Tohoku J. Exp. Med., 2016, **238**, 287-293

Review

Development of Point-of-Care Testing for Disaster-Related Infectious Diseases

Toshio Hattori,[1] Haorile Chagan-Yasutan,[1] Beata Shiratori,[1] Shinichi Egawa,[2] Takako Izumi,[3] Toru Kubo,[4] Chie Nakajima,[5] Yasuhiko Suzuki,[5] Toshiro Niki,[6] Bachti Alisjahbana[7] and Elizabeth Telan[8]

[1]Department of Disaster-related Infectious Disease, International Research Institute of Disaster Science, Tohoku University, Sendai, Miyagi, Japan
[2]Department of International Cooperation for Disaster Medicine, International Research Institute of Disaster Science, Tohoku University, Sendai, Miyagi, Japan
[3]Domestic Liaison Office, International Research Institute of Disaster Science, Tohoku University, Sendai, Miyagi, Japan
[4]Japanese Red Cross Nagasaki Genbaku Isahaya Hospital, Isahaya, Nagasaki, Japan
[5]Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan
[6]Faculty of Medicine, Kagawa University, Takamatsu, Kagawa, Japan
[7]Research Center, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia
[8]STD AIDS Cooperative Central Laboratory, San Lazaro Hospital, Manila, the Philippines

After disaster, the victims lose their safe lives and are even exposed to nature where they could suffer from animal bites and vectors followed by suffering from zoonosis or vector-born diseases. Because of the urgent need for rapid and cheap diagnosis for infectious diseases after disaster, anonymous questionnaire clarified that leptospirosis, dengue, diarrhea, and cholera were recognized as common disaster-related infections in the Philippines, while diarrhea and pneumonia were more common in Indonesia. It should also be noted that infectious disease itself such as tuberculosis associated with acquired immune deficiency syndrome in South Africa is a disaster. Thus, the possible occurrence of similar situation in Asia should be prevented. We have conducted an international collaborative research in the Philippines and Indonesia on dengue virus, leptospira and mycobacterium tuberculosis (MTB) infectious diseases. Development of point-of-care testing for molecular diagnosis and disease severity was the principal purpose of the research. Loop-mediated isothermal amplification assay, which does not require a source of electricity, was developed for leptospirosis, dengue and MTB and has been proved to be useful where resource is limited. The plasma levels of matricellular proteins, including galectin-9 and osteopontin, were found to reflect the disease severities in dengue virus and MTB infection, probably because matricellular proteins are one of the most functional extracellular proteins that are associated with inflammatory edema. The study on disaster-related infectious disease facilitates the international cooperation for development of point-of-care testing for tropical infectious diseases.

Keywords: disaster-related infectious disease; galectin-9; LAMP; osteopontin; point-of-care testing
Tohoku J. Exp. Med., 2016 April, **238** (4), 287-293.

Introduction

The Tohoku area in Japan suffered as a result of the Great East Japan Earthquake and Tsunami (GEJET) of March 11, 2011, which left nearly 20,000 people dead or missing (Shibahara 2011; Ishigaki et al. 2013). Since 1990, natural disasters have affected about 217 million people per year worldwide (Leaning and Guha-Sapir 2013). The immediate and longer-term effects of these disruptions on large populations constitute humanitarian crisis. In recent decades, public health interventions have improved the equity and equality of emergency assistance during humanitarian responses. Tohoku University founded the International Research Institute of Disaster Science (IRIDeS) in 2012.

The United Nation Development Programme proposed the concept of human security (HS) for the first time in their Human Development Report. In this document, the inter-

Received November 19, 2015; revised and accepted March 1, 2016. Published online March 26, 2016; doi: 10.1620/tjem.238.287.
Correspondence: Toshio Hattori, Department of Disaster-related Infectious Disease, Tohoku University, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan.
e-mail: toshatto@med.tohoku.ac.jp

national community focused on the new paradigm of HS, which is centered on the idea of protecting human life against poverty, environmental destruction, conflict and infectious diseases (United Nations Development Programme 1994; Ogata and Sen 2003). The idea could be the education principle for disaster medical science.

In this review, we will describe research projects, focusing especially on the development of point of care testing for diagnosis and identification of the severity of the disease.

