れていた。これは生物テロについても同様な事態を経験しうる可能性が有る。先にも述べたように、先に挙げた開発途上の医薬品を緊急時に使用することを想定した場合、今回のエボラ出血熱発生に伴って設立された厚労省の一類感染症の治療に関する専門家会議でも指摘されているように、「患者又は家族の同意を得るとともに、臨床研究プロトコル等の倫理的、医学的な判断が十分なされた方法に従って実施すべきものである」ことが重要である。治療的使用という側面と研究的側面の中間に位置する使用形態になることが想定される。症例数は限られるであろうから、患者が収容される病院数も限られるだろう。すると、基幹的に対応する病院が共通のプロトコルを事前に組んで緊急時に未承認薬を使用したとしてもデータを迅速に収集できる体制が有用と考えられる。2015年2月に開催された米国微生物学会バイオディフェンス会議では、グラクソスミスクライン社のSedani氏らより、炭疽菌抗毒素であるRaxibacumabについて、吸入炭疽症例が発症した際にフェーズ４スタディとして臨床研究を即座に実施するプロトコルが組まれていることが紹介されていた(Sedani S, et al. Raxibacumab Field Study: A Clinical Study for Rapid Implementation during a Public Health Emergency of Inhalation Anthrax. ASM Biodefense 2015. Feburary 2015, Washington DC, USA.)。このような臨床研究の事前準備体制、また病院間の研究ネットワーク化は、生物テロのみならず比較的稀な新興感染症についても高い汎用性があると考えられる。

○診断薬の必要性

診断については、国際的な連携を基に、ウイルス性出血熱や天然痘など、バイオセーフティ・バイオセキュリティに関わる病原体による感染症の診断システムを整備、改良、維持することが必要であるが、感染研等での最終診断については、整備されていた。一方で、より患者に近いいわゆる「ポイントオブコンタクト（POC）」で使用可能な診断薬やキット、そして大量な検体を捌けるシステムが必要であることが西アフリカでのエボラ出血熱のアウトブレイクから示唆された。

万が一、生物テロ等で患者が急速に増加することがあれば、より患者に近いところでの簡便なスクリーニング法の需要がある。インフルエンザ等で簡易キットが普及しているように、様々な病原体に対して迅速に簡易キットが供給できる体制が整えば、生物テロ発生後の混乱、特に「誰が感染しているかわからない、誰から感染させられるかわからない」といった社会を襲う恐怖感に対抗するために有用であろう。

○研究施設の必要性

日本には稼働が許可されたBSL-4施設がないことから、出血熱ウイルス感染症の診断システム開発において、また、薬剤の動物における感染某業実験の実施等において、海外との共同研究が欠かせず、国際的な研究機関との連携が欠かせないことが明らかである。これまで米国CDC、フランスの国立医学研究所のP4ラボラトリー、中国CDC、ナイジェリア・マイドゥーグリ大学、アルゼンチン・ラブラタ大学等の共同研究を通じて、診断システムおよび研究が実施されてきた。今後も国際的な連携を強化することがもとめられる。

これらの開発された診断システムの一部の診断等における有用性は、Global Health Security Action Groupなどの国際的連携の支援を得て行われている。国際的な研究機関との共同研究だけでなく、GHSAG等の国際的なフレームに積極的に関わっていくことも重要である。これまで本研究班の研究代表者である竹内勤博士が中心となり、日米バイオディフェンス会議が継続的に開催されてきた。今後もこのような連携が必要であることは言うまでもない。

これからはウイルス性出血熱の診断法の開発と整備だけでなく、病態を明らかにする研究、治療・予防法の研究が求められる。BSL-4施設稼働が必要であると考えられることを強調したい。BSL-4施設が稼働していないわが国の現状においてはBSL-4病原体を使用しない代替実験系の確立も研究開発を進める上で重要な課題である。

○米国等海外との共同研究体制の構築

日米バイオディフェンス研究シンポジウムは今回８回目を迎える会議である。米側コーディネーターを米国国立アレルギー・感染症研究所のタカフジ氏、日本側は本研究の業務責任者である竹内勤が務めてきた。回を重ねることによるメリットは、お互いが何を求め、どのような関係者との意見交換に双方にメリットが生じうるかをコーディネーターが理解し、会議での適切なマッチングを行える点にある。特に米側のタカフジ氏は国防総省と保健省に勤務経験があり、豊富な人脈があり、日本側の研究シーズとニーズに理解がある。今回エボラ出血熱を緊急にテーマとして設定したが、共同研究提案につながるディ

スカッッションも生じた。フランス・国立保健科学研究所(INSERM)とのエボラ出血熱対策にかかる共同研究調整会議においては、緊急時に迅速に海外との共同研究枠組みを立ち上げる困難さが明らかであり、事前の共同研究関係の構築は極めて重要であることが明らかであった。

先に述べたBSL4施設を用いた共同研究体制の構築がまず有用だが、さらに日本初のバイオディフェンス医薬品・診断薬の開発を目指すならば、バイオテロに使われる恐れのある病原体が自然発生しやすい途上国で、開発途上だがbesst availableな医薬品を発生時に迅速に治療的提供を行い知見を得るフレームワークに乗れるような協力関係が築かれている必要がある。

○新規技術導入の必要性

生物テロ対策に使用しうる薬剤開発や診断薬開発に資する iPS 細胞を活用したスクリーニング手法の開発は、米国で既に先行しており、我が国においても国内基盤技術としてその試験系の開発が急務である。感染性病原体を扱えない制約があっても、開発に有用な技術を有することで、海外研究機関との連携枠組みに参入し、開発プロセスに関与することができる。感染症研究分野のみならず、iPS 細胞といった日本に強みがある新技術を活用した薬剤開発や診断薬開発手法のバイオセキュリティ分野での応用を検討するべきである。

E．結論

業務項目①、②、③による成果を踏まえ、各種情勢を踏まえ、国内で優先的に開発すべき診断薬や治療薬等についての戦略的提言を検討した。

第一に、生物テロ対策薬剤の開発等としては、他国の開発パイプラインにあり、未承認であっても best available として発生時には使用を検討しうる医薬品・ワクチンについて、国内での臨床開発を進めること、あるいはそれを確実に入手可能な準備を行うこと、かつ、事態発生時にそれを臨床研究のフレームワークの中で迅速に実施する体制を準備しておく必要がある。診断薬としてはより患者に近いところで迅速かつ大量にスクリーニングが行える診断法が求められる。

第二に、医薬品・診断薬のパイプライン開発を進める上での研究インフラとして、国内の BSL4 研究施設稼働は必須である。稼働までの移行期間においては、海外研究機関との密な研究連携枠組みの構築が不可欠である。また、BSL４病原体代替病原体による実験系の構築が有用である。海外研究機関との連携においては、感染症発生時に臨床研究を行えるよう、海外フィールドでの臨床研究協力を視野に入れた連携体制が有用である

第三に iPS 細胞といった新技術を活用した薬剤開発や診断薬開発手法のバイオセキュリティ分野での応用を検討すべきである。

F．研究発表

1.　論文発表

なし

2.　学会発表

Inutsuka T. HiPSC in vitro assay system for biosecurity. 2015 US-Japan Annual Medical Biodefense Research Symposium. 2015年2月. 米国ワシントンDC.

