し、新型インフルエンザの患者もしくは疑われる者についての専門外来として運用する。流行のごく初期の、新型インフルエンザの患者の対応は、感染症指定医療機関や協力医療機関との連携を考慮する。しかしながら、そうした期間は短期であると予想する専門家が多い。

発生段階の第三段階のまん延期に入った場合には、発熱外来において軽症者と重症者のトリアージ（振り分け）により入院治療の必要性を判断する。病床にも限りがあることから、入院適応の基準を作る必要がある。

3．待機可能な医療の提供を一時的に減少させる

第一段階において、慢性疾患を有する定期受診患者については、この段階において定期薬の長期処方をしておく等、患者の状態に配慮しながら、第三段階のまん延期に医療機関を直接受診する機会を減らすよう調整する。

通常の外来、入院、手術件数などの現状を把握する。また、医療機関での待機可能な医療の提供を一時的に減少させるために待機的手術や入院の延期が、どの程度が可能か検討する。具体的には、ある月の手術や入院で１ヶ月から２ヶ月延期できた手術の件数を各科にアンケートを行う。

重症患者の治療を効率的に行うために、地域の他の病院・診療所、長期療養施設と連携し、インフルエンザ以外の患者のうち、引き続き入院加療が必要な者の転院や受け入れの計画を作る。また在宅でのケアの可能性についても家族やケアマネージャーを交えて調整することが必要になる。

透析や産科医療が集約化される可能性もある。こうした地域の医療体制については、保健所を中心として検討がすすめられることになっているので、これに医療機関としても密接に連携しながら対策を講じることが望まれる。

4．診療業務以外の部署の運営を確保する

診療を継続する上では、診療以外の業務が円滑に進むことが必要である。たとえば、事務部門ではカルテの迅速な作成と医療費の管理、警備部門では、混乱により押し寄せる患者やトラブルに対応する必要がある。また、死亡する患者も一時的に増加する可能性がある。死亡した患者も感染源になる可能性があるため、遺体を安置する場所の確保のためにも、地域の葬祭業者との連携が必要になる。患者や職員用の給食を提供する体制やシーツの消毒や清掃も流行時の診療を継続する上では不可欠である。

こうした業務は内部の職員が行う場合もあるが、外部の業者に委託していることも多い。まずはそうした委託をリストアップする。また、現段階でどのように対応をするのかを確認をしておく必要がある。場合によっては、代替の業者も確保するよう努める。その際には代替業者が新型インフルエンザに関しては十分な知識がない可能性があるため、感染予防の対処方法などについても説明し、理解を求めておくことが必要である。

5．診療継続のために確保できる職員数と必要な職員数の差について検討する

これまでの1．から4．によって検討された診療継続のために確保できる職員数とまん延期に必要となる職員数の差を想定し、その差を減らすための方法について検討する。たとえば、退職した職員、地域にいる医療従事者の活用、他の医療機関からの職員の派遣の可能性も考慮に値する。

6．倫理的側面や法的側面を検討する

まん延期には、限られた資源で最大限の効果を得ることが求められる。そうした状況のなかで、倫理的側面や法的側面について課題になることが多い。そのために、ある程度の計画ができた段階で、医療機関での倫理委員会を開催して議論することを検討する。倫理委員会には医療機関外の第三者も交えて行う。

チェックポイント

- ☐ 確保できる職員数を推定する
- ☐ 新型インフルエンザに関連する医療ニーズをできるだけ少なくする
- ☐ 待機可能な医療の提供を一時的に減少させる
- ☐ 診療業務以外の部署の運営を確保する
- ☐ 診療継続のために確保できる職員数と必要な職員数の差について検討する
- ☐ 倫理的側面や法的側面を検討する

アクション5.　職員の健康を管理する

前段階の職員の健康管理としては、1．感染予防策の教育、2．インフルエンザの予防接種の機会の提供、3．妊産婦など感染すると重症化するおそれのある職員を特定できる体制について検討する。

流行時には、医療従事者が感染だけではなく、過重労働やストレスなどによる影響を受ける可能性がある。職員の健康管理は診療継続のための必須条件となるものである。医療従事者自身が自分でケアできるよう必要な知識を提供する。また、専任で対応できる看護師などを配置する。ストレスのケアについては臨床心理士などの活用も検討する。その際、現場のニーズを調整し、可能な限り過剰なストレスに対応できるような支援を行う。

発熱やインフルエンザ様症状のある医療従事者や事務職員は出勤しないようにする。職員は1日2回は体温を測定し、発熱などがあれば健康管理を担当する職員に申し出て、治療の必要性について相談する。症状を呈する人が増加した場合には、医療機関の感染対策が不十分であった可能性も示唆されるため、感染管理について見直しを行う。