Disaster-related infectious diseases in Asian countries

We have launched a collaborative project between the Asian Pacific countries to develop collaborative research and education on disaster medicine (Hattori et al. 2012), because these nations are disaster-prone island countries (Guha-Sapir et al. 2013). In conjunction with these lectures, we have also administered an anonymous questionnaire on disaster medicine to medical school students, public health school students, and medical personnel. It was also found that significant disasters in the Philippines were geophysical, hydrological, or meteorological, whereas the significant disasters in Indonesia were geophysical or hydrological. Leptospirosis, dengue, diarrhea, and cholera were recognized as common disaster-related infections in the Philippines, whereas diarrhea and respiratory infection were the major disaster-related infections in Indonesia (Usuzawa et al. 2014). These results indicate that disaster-related infectious diseases differ from place to place.

Studies of disaster-related infectious disease

Infectious disease itself is a disaster

There were three times as many natural disasters from 2000 through 2009 as there were from 1980 through 1989. Although better communication may play a role in this trend, the growth is mainly comprised of climate-related events, which account for nearly 80% of the increase. During recent decades, the scale of disasters has expanded owing to increased rates of urbanization, deforestation, and environmental degradation, as well as intensifying climate variables, such as higher temperatures, extreme precipitation, and more violent wind and water storms (Leaning and Guha-Sapir 2013). Therefore, increases in both natural disasters and infectious diseases have been caused by ecological changes. Further, natural disasters are often associated with the emergence of new infectious diseases. In turn, infectious diseases could themselves be regarded as constituting natural disasters. Some microorganisms have been called natural weapon. For example, human immunodeficiency virus (HIV) infection as well as cigarette smoking are two major novel causes of mortality which both emerged in the twentieth century (Weiss and McMichael 2004). Such "weapons" could be a cause of disasters, if they are not treated appropriately. For example, deaths caused by AIDS and tuberculosis (TB) account for 47% of all deaths in South Africa (Directorate Epidemiology Cluster, HIMME National Department of Health, South Africa 2013). Increased HIV infections were seen in South Africa in 1990, indicating the invasion of HIV into TB-endemic area, which accounts for much of the rise of AIDS/TB in South Africa (Mee et al. 2014). Also drug-resistant TB emerged from this region can spread into other countries and became a challenge to international health (Cooke et al. 2011). We found that latent TB infection rate is quite high in the Philippines (Siddiqi et al. 2012), and along with HS course students, it was recently reported that the rate is high in Indonesia as well (Senoputra et al. 2015). We should be careful with regard to the occurrence of an AIDS/TB epidemic in Southeast Asia. The rate of HIV infection has been rising alarmingly over the past seven years in the subpopulation of men and who have sex with men (MSM) in the Philippines. In the year 2014 alone, there were 6,011 newly diagnosed cases of HIV, representing 27% of the total number of cases identified in the Philippines (22,527) since the epidemic began in 1984 (Ross et al. 2015). It is urgent to prevent HIV infection in the Philippines and other countries in Asia.

Infectious diseases caused by disasters

In daily life, human health is guarded from microorganisms by many systems and devices, such as tap water, gas heating, washing, and refrigeration. Disasters destroy these protective systems, and the victims will be exposed to natural threats such as contaminated water, animals, and disease vectors immediately after the disaster (Fig. 1). After a while, human-to-human communicable diseases occur due to the dense lives of the victims in affected camp. Such kinds of disaster-related diseases are listed in Table 1 (WHO, World Health Organization 2011). Although the type of infectious disease can vary depending on the site of disaster, dengue (a mosquito-borne disease), leptospirosis (zoonosis), and tuberculosis (dense-living disease) are frequently seen in San Lazaro Hospital (SLH; Manila, the Philippines) and Padjadjaran (PJU, Bandong, Indonesia), and effective management of these diseases would in turn result in the management of tropical infectious diseases as well as disaster-related infectious diseases in resource-limited low-income countries. Therefore, in collaboration with SLH and PJU, we have attempted to develop a point-of-care testing for the diagnosis of patients with these diseases.

Loop-mediated isothermal amplification assay as point-of-care testing for disaster-related infectious diseases

As the first symptoms of TB are usually nonspecific, correct diagnosis and treatment of an active TB infection is often delayed. TB is usually suspected only when the associated cough continues for more than 2 weeks, during which the infection continues to spread among the victims in a disaster setting. Late diagnoses and late interventions during the early post-disaster period are often caused by both a lack of awareness of TB and also the damage to and

Fig. 1. Buildings and sites that were destroyed by typhoon Haiyan at Tacloban City, the Philippines (January, 2015).
A-C: Types of damage in downtown Tacloban city near the shoreline.
D-F: Tacloban doctors medical center: Strong wind destructed windows (D), oxygen supply system (E) and stagnant water in the grounds of the hospital (F).