G．知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

III. 学会等発表実績

様式第１９

学　会　等　発　表　実　績

委託業務題目「バイオセキュリティの向上に資する基盤的研究」

機関名：聖路加国際大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
感染症の国際情報共有と国際保健規則	齋藤智也	第13回日本予防医学リスクマネージメント学会学術総会	2015年3月	国内
CBRNテロ対抗医薬品のプリペアドネス	齋藤智也	第20回日本集団災害医学会学術集会	2015年2月	国内
伊豆大島におけるポストパンデミックシーズン（2010/11）の季節性インフルエンザワクチンの有効性（口頭）	齋藤智也、稲益智子、須藤弘二、加藤真吾.	第18回日本ワクチン学会学術集会	2015年12月	国内
国産第三世代痘そうワクチンLC16m8のWHO推奨	丸野真一，金原知美，新村靖彦，横手公幸,齋藤智也,橋爪壮	第18回日本ワクチン学会学術集会	2014年12月	国内
合成生物学とセーフティ・セキュリティ	齋藤智也	新学術合成生物学・WPI地球生命研究所 ワークショップ 「合成生物学と社会」	2014年11月	国内
生物学的脅威に対抗するための医薬品の研究開発：米国の事例を中心に	天野修司、齋藤智也	第55回日本熱帯医学会大会・第29回日本国際保健医療学会学術大会	2014年11月	国内
伊豆大島におけるパンデミック・ポストパンデミックサーベイランスと公衆衛生対応（ポスター）	齋藤智也、出口弘、加藤真吾、稲益智子、藤本修平、市川学.	第73回日本公衆衛生学会	2014年10月	国内
伊豆大島の事例に基づくインフルエンザ感染プロセスと対策のエージェトベースモデル（ポスター）	出口弘、齋藤智也、市川学、藤本修平.	第73回日本公衆衛生学会	2014年10月	国内
薛キョウ、Dung Minh Nguyen、市川学、出口弘、齋藤智也、藤本修平. 感染症予防分野におけるエージェントベースモデルの活用事例（ポスター）	薛キョウ、DungMinh Nguyen、市川学、出口弘、齋藤智也、藤本修平.	第73回日本公衆衛生学会	2014年10月	国内
生物兵器の脅威認識	齋藤智也	テロ対策特殊装備展	2014年10月	国内
クリミア・コンゴ出血熱ウイルスの株間でのシュードタイプウイルスを利用した抗体への反応性の比較	須田遊人，谷英樹，西條政幸，堀本泰介，下島昌幸.	第62回日本ウイルス学会学術集会	2014年11月	国内
Challenges in MCM preparedness for EVD and other occasions in Japan	齋藤智也	2015 US-Japan Annual Medical Biodefense Research Symposium	2015年2月	国外
Rapid and simple detection of ebla viruses	安田二郎	2015 US-Japan Annual Medical Biodefense Research Symposium	2015年2月	国外

HiPSC in vitro assay system for biosecurity	犬塚隆志	2015 US-Japan Annual Medical Biodefense Research Symposium	2015年2月	国外
R&D efforts with antibodies for ebola virus disease	高田礼人、山下武美	2015 US-Japan Annual Medical Biodefense Research Symposium	2015年2月	国外

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Severe Fever with Thrombocytopenia Syndrome in Japan and Public Health Communication	齋藤智也、福島和子、梅木和宣,、中嶋建介	Emerging Infectious Diseases	2015	国外
An Analysis on Risk of Influenza-Like Illness Infection in a Hospital Using Agent-Based Simulation.	D. Minh Nguyen, 出口弘、市川学、齋藤智也、藤本修平.	Public Health Frontier	2014	国外
Development and validation of serological assays for viral hemorrhagic fevers and determination of the prevalence of Rift Valley fever in Borno State, Nigeria.	Bukbuk DN, Fukushi S, Tani H, Yoshikawa T, Taniguchi S, Iha K, Fukuma A, Shimojima M, Morikawa S, Saijo M, Kasolo F, Baba SS.	Trans R Soc Trop Med Hyg	2014	国外
Analysis of Lujo virus cell entry using pseudotype vesicular stomatitis virus.	Tani H, Iha K, Shimojima M, Fukushi S, Taniguchi S, Yoshikawa T, Kawaoka Y, Nakasone N, Ninomiya H, Saijo M, Morikawa S.	J Virol	2014	国外
Safety of attenuated smallpox vaccine LC16m8 in immunodeficient mice	Hiroyuki Yokote, Yasuhiko Shinmura, Tomomi Kanehara, Shinichi Maruno, Masahiko Kuranaga, Hajime Matsui, So Hashizume	Clin. Vaccine Immunol.	2014	国外

（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。

（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

IV. 研究成果の刊行物・別刷

Severe Fever with Thrombocytopenia Syndrome in Japan and Public Health Communication

Tomoya Saito, Kazuko Fukushima, Kazunori Umeki, Kensuke Nakajima

A fatal case of severe fever with thrombocytopenia syndrome was reported in Japan in 2013. The ensuing process of public communication offers lessons on how to balance public health needs with patient privacy and highlights the importance of multilateral collaborations between scientific and political communities.

Severe fever with thrombocytopenia syndrome (SFTS), caused by SFTS virus (SFTSV), was initially identified in China in 2011 (*1*). SFTS manifests with fever, vomiting, and diarrhea accompanied by clinical signs including low platelet and leukocyte counts; the illness can be fatal. The SFTSV vectors, *Haemaphysalis longicornis* and *Rhipicephalus microplus* ticks, inhabit Japan, but the virus had not been detected in ticks in this country, nor had there been a case report of SFTS from Japan. Thus, the public health risk from SFTS was not recognized until a fatal case of SFTS was confirmed in Japan in early 2013 (*2*,*3*).

The Case

At the end of December 2012, a virologist successfully isolated an unknown virus from a clinical sample from a person in Japan who had died of unknown causes. Whole-genome sequencing showed that the isolate's gene sequences were highly similar to those of SFTSV (*4*). The SFTS diagnosis was confirmed by the Japan National Institute of Infectious Diseases (NIID) on January 29, 2013.

On January 30, a rapid communication on the website of the Infectious Agents Surveillance Report (IASR) described this case as the first case of SFTS in Japan (*2*). In addition, health officials from Yamaguchi Prefecture, where the patient resided, and from the Ministry of Health, Labour and Welfare (MHLW) announced the identification at a press conference. On the same day, the MHLW issued a notice requesting that medical doctors voluntarily report suspected cases that fulfilled the interim SFTS case definition (Table). From that date through March 31, a total of 23 suspected cases were reported, blood samples were submitted, and a retrospective study was conducted (*5*). NIID testing confirmed 11 SFTS cases (median patient age 71 years, range 50–84 years), including a case from 2005. Officials from prefectures in which cases were confirmed made public announcements for most of these cases, and the MHLW issued a press release to convey the information nationwide. Clinical details of retrospective cases were reported on the IASR website (*6*,*7*).

