen referral as an area for improvement.

DISCUSSION

Ten years after IHR (2005) entered into force, the communication mechanism set up by IHR (2005) has been functional in supporting Member States to report potential public health risks to WHO and other countries. All States Parties in the Western Pacific Region have made contact with the WPRO IHR CP, and all but one made a notification of potential PHEICs to WPRO. IHR event communication has also been used for sharing information with WHO on events that do not constitute a PHEIC. WPRO has used IHR event communication to verify media and other reports with NFPs. Countries that are actively screening media or other information sources for public health risks used IHR event communication to verify information from WHO or another country. The network has become an important information source for risk assessment to both WHO and the countries. It is an integral component of global epidemic intelligence system.

Fig. 4. **Member States' participation and performance in IHR Exercise Crystal, 2008–2016**



* All 27 countries in the Region were invited to participate in IHR Exercise Crystal, except in 2014, when 11 countries were invited to participate in a joint IHR-INFOSAN exercise. In 2016, eight territories and areas in the Region were invited in addition to the 27 countries.

The IHR communication mechanism has been widely used by NFPs for inter-country collaboration and assistance. The majority of IHR communication occurred between countries for information sharing, contact tracing and follow-up of patients to ensure continuity of infectious disease management.

IHR communication has an all-hazards approach. While most of the events reported through IHR communication were infectious diseases, other public health concerns, including natural disasters, nuclear accidents and food safety issues were reported through IHR.

Timely communication during epidemics (the H1N1 pandemic influenza, Zika virus disease, MERS) exemplifies the importance of investment in public health preparedness in peaceful times between major public health emergencies to build confidence and trust between WHO and Member States in information sharing. The capacity of NFPs has been strengthened in the past 10 years, which can be observed through the simulation exercises: increasing numbers of NFPs could complete the tasks of making notifications and developing an EIS posting in the exercises. IHR Exercise Crystal is being replicated globally as a model to test and improve the functions of IHR communication.

The analysis had several limitations. First, multiple IHR articles may apply to the same event, and countries reported events of similar nature to WHO citing different IHR articles. We classified the events under each IHR article based on our best understanding of the content and context, while acknowledging the classification might be subjective in some events and we didn't attempt to analyse how many times articles in other parts of IHR (for example, Part IV Points of entry, Part V Public health measures) have been applied. Second, only emails were analysed. Other means of IHR event communication have been used, for example telephones and fax, although it is rare that events are reported without any email record. Additionally, emails received from May to July 2010 could not be retrieved, and emails sent by the WPRO IHR CP were not systematically archived. The WPRO IHR CP could potentially improve its information management by developing a system to routinely archive messages. Third, we likely underestimated the number of verifications from WHO. In countries with WHO country offices, the requests for verifying media reports and other reports were often communicated through WHO country offices, which then facilitated communication with the in-country counterparts. These communications may not have involved direct communication between the WPRO IHR CP and NFPs, and therefore were not covered by this analysis. Fourth, we also likely underestimated the number of inter-country communications as the WPRO IHR CP was not always copied in communications between NFPs. Given the communications not covered in the

analysis, this report presents a conservative picture of the extent of IHR communication within the Region.

In conclusion, IHR communication has played a pivotal role in communicating PHEIC and other public health risks between countries and WHO and among countries. IHR Exercise Crystal played a positive role in strengthening IHR communication and collaboration. The capacity of NFPs improved as shown in IHR Exercise Crystal.

Timely IHR event communication between NFPs and WHO is an integral component of the global and regional surveillance and risk assessment system that protects national, regional and global health security. With the establishment and implementation of the WHO new Health Emergencies Programme,[8] it is expected that the functions of the NFPs and the WHO IHR CPs will be further strengthened and advanced. The experiences and lessons from the Western Pacific Region could be a useful contribution to the achievement of the mission of the global programme to strengthen the capacity to prevent, detect and respond to public health threats worldwide.

Ethics statement

Ethical review is not required since reviewing the information communicated through the IHR mechanism is a public health practice activity and the purpose of the analysis is to evaluate and improve the IHR communication mechanism.

Acknowledgements

The authors would like to thank colleagues from Member States in the Western Pacific Region, WHO country offices and the Health Emergencies Programme at the WHO headquarters.

Funding

This is a public health activity of the WHO Regional Office for the Western Pacific, and no funding from direct external sources was involved.

Conflicts of interest

Dr Ailan Li is a staff member of the WHO Regional Office for the Western Pacific and oversees WHO activities in the Region in health emergency responses and health security, including IHR communications and IHR simulation exercises. Dr Xi Li served as the first-line officer of the regional IHR contact point and as the editor of the *Western Pacific Surveillance and Response Journal*. She participated in IHR Exercise Crystal in 2016.

References

1. International Health Regulations (2005). Geneva: World Health Organization; 2008 (https://www.who.int/ihr/publications/9789241580496/en/).
2. Asia Pacific strategy for emerging diseases and public health emergencies (APSED III): advancing implementation of the International Health Regulations (2005). Manila: WHO Regional Office for the Western Pacific; 2017 (https://iris.wpro.who.int/handle/10665.1/13654)
3. WHO event management for international public health security: Operational procedures. Geneva: World Health Organization; 2008 (https://www.who.int/ihr/publications/WHO_HSE_EPR_ARO_2008_1/en/).
4. IHR Exercise Crystal. (2015). Manila: WHO Regional Office for the Western Pacific; 2015 (https://apps.who.int/iris/handle/10665/246428).
5. Asia Pacific strategy for emerging diseases: evaluation report 2005–2015. Manila: WHO Regional Office for the Western Pacific; 2018 (https://iris.wpro.who.int/handle/10665.1/14028).
6. Meeting of the Technical Advisory Group on the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III). Manila, Philippines, 11–13 July 2017: meeting report. Manila: WHO Regional Office for the Western Pacific; 2017 (https://iris.wpro.who.int/handle/10665.1/13980).
7. Xu Z et al on behalf of the WHO Regional Office for the Western Pacific Emergency Support Team. Ebola preparedness in the Western Pacific Region, 2014. Western Pac Surveill Response J. 2015 Jan 26;6(1):66-72. doi:10.2471/wpsar.2014.5.4.004
8. WHO Health Emergencies Programme: progress and priorities, Financing dialogue 31 October 2016. Geneva: World Health Organization; 2016 (https://www.who.int/about/finances-accountability/funding/financing-dialogue/whe-update.pdf).

World Health Organization
Western Pacific Region

WPSAR
Western Pacific Surveillance and Response Journal

wpsar@who.int | https://ojs.wpro.who.int/