Table 1. Epidemics after disaster.

Classification	Diseases
Water-related Infectious Diseases	Enterotoxigenic *Escherichia coli*
	Cholera epidemic
	Paratyphoid fever
	Hepatitis A and E
	Leptospirosis
	Melioidosis
Diseases Associated with Crowding	Measles
	Neisseria meningitis
	Acute respiratory infections
Vector Borne Diseases	Malaria
	Dengue
	Yellow fever
	Chikungunya
	West Nile
Other Diseases Associated with Natural Disasters	Tetanus
	Coccidiomycosis
	Tuberculosis

Summarized from the website (WHO 2011).

subsequent shortages of diagnostic equipment. The need for an easy and specific tool that can determine the pathogen leads to the development of loop-mediated isothermal amplification assay (LAMP). It should be mentioned that, in contrast to the other TB diagnostic methods, performing LAMP does not require a source of electricity. Further, LAMP equipment is easily transportable and the testing procedures do not require a trained operator. Recent nucleic acid extraction kits enable mycobacterium TB (MTB) DNA to be obtained directly from the patient's spu-

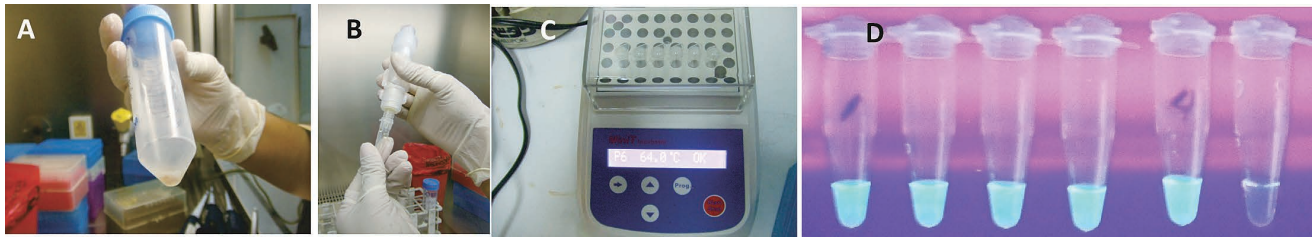

Fig. 2. Detection of tuberculosis DNA in the patient's sputum by LAMP.
Sputum specimen (A) is added to the DNA extraction kit and the obtained DNA (B) is mixed with a set of specific primers and incubated under isothermal conditions for 1 h (C). Positive results appear as fluorescence, which is visualized under an ultraviolet lamp (D).

tum, even if the number of bacilli is very low. Only a small amount of extracted DNA is mixed with the set of MTB-specific primers and the amplification reaction is run under isothermal conditions for 1 h in a water bath. The products of the amplification reaction are read by turbidimeter; however, the results can be read also via the naked eyed under an ultraviolet lamp. Hence, LAMP can also be quantitative. In-tube detection of DNA amplification is possible using manganese-loaded calcein, which starts fluorescing upon complexation of manganese by pyrophosphate during in vitro DNA synthesis (Fig. 2) (Tomita et al. 2008). Such conditions are manageable even in disaster situations, when electricity supply is often unavailable, making the LAMP method suitable for the diagnosis of disaster-related infectious diseases. We previously evaluated the reliability of LAMP for detecting MTB in acute pulmonary TB patients from SLH in the city of Manila and successfully confirmed MTB infection in all of the samples from SLH (Shiratori et al. 2014).

LAMP was conducted also for dengue virus infections. Dengue is a mosquito-borne viral disease that has rapidly spread in all WHO regions in recent years. Dengue virus is transmitted by female mosquitoes, mainly the species *Aedes aegypti* and to a lesser extent *Aedes albopictus*. The disease is widespread throughout the tropics, with local variations in risk that are influenced by rainfall, temperature, and unplanned rapid urbanization. Severe dengue, also known as dengue hemorrhagic fever (DHF), was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Today, severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children in these regions. Because of its high prevalence, it is considered one of the representing disaster-related infectious diseases. We have used LAMP to identify dengue genotypes in 27 out of 65 samples (42%). Amongst the 27 patients at SLH who were included in our study, Dengue virus 1, 2, 3, and 4 were found in 13, four, seven, and three patients, respectively (Chagan-Yasutan et al. 2013).