Effective March 4, 2013, the MHLW revised the Order for Enforcement of the Infectious Disease Control Act to include SFTS as a class IV infectious disease. These diseases are notifiable, but mandatory hospitalization or restrictions of a patient's activities are not warranted. After that date, the MHLW began to report only the case numbers in each prefecture in the Infectious Disease Weekly Report. New infections were reported starting in April 2013. Descriptions of clinical manifestations for new case-patients were also shared promptly on the IASR website (*8*–*10*).

NIID developed a reverse transcription PCR to detect the Japanese strain of SFTSV, and PCR primers and reagents were distributed from NIID to 79 local public health laboratories by the end of March 2013 to establish country-wide diagnostic capacity. Laboratory results were initially confirmed by NIID, acting in a reference capacity for local laboratories (*11*).

To investigate the epidemiology, pathology, life cycle, countermeasures, and geographic distribution of SFTSV in Japan, the government established a 3-year research project in May 2013. Japan has 47 indigenous tick species, but the specific vectors of SFTSV and their habitats, proportion of virus carriers, and interactions with wild animals are unknown. Systems were developed to detect the SFTSV gene in ticks and SFTS antibodies in animal blood samples (*8*). Results of an interim investigation of ticks and of blood samples from hunting dogs, wild deer, and wild boar suggest that, despite the limited reports of human cases from the western part of Japan, the geographic distribution of virus is more extensive than previously understood (*12*,*13*). *H. longicornis* and *Amblyomma testudinarium* ticks were identified as SFTSV vectors in Japan; however, other species may also be carriers of the virus (*13*).

The initial case of SFTS in Japan attracted substantial public attention, creating the challenge of balancing public health needs with the protection of patient privacy. One of the basic philosophies of the Infectious Disease Control Act is the proactive disclosure of information on the situation, trends, cause, and disclosure of information necessary for prevention and treatment of infectious diseases. At the same time, the Minister of Health, Labour and Welfare and

Author affiliations: Health Service Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan (T. Saito, K. Fukushima, K. Umeki, K. Nakajima); National Institute of Public Health, Saitama, Japan (T. Saito)

DOI: http://dx.doi.org/10.3201/eid2103.140831

Table. Interim case definition for retrospective or prospective voluntary case reports of suspected severe fever with thrombocytopenia syndrome, Japan*

Criteria
Fever >38°C
Gastrointestinal tract symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea, melena)
Thrombocytopenia, $<100 \times 10^9$ platelets/L
Leucopenia, $<4 \times 10^9$ leukocytes/L
Elevated levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase
Absence of other causes
Death or admission to an intensive care unit because of symptoms

*All criteria required for case confirmation.

the governors of local governments must remain mindful of the protection of personal information when disclosing information about cases (Paragraph 2, Article 16, Infectious Disease Control Act). The amount of personal identifying information to disclose must be evaluated on a case-by-case basis and must be consistent with the philosophy of the Act. Some public health plans, such as the Smallpox Preparedness Guideline (*14*), include a press release template, which includes disclosure of sex, age, and municipal area of residence. However, the risk communication guidelines in the Guidelines for Pandemic and New Infectious Diseases do not specify the items of patient information to be disclosed, although, in principle, the area of patient's residence at a municipal level should be disclosed to inform the public of the area(s) in which human-to-human spread is a risk (*15*).

Disclosure of personal information for the initial SFTS case-patient was limited to sex, adult status, and prefecture of residence; this information was limited to respect the wishes of the bereaved family. Age, municipal area of residence, and date of death were not disclosed because of the risk that these variables would result in patient identification. However, the amount of information disclosed about the initial case-patient was criticized at the House of Representatives Budget Committee meeting on April 2, 2013. A House of Representatives member claimed that more detailed information about the patient's area of residence was needed so that the geographic area of risk could be identified and residents could be alerted. The Minister responded by saying that the risk for SFTSV infection was not limited to the area surrounding the patient's residence and that tick bite precautions should be practiced throughout the country.

The case information disclosure policy was tempered as public attention waned; after the first 5 reported cases, the patient's age category was disclosed. Overall, the proportion of publicized SFTSV case reports, including the area of residence of patients at a municipal level, increased from 4/12 (30%) for cases occurring before 2012 to 24/40 (60%) for cases occurring during 2013.

Conclusions

A total of 40 SFTS cases were reported in Japan during 2013, which suggests that underdiagnosis might have occurred before the index case was identified. The success of the initial diagnosis of SFTS in the country was the result of a persistent investigation of a death by unknown causes conducted by hospital clinicians who were not aware that the patient had a history of a tick bite. However, the clinicians consulted an animal viral disease expert for assistance in isolating the causative agent because the clinical picture was a virus-associated hemophagocytic syndrome (Dr. Takahashi and Dr. Ishido, pers. comm.).

Our report shows that multilateral collaborations among investigators, including medical infectious disease specialists, epidemiologists, pathologists, virologists, entomologists, and veterinarians, were required for a timely response to this emerging vector-borne disease. Cooperation from professional organizations such as Dainihon Ryoyukai, a hunters' organization, was crucial for obtaining blood samples from wild animals. Maximizing the use of local government resources is essential for a prompt national investigation (e.g., tick collection and blood sample collection from wild animals). Further collaborative investigation is expected to lead to a better understanding of SFTS and SFTSV in Japan.

Dr. Saito was a deputy director at the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare of Japan at the time of this study. He is currently a chief senior researcher in the Department of Health Crisis Management, National Institute of Public Health, Japan. His primary research interest is biosecurity and public health emergency preparedness.

References

1. Yu X-J, Liang M-F, Zhang S-Y, Liu Y, Li J-D, Sun Y-L, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med. 2011;364:1523–32. http://dx.doi.org/10.1056/NEJMoa1010095
2. Saijo M, Shimojima M, Yamagishi T, Ohishi K, Morikawa S, Hasegawa HA. Severe fever with thrombocytopenia syndrome (SFTS), a new tick-borne virus infection—the first case diagnosed in Japan, 2012 [in Japanese]. Infectious Agents Surveillance Report. 2013;34:40–1.
3. Takahashi T, Maeda K, Suzuki T, Ishido A, Shigeoka T, Tominaga T, et al. The first identification and retrospective study of severe fever with thrombocytopenia syndrome in Japan. J Infect Dis. 2014;209:816–27. http://dx.doi.org/10.1093/infdis/jit603
4. Maeda K. Isolation of severe fever with thrombocytopenia syndrome virus and the recent findings [in Japanese]. Kagakuryouhou no Ryouiki (Antibiotics & Chemotherapy). 2014;30:291–304.
5. National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare. Severe fever with thrombocytopenia syndrome (SFTS) in Japan, 2013. Infectious Agents Surveillance Report. 2014;35:31–2.

6. Saijo M, Shimojima M, Fukushi S, Tani H, Yoshikawa T, Yamagishi T, et al. Two additional severe fever with thrombocytopenia syndrome (SFTS) cases, which were detected retrospectively in Japan [in Japanese]. Infectious Agents Surveillance Report. 2013;34:108–9.
7. Saijo M, Shimojima M, Fukushi S, Tani H, Yoshikawa T, Yamagishi T, et al. Eight cases of SFTS so far confirmed in Japan; a short summary as of March 13, 2013 [in Japanese]. Infectious Agents Surveillance Report. 2013;34:110.
8. Iuchi A, Aono Y, Fukuno H, Asada K, Nagase N, Saijo A, et al. A mild case of severe fever with thrombocytopenia promptly diagnosed after a tick bite [in Japanese]. Infectious Agents Surveillance Report. 2013;34:207–8.
9. Honma Y, Murakami K, Yamamoto C, Kawakami T, Shimizu Y, Yamashita Y, et al. Clinical characteristics of five severe fever with thrombocytopenia syndrome (SFTS) cases including two cases of interfamilial infection, May-July 2013 [in Japanese]. Infectious Agents Surveillance Report. 2013;34:312–3.
10. Takahashi T, Ishido A, Tanaka T, Tanaka S, Inoue Y, Fukushi S, et al. A contact survey of a severe fever with thrombocytopenia syndrome case in a medical facility, 2013—Yamaguchi Prefecture [in Japanese]. Infectious Agents Surveillance Report. 2013;34:269–70.
11. Fukushi S, Yoshikawa T, Tani H, Fukuma A, Shimojima M, Saijo M. Laboratory tests of SFTS [in Japanese] Infectious Agents Surveillance Report. 2014;35:40–1.
12. Morikawa S, Uda A, Kaku Y, Kimura M, Imaoka K, Fukushi S, et al. Geographical distribution of severe fever with thrombocytopenia syndrome (SFTS) cases in Japan (1st report) [in Japanese]. Infectious Agents Surveillance Report. 2013;34:303–4.
13. Morikawa S, Uda A, Kimura M, Fujita O, Kaku Y, Imaoka K, et al. Geographical distribution of severe fever with thrombocytopenia syndrome (SFTS) virus in Japan (2nd report) [in Japanese]. Infectious Agents Surveillance Report. 2014; 35:75–6.
14. Tuberculosis and Infectious Disease Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare. Smallpox preparedness guideline [in Japanese]. 5th edition. May 14, 2004 [cited 2014 Nov 26]. http://www.mhlw.go.jp/kinkyu/j-terr/2004/0514-1/
15. Inter-ministerial Pandemic and Avian Influenza Committee. Guidelines for pandemic and new infectious diseases [in Japanese]. June 26, 2013 [cited 2014 Nov 26]. http://www.cas.go.jp/jp/seisaku/ful/keikaku/pdf/gl_guideline.pdf

Address for correspondence: Tomoya Saito, Department of Health Crisis Management, National Institute of Public Health, 2-3-6 Minami, Wako, Saitama 351-0197, Japan; email: tsaito@niph.go.jp

An Analysis on Risk of Influenza-like Illness Infection in a Hospital Using Agent-Based Simulation

D. Minh Nguyen[1], Hiroshi Deguchi[2], Manabu Ichikawa[3], Tomoya Saito[4], and Shuhei Fujimoto[5]

[1,2,3,4]Department of Computational Intelligence and Systems Science, Interdisciplinary Graduate School of Science and Engineering, Tokyo Institute of Technology, Suzukakedai Campus: 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa, 226-8502 Japan

[5]Department of Bacteriology and Banterial Infection, Division of Host Defence Mechanism, Tokai University School of Medicine, 143 Shimokasuya Isehara, Kanagawa, 259-1193 Japan

[1]nguyen09@cs.dis.titech.ac.jp; [2]deguchi@dis.titech.ac.jp;
[3]ichikawa@dis.titech.ac.jp;[4]ts@biopreparedness.jp;[5]sfujimot@tokai-u.jp

Abstract- **The purpose of the research is to develop a simulation framework to assess the risk of a highly contagious and mortal influenza-like illness infection to health care workers in a hospital under different scenarios of infection control. The method is to build an agent-based model for simulating infection of the virus in the hospital and use an open-source software to visualize a risk graph of infection. The simulation results show a high risk of infection among health care workers who directly take care of inpatients and the evidence of the risk is visualized in the form of graphs. The research contributes to literature by introducing a novel risk assessment method for hospital staff to prepare for an influenza pandemic in the future.**

Keywords- *Nosocomial Infection; HAIs; Infection Control; Agent-based Simulation; Risk Assessment.*

I.INTRODUCTION

Nosocomial infections, also known as hospital-acquired infections (HAI) occurs worldwide and it represents a major source of morbidity and mortality for hospitalized patients [1]. Influenza A virus is among the most severe and frequent causes of hospital-acquired viral respiratory illness and infects persons in all age groups, especially in patients older than 65 years old and children [2]. Influenza can be transmitted between patients and health care workers (HCW) in the hospital setting. Contact with high-risk patients is an important potential source of influenza exposure for HCW. The US Center for Diseases Control (CDC) recommends vaccination and amantadine prophylaxis for HCW, with particular emphasis on patient-care staff. Quarantine measures, including isolating patients who have symptoms of influenza from the others, HCW washing hands and wearing mask and restricting hospital visitors are also recommended [3].

In recent years, with the worldwide spread of severe acute respiratory syndrome (SARS) and the 2009 influenza pandemic, research in infection prevention and control in hospitals become increasingly important. Computer simulation can be an experimental and educational tool for hospital administrators to test strategies for controlling nosocomial infections. A Monte Carlo simulation model was developed for the spread of antibiotic-resistant bacteria in hospital units [4]. Recently, several agent-based simulation models have been used to simulate nosocomial transmission in health care settings [5–8]. Agent-based simulation or agent-based modeling (ABM) is a systems approach, [9, 10] of which the bottom-up architecture can be used as an efficient tool to get macro-level statistical experiment results from micro-level evolution of agent interactions. These models have exploited the advantage of agent-based modeling to evaluate the efficiency of infection control measures against nosocomial infection. Although agent-based modeling is still a relatively new methodology and its application to infectious disease control in only introduced recently, it offers many advantages in integrating real data such as electronic medical record information or sensor information.

Another systems approach that recently gains a lot of interest in epidemiology is social network analysis [11]. A social network for contacts sufficient to transmit influenza has been constructed and analyzed [12]. The usage of contact network analysis is to capture interactions that cause the spread of diseases [13, 14]. Contact network approach is relatively applied in large-scale model (countrywide or global) rather than community level model. Especially, relatively little work exists in applying contact network analysis to nosocomial infection, which is the originality of the current work. Since most of pathogen transmissions in healthcare settings occur via close contact, either between healthcare worker (HCW) or between HCW and patients, the aim of the research is to visualize and detect those contacts.

II.SIMULATION FRAMEWORK

A.Simulation Model

Simulation model was built under several assumptions.