LAMP methods were also used to detect rrs, which is a 16S rRNA gene of the pathogenic *Leptospira spp.*, in urine. The method enables the detection of two leptospiral cells per reaction following boiling of urine specimens. The sensitivity of this method is higher than those of culture or of flaB-nested polymerase chain reactions (Koizumi et al. 2012). The combination of DNA detection and antibody detection will enhance the accuracy for diagnosis of leptospirosis (Iwasaki et al. 2016).

In conclusion, owing to its speed, simplicity, and high sensitivity and specificity, LAMP is attractive as a diagnostics platform in resource-poor settings. The above studies using LAMP gave correct diagnosis of disaster-related infectious diseases and allowed us to study disease specific bio-markers as follows.

Biomarkers for severity and/or resilience

When one suffers from infectious diseases, edema is the most common symptom of the affected organs. Hydrophilic swelling is associated with a reversible increase in cell volume, and exudates are associated with edema. Therefore, edema is constituted of exudates which contain inflammatory cells and fluids. The inflammatory cells and proteins in exudates vary depending on the causes of the inflammation. In 2000, Bornstein proposed that there was a family of secreted extracellular matrix (ECM) proteins that could be linked through their common functionality. He termed these proteins "matricellular" to highlight their influence on cell-matrix interactions. Matricellular proteins (MCPs) are important during wound repair, interact with cell surface receptors, (such as integrins) and are able to bind to growth factors. Based on this definition, several proteins have now been identified as MCPs (Bornstein and Sage 2002), including connective tissue growth factors, thrombospondins (Leask and Abraham 2006), galectins (Elola et al. 2007), and osteopontin (OPN) (Murphy-Ullrich and Sage 2014).

MCPs are secreted into the extracellular environment, or matrix, but do not play a primary structural role in this location. Rather, these proteins modulate cell function by interacting with cell-surface receptors, proteases, hormones, and other bioeffector molecules, as well as with structural matrix proteins such as collagens. The complexity of the functions of most MCPs results from the fact that these functions are, in large part, contextual. In other words, the functions derive from the different structural proteins, cell-surface receptors, proteases, and cytokines with which these

proteins come in contact in the local environment of different tissues. We thought that these proteins could be biomarkers of disaster-related infectious diseases because edema is often associated with inflammation caused by tissue damage, as well as infection.

Hirashima (1999) reported galectin-9 (Gal-9) as eosinophil chemotactic activity. Galectins constitute a family of mammalian lectins that have an affinity for β-galactoside. These proteins are released into the extra-cellular environment under stress conditions including infection, during which they serve as "danger signals" or exert their actions on other cells (Sato et al. 2009). On the other hand, Gal-9 is reported to induce regulatory cells and is produced by them in autocrine matter, indicating that they have immune-regulatory functions (Oomizu et al. 2012). In a collaborative study with SLH, we have been clarifying the role of Gal-9 in dengue virus infection, which is one of the representative mosquito-borne disaster-related infectious diseases. During the critical phase, Gal-9 levels were significantly higher in dengue virus-infected patients than in healthy persons or those with non-dengue febrile illness. The highest Gal-9 levels were observed in patients with DHF than in patients with dengue fever (DF). In the recovery phase, Gal-9 levels significantly declined from peak levels in DF and DHF patients. Gal-9 levels tracked viral load, and were associated with multiple cytokines and chemokines including monocyte frequencies and hematologic variables of coagulation. We proposed that Gal-9 could serve as an important novel biomarker of acute dengue virus infection and reflect disease severity (Chagan-Yasutan et al. 2013). It was also suggested that manipulating Gal-9 signals may have immunotherapeutic potential and could represent an alternative approach for improving immune responses to virus infections and/or vaccines (Merani et al. 2015).

We have examined if another MCP, OPN, is involved in acute virus infections. OPN is a highly phosphorylated and glycosylated MCP and proteolytic cleavage of OPN by thrombin (between Arg168 and Ser169) generates a functional fragment of N-terminal OPN (thrombin-cleaved OPN:trOPN). In dengue virus infection, plasma leakage associated with mild thrombocytopenia is frequently observed in dengue shock syndrome under fatal conditions. It has been reported that the levels of OPN, trOPN, d-dimer, thrombin-antithrombin complex (TAT) protein, and thrombomodulin were significantly elevated in the critical phase in both patients with DF and those with DHF, as compared with healthy individuals. During the recovery phase, OPN levels declined, whereas trOPN levels further increased dramatically in both DF and DHF patients. The OPN level was found to directly correlate with d-dimer and ferritin levels, while the generation of trOPN was positively associated with TAT level, platelet count, and viral RNA load (Chagan-Yasutan et al. 2014). These findings indicate that OPN and trOPN could reflect immuno-coagulation cross-talk and that high trOPN levels could reflect recovery.

Finally, it was found that dengue patients with lower levels of platelets in recovery phase had higher levels Gal-9 in critical phase, while the OPN levels were not different in the same group (Fig. 3). These finding encouraged us to find out the bio-markers which indicate a good prognosis (resilience marker) and these studies are underway.

A recent study showed that involvement of OPN and Gal-9 levels are found in confirmed MTB cases, and suggest that these molecules help to maintain the balance in local immune response, which are important for proper elimination of the bacteria. HS Students from PJU collected samples for this experiment in Indonesia and conducted the experiments at the Department of Disaster-related Infectious Disease, IRIDeS (Hasibuan et al. 2015).

Emerging zoonosis in global warming

Leptospirosis is a zoonotic and disaster-related infectious disease. It is mainly endemic in subtropical or tropical countries and has not been reported since 2009 in the Tohoku region (northern Japan), including in the Yamagata or Miyagi Prefectures. However, we experienced four patients with leptospirosis in the Tohoku region from 2012

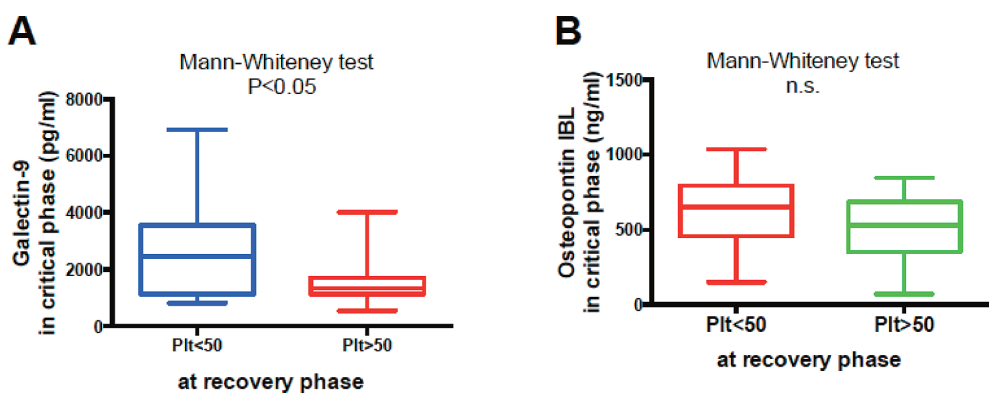

Fig. 3. The correlation of MCP levels in critical phase with platelet counts in recovery phase.
Plasma levels of Galectin-9 (A) and Osteopontin (B) in critical phase of dengue fever of high (> 50) and low (< 50) platelet (Plt) count groups in recovery phase. Plt < 50: below 50,000/μl of platelet counts. Plt > 50: above 50,000/μl of platelet counts. Patients were from the report with Chagan-Yasutan et al. (2013).

to 2014; three patients lived in the agricultural areas of the Yamagata Prefecture and one patient was a visitor to the Miyagi Prefecture. The presence of the three patients in the Yamagata Prefecture implies that leptospirosis has re-emerged in the Tohoku region, probably as a result of global warming (Saitoh et al. 2015). We have not encountered an outbreak of leptospirosis patients after flooding in Japan, but such outbreaks are frequently observed in Manila and many patients are hospitalized in SLH after flood. Leptospirosis is a zoonosis caused by pathogenic *Leptospira spp*. The spectrum of symptoms of leptospirosis is extremely broad. Early and accurate diagnosis of leptospirosis is important for proper and prompt treatment because antibiotic treatment is most effective during the initial course of the disease, and can be life-saving for patients with severe illness (Faine et al. 1999). A total of 5-10% of patients with leptospirosis can potentially develop a severe form of the disease, with fatality rates of more than 10% in Weil's disease and up to 70% in leptospirosis pulmonary hemorrhage syndrome (Gouveia et al. 2008). Flooding and heavy rainfall have been associated with numerous outbreaks of leptospirosis around the world. In the context of global climate change, extreme weather events such as cyclones and floods are expected to occur with increasing frequency and greater intensity. Because these changes involve increased contact with contaminated water, they could potentially result in an upsurge in the disease incidence, as well as in the magnitude of leptospirosis outbreaks (Lau et al. 2010).