- An agent is autonomous individual which represents a patient or a visitor, a doctor, a nurse of a hospital staff. An agent has the following parameters: sex, age group, job, vaccination status, health condition, and parameters of influenza infection.
- An agent is goal-oriented, having a set of rules of behaviors to achieve its own goal. The rule of behavior depends on his own state. For example, a doctor agent commutes to the hospital at 8pm, takes care of patients and then goes back home at 5pm. Another instance is that if a patient has high fever and cough then he goes to hospital to search for consultation and medical care.
- An agent interacts with other agents in the environment when they exist. The environment is called a "spot". Each spot in the model represents a room in the hospital. For example, a patient agent comes into a consultation room to meet a doctor. After examination, as prescribed by the doctor, the patient agent can be either hospitalized or advised to go home.
- Spot and agent can communicate and exchange information. For example, agent can read the waiting list in reception desk and wait for its own turn.
- Agent is accepted to interact freely with every spot, but direct interactions with other agents are prohibited. The interactions between agents are made indirectly via spots.
- Time of the simulation is modeled in discrete time steps. Each time step lasts for 10 minutes which is considered to be appropriate for modeling human activities in the hospital. The simulation starts at time step zero and proceeds as long as desired, or until all the agents are out of action. The format of simulation time is dd/hh/mm (day/hour/minute).
- The simulation model contains some elements of randomness. For instance, the agents have initial physical condition that is assigned from a random distribution every day in the simulation.

The simulation model is developed with an agent-based simulation language called SOARS (Spot Oriented Agent Role Simulator) [15, 16]. The simulation engine and related built-in functional objects are implemented in Java language.

Figure 1 describes the organizational structure of a typical hospital. The hospital consists of a reception desk, a waiting room, a consultation room, a laboratory, a dispensary, a nurse station, a staff room, a doctor room, a locker room and 4 wards. It is assumed that there are 18 nurses working in 3 shifts a day, 7 doctors working in rotation, 1 clerk, 1 receptionist, 1 examiner, 1 dispenser, 1 cashier and 1 cleaner. Agents' activity pattern is described in Fig. 2.

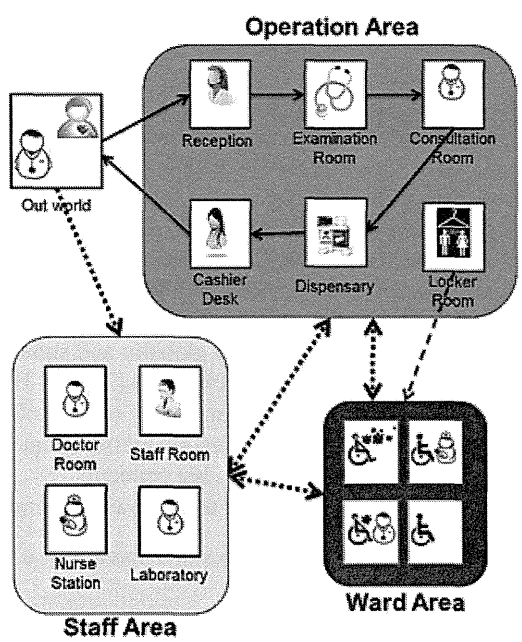

Fig. 1 Struture of an artificial hospital. Arrows illustrate movement directions of agents in hospital. Solid lines illustrate movement directions of patient and visitor agents, dot lines illustrate movement directions of health care worker agents.

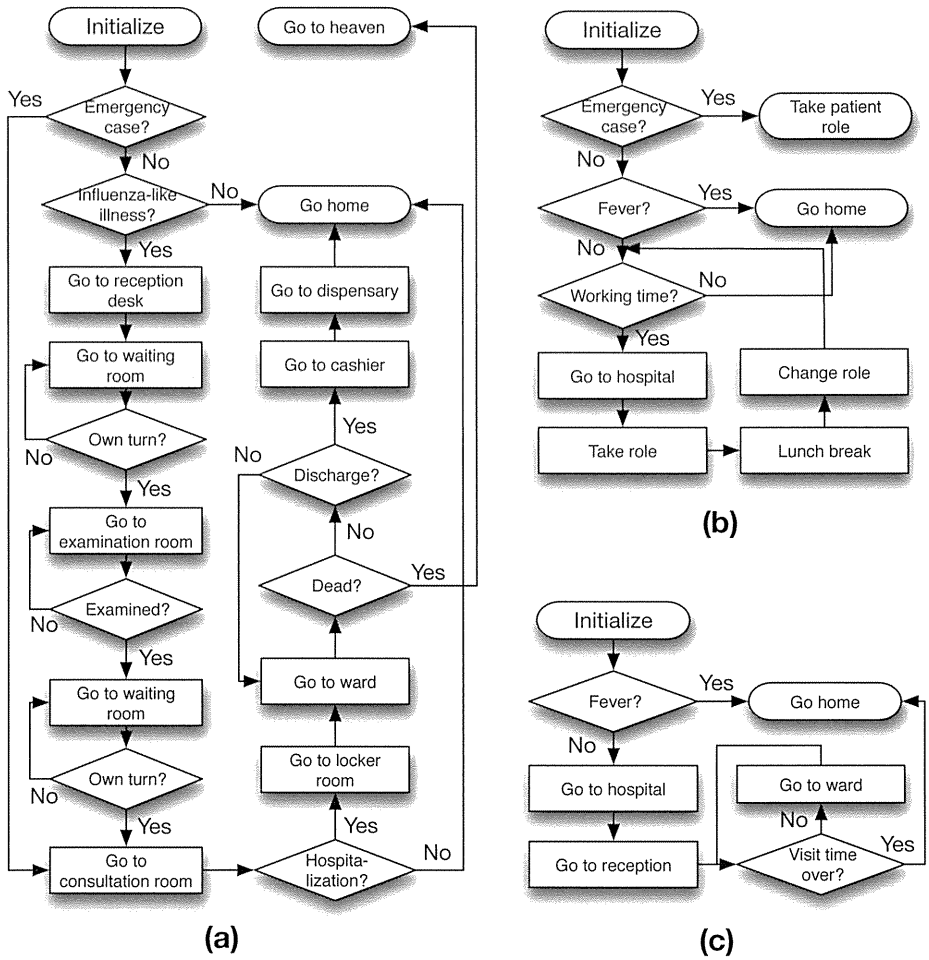

Fig. 2 Flowchart of movement of patients (a) , healthcare workers (HCW) (b) and visitors (c) in the hospital.

B.Infection process modeling

In this study, influenza-like illness (ILI) symptoms are defined as fever (>100 °F) and cough or sore throat. There are three types of infection relevant to influenza are contact transmission, which are droplet transmission, and airborne transmission [17]. Traditionally, influenza viruses are believed to spread from person to person mostly through droplet transmission. These droplets travel only short distances (< 6 feet) and do not stay suspended in the air. Airborne transmission via small particle may also occur. Those particles, in contrast to droplets, can remain suspended in the air. Another indirect transmission envoled with influenza infection is hand transfer from contaminated surfaces to mucous membrane of nose or mouth. However, the percentages of influenza transmission by these three types have not been established yet [18].

Recently emerged swine influenza (H1N1) continues to spread globally and shows a higher transmission than seasonal influenza [19]. Evidence of human to human transmission has been observed [20, 21]. Highly pathogenic avian influenza (H5N1) still exists in poultry worldwide. It rarely infects humans but has mortality of over 60%. Pig is susceptible to both human and avian influenza viruses, so it could serve as a "mixing vessels" in genetic reassortment events [22]. Although the opportunity for genetic reassortment is small, the severity of such rare outcome is a big concern.