In a recent study, leptospires were isolated from almost all of the investigated sites in two of the areas that were hardest hit by Super Typhoon Haiyan. The DNA of pathogenic *Leptospira* species was detected in about half of the soil samples. It was suggested that leptospires are ubiquitous in the Philippines and are soil bacteria. Based on the results of this recent study, it was hypothesized that soil serves as an important reservoir of pathogenic *Leptospira* spirochetes, which may cause outbreaks of leptospirosis during floods caused by typhoons and/or heavy rains (Saito et al. 2014). Therefore, it is expected that walking through mud without protective footwear (for example, during farm work, water-based recreation, or wading after a flood) would place a person at high risk for acquiring infection with *Leptospira*. It should also be mentioned that other infectious diseases can also occur after flooding, including melioidosis. Meliodosis is caused by a gram-negative bacterium, *Burkholderia pseudomallei*, which is found in soil and water. It is of public health importance in endemic areas, particularly in Thailand and northern Australia (Apisarnthanarak et al. 2012). The disease exists in acute and chronic forms. Signs and symptoms may include pain in the chest, bones, or joints; cough; skin infections; lung nodules; and pneumonia. More epidemiological studies are needed to investigate disease spread during disasters.

Conclusions

Research on disaster-related infectious diseases at IRIDeS began with a research and educational partnership with the HS program at Tohoku University. The research against disaster-related infectious disease contributes to the prevention of tropical diseases as well. International cooperation is vital to combating diseases in the era of global warming.

Acknowledgments

This study was supported by a special research grant from the International Research Institute of Disaster Science (IRIDeS) of Tohoku University, as well as a grant from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan for the Joint Research Program of the Research Center for Zoonosis Control, Hokkaido University. The work was also supported in part by the Ministry of Education, Science and Culture (Grants-in-Aid for Scientific Research; Fundamental Research A, Grant Number 23256004, 26257506: Overseas Academic Investigation). The authors are also indebted to the teachers who gave lectures on human security, and all HS course students, patients and volunteers who participated in this study.

Author Contributions

H.C.-Y. and B.S. worked on LAMP and bio-markers of dengue and MTB infection. Y.S., C.N. and T.K. developed LAMP assay. T.N. measured Gal-9, S.E., T. I. contributed to HS education, and E.T. and B.A. collected the samples for research. T.H. organized these studies and wrote a paper.

Conflict of Interest

The authors declare no conflict of interest.

References

Apisarnthanarak, A., Khawcharoenporn, T. & Mundy, L.M. (2012) Flood-associated melioidosis in a non-endemic region of Thailand. *Int. J. Infect. Dis*., **16**, e409-410.

Bornstein, P. & Sage, E.H. (2002) Matricellular proteins: extracellular modulators of cell function. *Curr. Opin. Cell Biol*., **14**, 608-616.

Chagan-Yasutan, H., Lacuesta, T.L., Ndhlovu, L.C., Oguma, S., Leano, P.S., Telan, E.F., Kubo, T., Morita, K., Uede, T., Dimaano, E.M. & Hattori, T. (2014) Elevated levels of full-length and thrombin-cleaved osteopontin during acute dengue virus infection are associated with coagulation abnormalities. *Thromb. Res*., **134**, 449-454.

Chagan-Yasutan, H., Ndhlovu, L.C., Lacuesta, T.L., Kubo, T., Leano, P.S., Niki, T., Oguma, S., Morita, K., Chew, G.M., Barbour, J.D., Telan, E.F., Hirashima, M., Hattori, T. & Dimaano, E.M. (2013) Galectin-9 plasma levels reflect adverse hematological and immunological features in acute dengue virus infection. *J. Clin. Virol.*, **58**, 635-640.

Cooke, G.S., Beaton, R.K., Lessells, R.J., John, L., Ashworth, S., Kon, O.M., Williams, O.M., Supply, P., Moodley, P. & Pym, A.S. (2011) International spread of MDR TB from Tugela Ferry, South Africa. *Emerg. Infect. Dis*., **17**, 2035-2037.

Directorate Epidemiology Cluster, HIMME National Department of Health, South Africa (2013) The 2012 National Antenatal Sentinel HIV & Herpes Simplex Type-2 Prevalence Survey in South Africa.

Elola, M.T., Wolfenstein-Todel, C., Troncoso, M.F., Vasta, G.R. & Rabinovich, G.A. (2007) Galectins: matricellular glycan-binding proteins linking cell adhesion, migration, and survival.

Cell. Mol. Life Sci., **64**, 1679-1700.
Faine, S., Adler, B., Bolin, C. & Perolat, P. (1999) *Leptospira and leptospirosis*. MediSci, Melbourne, Australia.
Gouveia, E.L., Metcalfe, J., de Carvalho, A.L., Aires, T.S., Villasboas-Bisneto, J.C., Queirroz, A., Santos, A.C., Salgado, K., Reis, M.G. & Ko, A.I. (2008) Leptospirosis-associated severe pulmonary hemorrhagic syndrome, Salvador, Brazil. *Emerg. Infect. Dis*., **14**, 505-508.
Guha-Sapir, D., Hoyois, P. & Below, R. (2013) *Annual Disaster Statistical Review 2012: The numbers and trends*, Université catholique de Louvain, Brussels, Belgium.
Hasibuan, F.M., Shiratori, B., Senoputra, M.A., Chagan-Yasutan, H., Koesoemadinata, R.C., Apriani, L., Takahashi, Y., Niki, T., Alisjahbana, B. & Hattori, T. (2015) Evaluation of matricellular proteins in systemic and local immune response to Mycobacterium tuberculosis infection. *Microbiol. Immunol*., **59**, 623-632.
Hattori, T., Usuzawa, M., Egawa, S., Tomita, H., Fukumoto, M., Meguro, K., Oshitani, H., Kaku, M., Kushimoto, S. & Uehara, N. (2012) Human security and disaster medicine; A brief introduction for new collaborating research and education program in Tohoku University. 8th Research Symposium on Multi-Hazards Around the Pacific Rim, Sept. 20-22, Sendai, Japan.
Hirashima, M. (1999) Ecalectin as a T cell-derived eosinophil chemoattractant. *Int. Arch. Allergy Immunol*., **120** Suppl 1, 7-10.
Ishigaki, A., Higashi, H., Sakamoto, T. & Shibahara, S. (2013) The Great East-Japan Earthquake and devastating tsunami: an update and lessons from the past Great Earthquakes in Japan since 1923. *Tohoku J. Exp. Med.*, **229**, 287-299.
Iwasaki, H., Chagan-Yasutan, H., Leano, P.S., Koizumi, N., Nakajima, C., Taurustiati, D., Hanan, F., Lacuesta, T.L., Ashino, Y., Suzuki, Y., Gloriani, N.G., Telan, E.F. & Hattori, T. (2016) Combined antibody and DNA detection for early diagnosis of leptospirosis after a disaster. *Diagn. Microbiol. Infect. Dis*., **84**, 287-291.
Koizumi, N., Nakajima, C., Harunari, T., Tanikawa, T., Tokiwa, T., Uchimura, E., Furuya, T., Mingala, C.N., Villanueva, M.A., Ohnishi, M. & Suzuki, Y. (2012) A new loop-mediated isothermal amplification method for rapid, simple, and sensitive detection of Leptospira spp. in urine. *J. Clin. Microbiol*., **50**, 2072-2074.
Lau, C.L., Smythe, L.D., Craig, S.B. & Weinstein, P. (2010) Climate change, flooding, urbanisation and leptospirosis: fuelling the fire? *Trans. R. Soc. Trop. Med. Hyg*., **104**, 631-638.
Leaning, J. & Guha-Sapir, D. (2013) Natural disasters, armed conflict, and public health. *N. Engl. J. Med.*, **369**, 1836-1842.
Leask, A. & Abraham, D.J. (2006) All in the CCN family: essential matricellular signaling modulators emerge from the bunker. *J. Cell Sci*., **119**, 4803-4810.
Mee, P., Wagner, R.G., Gómez-Olivé, F.X., Kabudula, C., Kahn, K., Madhavan, S., Collinson, M., Byass, P. & Tollman, S.M. (2014) Changing use of traditional healthcare amongst those dying of HIV related disease and TB in rural South Africa from 2003-2011: a retrospective cohort study. *BMC Complement Altern. Med.*, **14**, 504.
Merani, S., Chen, W. & Elahi, S. (2015) The bitter side of sweet: the role of Galectin-9 in immunopathogenesis of viral infections. *Rev. Med. Virol*., **25**, 175-186.
Murphy-Ullrich, J.E. & Sage, E.H. (2014) Revisiting the matricellular concept. *Matrix Biol*., **37**, 1-14.
Ogata, S. & Sen, A. (2003) Foreword. In *Human Security Now, edited by the United Nations Commission on Human Security*, United Nations Commission on Human Security, New York, NY, pp. iv-v.