In this paper, infection process of the disease is modeled under the following assumptions.

- A novel contagious and deadly influenza-like illness emerges and spreads in a community. It causes an outbreak in the community hospital.
- The virus is transferred via both direct and indirect transmission.
- Influenza virus refers to an acute respiratory virus that causes severe influenza-like illness with cough or sore throat, plus measured fever, shortness of breath and need for hospitalization.
- Current vaccine of seasonal influenza is effective to the new disease.

- For critically ill patients, treatment with oseltamivir within 24 hours of hospitalization reduces mortality.
- For easiness of simulation, we choose a strong pathogen to simulate. However, these parameters can be changed easily to adapt to other pathogens.

The calculation of infection probability based on the interactions of agents within the environment is described below [23]. Define a set of agent i who exits in a set of location (we call "spot") k. Define Agent Virus Excretion Level ($AVEL$) of agent i at time t ($0 \leq AVEL[i](t) \leq 1$) as scale of virus excretion of the agent at the specific time. This parameter depends on the disease state of the agent (See TABLE I). Define Agent Hazard Level of an agent i at time t ($AHL[i](t)$) as the amount of virus excretion of the agent into the environment at the specific time. Then,

$$AHL[i](t) = AVEL[i](t) \times VEP[i](t) \tag{1}$$

, where Virus Excretion Protection ($0 \leq VEP[i](t) \leq 1$) represents the effects of protection measures (e.g., mask wearing) on virus excretion of the certain infected agent. The smaller VEP, the more effective the protection measure is (See TABLE III).

Define Spot Contamination Level $SCL[k](t)$ as the level of virus contamination of a spot k at time t. Contamination level of the spot in the certain time t is the sum of total amount of virus excretion of agents in the spot and the contamination level of the spot at time $(t-1)$.

$$SCL[k](t) = \sum_{i \in Spot[k]} AHL[i](t) + SCL[k](t-1) \times SSL[k](t) \tag{2}$$

, where Spot Sterilization Level ($0 \leq SSL[k](t) \leq 1$) represents the effects of attenuation and sterilization on the certain spot. The smaller SSL, the more effective the protection measure is (See TABLE III).

Define Agent Contamination Level $ACL[i](t)$ as the amount of virus that an agent i has absorbed from the spot k where he stands at the specific time t.

$$ACL[i](t) = ACL[i](t-1) \times AF[i](t) + SCL[k](t) \times VD[k] \tag{3}$$

, where Attenuation Filter ($0 \leq AF[i](t) \leq 1$) represents the effect of attenuation protection on infection (e.g., hand washing) (See TABLE III) and Virtual Density ($0 \leq VD[k] \leq 1$) represents the density of the spot k (the bigger place, the smaller VD).

When an agent i at time t absorbs a significant amount of influenza virus, he will be infected and his state will change from susceptible to infected. The probability of agent i at the time t to get infected is calculated as below.

$$p[i](t) = 1 - \exp[-PC[i](t) \times ACL[i](t)] \tag{4}$$

, where $PC[i](t)$ is the Physical Condition of agent i at time t ($0 \leq PC[i](t) \leq 1$). Physical condition depends on vaccination status, heath condition, age, sex. The healthier agent (smaller PC), the smaller infection probability is. If the agent is immune to the virus, PC is equal to 0, that means probability of infection is equal to 0.

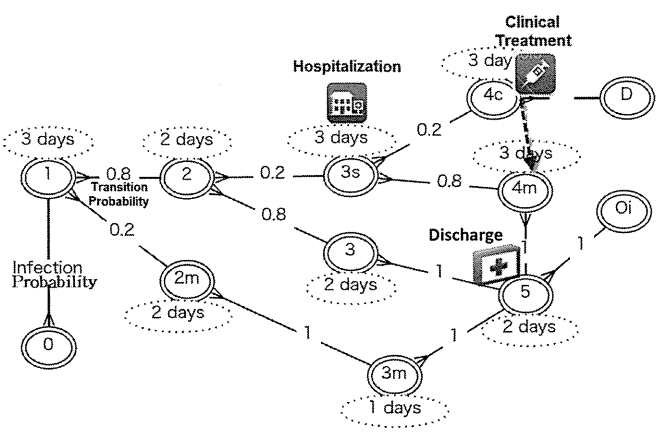

Fig. 3 State transition of influenza-like illness with high contagion, high mortality and clinical pathway for infected patient.

TABLE I Disease state definition and value of Agent Virus Excretion Level ($AVEL$)

Stage	Definition	Fever	$AVEL$
0	Not infected	No	0.0
1	1^{st} stage	Little	0.2
2	2^{nd}stage	High	0.6
2m	2^{nd} mild stage	Little	0.4
3	3^{rd} stage	Little	0.6
3m	3^{rd} mild stage	Little	0.5
3s	3^{rd} serious stage	High	0.6
4c	4^{th} critical stage	High	0.5
4m	4^{th} mild stage	Little	0.5
5	Recovered stage	No	0.0
0i	Recovered with immunity	No	0.0
D	Death	No	0.0

III.SIMULATION PARAMETERS

Simulation parameters are summarized in TABLE II. Simulation is executed in 30 days and repeats 30 times. The simulation program generated 30 files of each log files. The log files contain information on each agent and each spot at each hour in 30 days. The information on each agent included name, job, the place where he is, disease status, immunity status, influenza virus contamination level, probability of infection, etc. The information on each spot included the level of contamination. Simulation log files also included the numbers of outpatients, inpatients, number of influenza infected patient, number of infected HCW, number of visitors, list of infected HCW, list of dead patients, list of dead HCW, list of contacts of each agent, etc. The community structure and hospital structure are set based on health and population statistical data of Vietnamese General Statistics Office. However, these parameters can be changed to adapt to any other community and hospital.

Preventing transmission of influenza virus within healthcare settings is important for hospital management. Spread of influenza virus can occur among patients, HCW, and visitors; in addition, HCW may acquire influenza from persons in their household or community. The fundamental elements of nosocomial influenza infection control include influenza vaccine campaign, respiratory hygiene, monitoring HCW's health, droplet precautions, hand hygiene, environment sterilization and managing visitor access and movement within the facility [18].

Values of parameters for infection control measures are shown in TABLE III. Vaccinating children, adolescents, and young adults seems to be an appropriate vaccination strategy to reduce morbidity of the disease [24]. Based on studies of efficacy comparison of several hand hygiene products [25] and masks [26], we set values for hand hygiene and droplet precaution control measures. Biological efficacy and rate of recontamination (parameter SSL) is adopted from [27].

To study the impact of infection control on nosocomial infection, we vary parameters of infection control in 4 scenarios. Parameters for the four scenarios are summarized in TABLE IV. High Control and High Vaccine scenario represents for the circumstance of hospital with high resource of infection control and vaccination rate in the community is high. Scenario of Low Control and Low Vaccine represents the circumstance of hospital with low level of infection control and vaccination rate in the community is low.