Oomizu, S., Arikawa, T., Niki, T., Kadowaki, T., Ueno, M., Nishi, N., Yamauchi, A., Hattori, T., Masaki, T. & Hirashima, M. (2012) Cell surface galectin-9 expressing Th cells regulate Th17 and Foxp3+ Treg development by galectin-9 secretion. *PLoS One*, **7**, e48574.
Ross, A.G., Ditangco, R.A., Belimac, J.G., Olveda, R.M., Mercado, E.S., Chau, T.N.P. & Crowe, S.M. (2015) The dire sexual health crisis among MSM in the Philippines: an exploding HIV epidemic in the absence of essential health services. *Int. J. Infect. Dis*., **37**, 6-8.
Saito, M., Miyahara, S., Villanueva, S.Y., Aramaki, N., Ikejiri, M., Kobayashi, Y., Guevarra, J.P., Masuzawa, T., Gloriani, N.G., Yanagihara, Y. & Yoshida, S. (2014) PCR and culture identification of pathogenic Leptospira spp. from coastal soil in Leyte, Philippines, after a storm surge during Super Typhoon Haiyan (Yolanda). *Appl. Environ. Microbiol*., **80**, 6926-6932.
Saitoh, H., Koizumi, N., Seto, J., Ajitsu, S., Fujii, A., Takasaki, S., Yamakage, S., Aoki, S., Nakayama, K., Ashino, Y., Chagan-Yasutan, H., Kiyomoto, H. & Hattori, T. (2015) Leptospirosis in the Tohoku region: re-emerging infectious disease. *Tohoku J. Exp. Med*., **236**, 33-37.
Sato, S., St-Pierre, C., Bhaumik, P. & Nieminen, J. (2009) Galectins in innate immunity: dual functions of host soluble beta-galactoside-binding lectins as damage-associated molecular patterns (DAMPs) and as receptors for pathogen-associated molecular patterns (PAMPs). *Immunol. Rev*., **230**, 172-187.
Senoputra, M.A., Shiratori, B., Hasibuan, F.M., Koesoemadinata, R.C., Apriani, L., Ashino, Y., Ono, K., Oda, T., Matsumoto, M., Suzuki, Y., Alisjahbana, B. & Hattori, T. (2015) Diagnostic value of antibody responses to multiple antigens from Mycobacterium tuberculosis in active and latent tuberculosis. *Diagn. Microbiol. Infect. Dis*., **83**, 278-285.
Shibahara, S. (2011) The 2011 Tohoku earthquake and devastating tsunami. *Tohoku J. Exp. Med.*, **223**, 305-307.
Shiratori, B., Leano, S., Nakajima, C., Chagan-Yasutan, H., Niki, T., Ashino, Y., Suzuki, Y., Telan, E. & Hattori, T. (2014) Elevated OPN, IP-10, and neutrophilia in loop-mediated isothermal amplification confirmed tuberculosis patients. *Mediators Inflamm*., **2014**, 513263.
Siddiqi, U.R., Leano, P.S., Chagan-Yasutan, H., Shiratori, B., Saitoh, H., Ashino, Y., Suzuki, Y., Hattori, T. & Telan, E.F. (2012) Frequent detection of anti-tubercular-glycolipid-IgG and -IgA antibodies in healthcare workers with latent tuberculosis infection in the Philippines. *Clin. Dev. Immunol*., **2012**, 610707.
Tomita, N., Mori, Y., Kanda, H. & Notomi, T. (2008) Loop-mediated isothermal amplification (LAMP) of gene sequences and simple visual detection of products. *Nat. Protoc.*, **3**, 877-882.
United Nations Development Programme (1994) *Human Development Report 1994*, Oxford University Press, New York, NY.
Usuzawa, M., Telan, E., Kawano, R., Dizon, C., Alisjahbana, B., Ashino, Y., Egawa, S., Fukumoto, M., Izumi, T., Ono, Y. & Hattori, T. (2014) Awareness of disaster reduction frameworks and risk perception of natural disaster: a questionnaire survey among Philippine and Indonesian health care personnel and public health students. *Tohoku J. Exp. Med*., **233**, 43-48.
Weiss, R.A. & McMichael, A.J. (2004) Social and environmental risk factors in the emergence of infectious diseases. *Nat. Med*., **10**, S70-76.
World Health Organization (WHO) (2011) Disaster Risk Management for Health, Communicable Diseases. *Global Platform, May 2011*.
http://www.who.int/hac/events/drm_fact_sheet_communicable_diseases.pdf
[*Accessed*: September 11, 2014].