Since simulation model is an abstraction of the real world, each parameter setting corresponds to the set of assumptions made by the model. The strength of simulation is that it can simulate the real world as in a variety of circumstances. Experiments can be set up and repeated many times, using a range of parameters. Those parameter changes can easily be made before the simulation. Scenarios can be duplicated, copied and pasted and modified in instance using experimental setting function of SOARS [16].

TABLE II Description and value of simulation parameter

Simulation parameters	
Simulation time	30 days
Simulation replication	30 times
Time step	10 min
Log time	1 hour
City population structure	
Total population	10,000 people
Age distribution	Proportion
Child: 0- 4 y/o	8.5%
Teenager: 5- 14 y/o	16.5%
Adolescent:15-19 y/o	10.2%
Adult: 20- 34 y/o	26.0%
Middle-aged: 35-59 y/o	29.9%
Elderly: Over 60 y/o	8.9%
Hospital structure	
Number of doctors	7
Number of nurses	18
Number of beds	28
Number of outpatient	Average of 60/day
Number of visitor	Average of 20/day

TABLE III Description and value of infection control parameter

Vaccination Target	(Probability of vaccination)
Child	0.3
Teenager	0.5
Adolescent	0.2
Adult	0.2
Mid-aged	0.15
Elderly	0.1
Vaccinated Population	(Percentage of population)
	High (20%)
	Medium (10%)
	Low (5%)
Mask wearing	(Value of VEP)
No mask	1.0
Surgical mask	0.5
N95 mask	0.1
Hand Hygiene	(Value of AF)
Soap and water	0.62
Alcohol-based hand rubs	0.73
No treatment	1
Environmental Infection Control	(Value of SSL)
No cleaning	0.6
After cleaning	0.4
After HPV decontamination	0.03
Monitor and Manage Ill Healthcare Personnel	Not to go to work, or if at work, to stop patient-care activities, leaving work
Patient Isolation Policy	Isolate critical influenza patients from patients of other diseases and from visitors
Manage Visitor Access	Limit visitors' access. Check visitors' temperature before entering the hospital

TABLE IV Infection control parameter of four scenarios

Scenario Name	**A**	**B**	**C**	**D**
Infection Control	High Control	High Control	Medium Control	Low Control
Vaccinated Population	High Vaccine	Medium Vaccine	Low Vaccine	Low Vaccine
Hand Washing	Soap and water	Soap and water	Alcohol-based hand rubs	No
Mask	N95	N95	Surgical	No
Patient Isolation	Yes	Yes	No	No
Cleaning	Yes	Yes	Yes	No
HPV Decontamination	Yes	Yes	No	No
Vaccinated Population	2000 (20%)	1000 (10%)	500 (5%)	500 (5%)

IV.SIMULATION RESULTS

We demonstrate simulation results by macro and micro analysis. In micro analysis, the number of infected patients and health care workers are observed in one month. Macro analysis is performed by calculating of the amount of virus in spots and in agents, respectively.

A.Macro Analysis

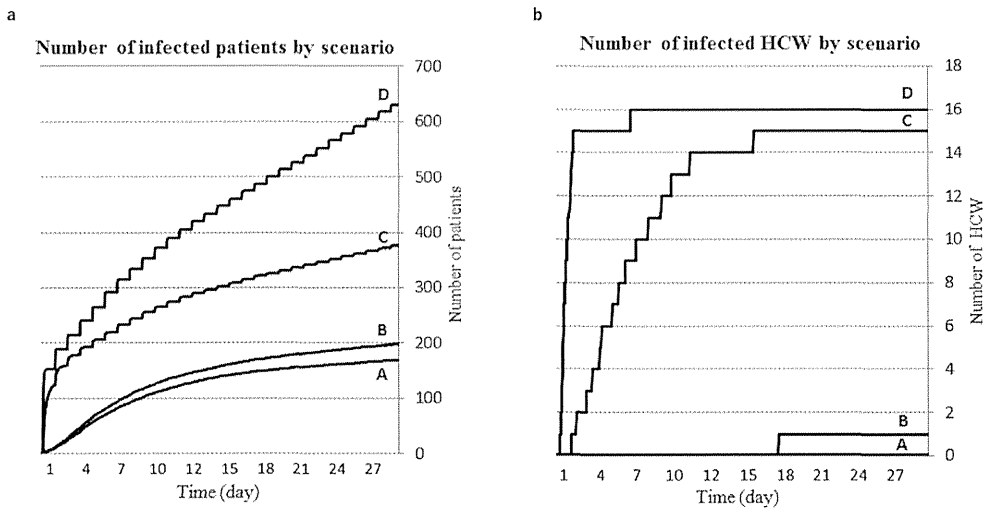

Fig. 4 Variation in average number of infected patients and health care workers (HCW) over time in the four scenarios.

The aggregate number of infected patients and HCW are displayed in Figure 4a and Figure 4b, for each scenario A, B, C, D. In the Figure 4a, the number of infected patients increases rapidly from 168 in scenario A and 198 in scenario B to 377 in scenario C and to 630 patients in scenario D. The relative standard deviations differ from one scenario to another, but converge around 10% in 30 days. The number of infected patients shows an increasing trend after 30 days, however with a considerably lower speed as compared to the high increasing rate at the early stage of the simulation. The infected rate among outpatients for each scenario A, B, C, D is 9%, 11%, 24% and 39%, respectively (the average number of outpatients in scenario A, B is 1800 and in scenario C, D is 1600, respectively). Scenario A and B have the same parameters for infection control but differ in vaccination rate. The simulation results imply that vaccination rate plays an important role in influenza outbreak suppression in the nosocomial environment. Note that the simulation model counts the number of people who get infected within the whole hospital, so these ratios indicate the infection risk level for every patient who is present at the hospital.

In the Figure 4b, the average number of infected HCW increases dramatically from 0 and 1 in scenario A and B to 15 and 16 in scenario C and D. The relative standard deviations of number of infected HCW in scenario A and B were not calculated (since the average number is between 0 and 1). The relative standard deviation of number of infected HCW in scenario C and

TABLE V Infection control parameter of additional scenarios

Scenario Name	**E**	**E - washing hand**	**E - wearing mask**
Hand Washing	Soap and water	No	Soap and water
Mask	Surgical	Surgical	No
Patient Isolation	Yes	Yes	Yes
Cleaning	Yes	Yes	Yes
HPV Decontamination	No	No	No
Vaccinated Population	300 (3%)	300 (10%)	300 (3%)

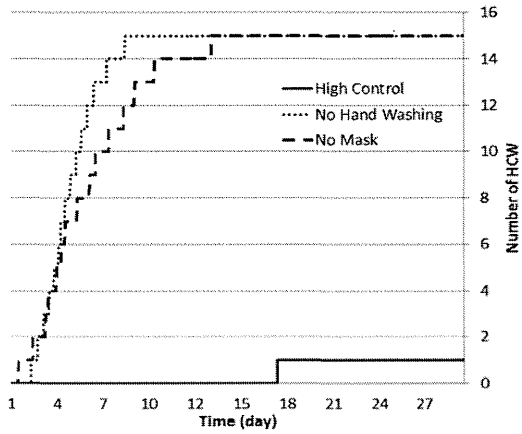

Fig. 5 Variation in average number of infected health care workers (HCW) over time in scenario E, scenario E with no staff washing hand and scenario E with no staff wearing mask.

D converges at 14% and 17%, respectively. The number of infected HCW sees an exponential increase in scenario C and D within 2 weeks but levels off afterwards. The infected rate among HCW is 0%, 3%, 50% and 53% in scenario A, B, C and D, respectively. The simulation results imply that infection control plays a significant role in protecting HCW from nosocomial influenza infection.

To shed more light on which infection control has the most impact on preventing nosocomial influenza in HCW, we have simulated three more scenarios. In these scenarios, same low vaccination rate (3%) was set. In scenario E, high infection control measures were implemented. In scenario "E - washing hand" and "E - wearing mask", staff washing hand and wearing mask control measures were excluded, respectively. The number of infected HCW in each scenario is shown in Figure 5. The result shows that staff washing hand combining with wearing mask could significantly reduce the number of infected HCW.

Although washing hand and wearing mask control measures were recommended worldwide, the extent to which these measures can help prevent influenza transmission has not been firmly established. Recent studies have evaluated the efficiency of those control [28, 29]. The authors agree with the suggestion that use of masks should always be paired with regular hand washing. In the circumstance of limited vaccine availability, using surgical mask and washing hand with soap, which are relatively inexpensive and practical, could be a good strategy in dealing with nosocomial influenza infection.

The main characteristic of simulation model is that the results reflect the chosen parameters. As mentioned in previous section, parameter changes can be made easily before the simulation. The great advantage of simulation model is that they anable experiments which are impossible or undesirable. Although there was no observed data fitted the simulation results, outputs are qualitatively similar to observed phenomenon in the real world.

B.Micro Analysis

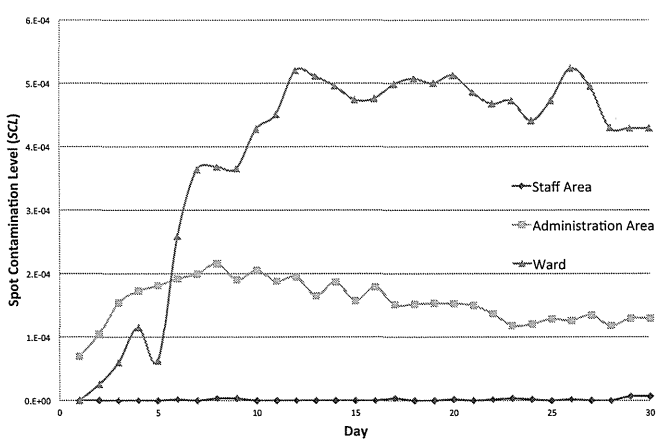

Fig. 6 Variation of Virus Contamination of areas in the hospital in scenario A

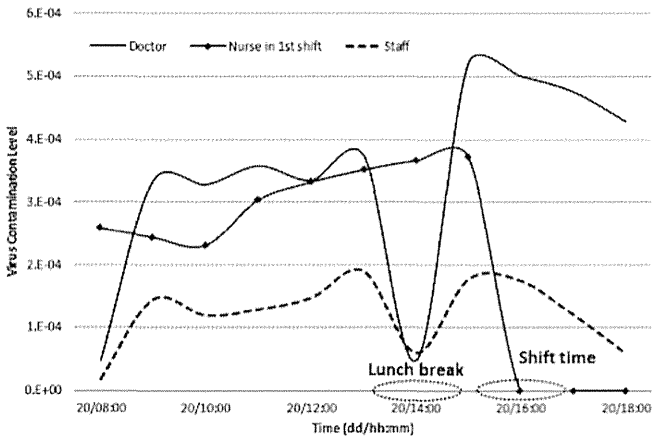

Fig. 7 Variation of virus contamination level of HCW in a working day in scenario A

In section II.B, we have demonstrated the algorithm to calculate the amount of virtual influenza virus existing in spot and agent. Spot Contamination Level at the certain time t is the sum of total amount of virus excretion of agents in the spot and the contamination level of the spot at time $(t-1)$. It depends on the number and the disease condition of infected agents existing in the spot. Figure 6 shows the average contamination level of Ward area, Operation area and Staff area in scenario A of High Control and High Vaccine. The results show that the Ward area is the most contaminated area. The Operation area ranks the second while the Staff area is almost clean. The result implies that wards in hospital are likely contaminated with influenza virus when an outbreak of influenza emerges in the community.

Agent Contamination Level $ACL[i](t)$ is the amount of virus that an agent i has absorbed from the spot k where he stands at the specific time t. The Figure 7 describes the average virus contamination level of doctors, nurses and other staff in working time in 20^{th} day when the number of inpatients reaches its peak in the scenario of A [High Control High Vaccine]. The average virus contamination level of doctors and nurses are higher than those of other staff. This could be explained by the fact that doctors and nurses work in ward area more than other staff. Sharp drops recorded in the contamination level among HCW strongly correlate with daily routines of the HCW concerned. The virus contamination levels of doctors and other staff falls to their troughs at the time of lunch break (from 13:00 to 14:00). The virus contamination level of nurses also decreases rapidly when they change their shift and leave the hospital.

The conclusion of micro analysis is that doctors and nurses, who provide direct care to influenza patients have higher risk of catching influenza virus within the hospital. This conclusion supports long-standing belief in hospital infection control that annual influenza vaccination should be required for every health care worker who have direct contact with patient.

Although the modeling method of infection process described in this paper is still in its development, it provides a flexibility of changing parameters to apply to other diseases rather than influenza-like illness. The computation on dynamical change of virtual influenza virus is innovative in the research field. Even though the computational effort of the modeling method is hard, with the evolution of computing, time execution of the simulation model is constantly reduced.

V.ANALYSIS ON CONTACT NETWORK

The aim of the research is to visualize the infection risk of health care workers in the hospital settings. In order to do that, we analyze the contact network, which is generated by interactions of agents in the simulation of scenario D. We assume that once two agents come into a same spot, one contact is made between them. Each agent carries a contact list of agents who are in the same spot with him at the time t. The contact lists varies by time when agents are moving inside the hospital. The log of contact lists is converted to .csv file in order to be imported to Gephi [30], an open source graph visualization software.

Figure 8 illustrates the visualization of contact network, that we call "risk graph". Each node in the graph represents an agent in the simulation model. Lines in the graph illustrate aggregate of contact between agents the simulation of scenario D. The thicker the line, the more frequent contact between the agents has been made. The size of the node is proportional to the degree, which indicates how many agents he had made contact with. The layout of the graph is Force Atlas, in which the connected nodes are attracted into the center of the graph and unconnected nodes are pushed out off the outside.

Visual conclusions of the risk graph:

- The dispenser, the clerk and the examiner (there is only one dispenser, one clerk and one examiner in the hospital) nodes are the three biggest nodes (in degree). It implies that the three heath care workers have made the most contact with patients. However, most of the contacts were made with outpatients, so the nodes represent them are pulled out off center of the graph.