チェックポイント

- □ 職員に対して感染やストレスの影響から自分を守れるよう教育する
- □ 流行時の職員の健康管理ができる職員を選任または育成する

アクション６. 職員、関連機関、地域住民との緊急連絡体制を整備する

職員、関連機関との緊急連絡体制を整備しておく必要がある。連絡体制は、医療機関からの発信と、医療機関の受信との双方向が必要である。

連絡体制の整備にあたり、連絡先のリスト作成だけではなく、医療機関内でだれがどういう情報を発信し、受信するかを決めておく。まん延期に人員の確保や調整ができるよう職員との連絡体制を整備しておく必要がある。可能であれば、携帯電話やパソコンのメール機能を活用して、効率よく情報提供ができる体制が望ましい。医療機関の職員が発症したり、家族の都合により来れなくなった場合の連絡を集約できるような院内の担当者も決める。

地域の関連する機関（医療機関、行政機関や関連業者を含む）の緊急連絡体制の整備を行う。たとえば、管轄の保健所、転送可能な長期療養施設、給食業者、医薬品業者などがある。こうした緊急連絡体制は先方の連絡先や担当者が変わる可能性があるため、半年または１年に１回は定期的に見直す。これらは地震などの災害対策として既に地域ごとに取りまとめられている可能性があるので、院内の担当者に確認しておく。

流行が始まると地域住民への情報発信も必要となる。医療機関での発熱外来の設置場所（感染拡大させない動線の周知）や提供可能な医療の現状、場合によってはマスコミの対応も求められる。地域住民に対する情報はインターネットだけではなく、張り紙や地域の民生委員などあらゆる手段を用いて伝達することが必要となるため、地域の行政機関とも連携する。

チェックポイント

- □ 緊急連絡先のリストを作成する
- □ だれがどの情報を発信し、受信するかを決める。また院内での情報を集約する担当者を決める
- □ 地域への情報発信のあり方を検討する

アクション７. 地域の医療機関と行政機関との連携を始める

アクション６においては、連絡体制を整備した。アクション７では連携を始める。これは一つの医療機関だけでは対応が難しいが、まずは新型インフルエンザを機会をみつけて話題にするなど少しずつでも自主的に始めることによって地域での取り組みが進むきっかけとなる。

医療体制に関するガイドラインにおいては、都道府県は、原則として二次医療圏を単位とし、

保健所を中心として、地域医師会、地域薬剤師会、国立病院機構や大学病院等を含む医療機関、薬局、市町村、消防等の関係者からなる対策会議を設置することになっている。こうした対策会議が今後行われる予定であり、医療機関の代表者は積極的に参加することが求められる。

チェックポイント
- □ 地域の医療機関、診療所、長期療養施設などで話題にして連携を始める
- □ 保健所などでの地域の会合の場があるかを確認する

アクション8. 医薬品や必要物品を確保できるか確認する

新型インフルエンザの流行の一つの波は、対策を何もしない場合約2ヶ月続く可能性がある。その間に必要となる医薬品や医療機器（例：静脈注射用ポンプ、人工呼吸器など）や感染防護具（例：マスク、ガウン、手袋など）、手の消毒剤の量を推定し、確保できるようにする。

チェックポイント
- □ 流行時に必要となる物品とその量の推定を行う
- □ 流行時に確保できるよう業者との連携を始める

アクション9. 職員の行動を明確にする

アクション3～8において作成した医療機関としての行動計画を元に、部署や職種ごとの具体的な行動を記した職員用のマニュアルを作成する。職員用のマニュアルも、流行の段階ごとにおいて示す。

作成した後は教育の機会などで周知徹底を行う。マニュアルには、感染防護策と診療継続体制のあり方を示す。マニュアルも最初から完璧なものではなく、アクション10で演習を行い改訂を行う。

チェックポイント
- □ 行動計画をもとにした医療機関の部署や職種の具体的な行動を決める
- □ マニュアルの作成を行い、周知させる

アクション10. 訓練を実施する

診療継続計画やマニュアルをもとに医療機関で訓練の実施を行い、解決できていない課題を明らかにして、継続して検討する。

訓練の例として次の2つをあげる。1．国内において流行が始まって初期の第1例目が地域

で出た場合（第二段階）、2．国内でまん延した場合（第三段階まん延期）である。それぞれのシナリオとして次のものが上げられる。

シナリオ 1.

20XX 年 XX 月 XX 日。アジアのある国で新型インフルエンザの患者が発生したという報道があって 14 日目。日本国内のある地域（医療機関から 300km ほど離れた場所）で新型インフルエンザに感染したと診断された第 1 例目の患者が報告された。国内で第 1 例目が確認されてから 5 日目の今日、あなたの医療機関の地域ではこれまで新型インフルエンザの発生が報告されていなかったが、保健所の設置した発熱相談センターを受診せずに、インフルエンザ様症状を発症した患者が来院していると外来から連絡があった。現在はこの地域では第二段階である。

医療機関としてどのように対応するか？

討論すべきことの例

1．医療機関での意思決定と初期対応
2．保健所や発熱相談センターへの報告
3．患者の治療のあり方
4．地域との連携
5．職員やその他の患者の感染管理
6．報道の対応
7．接触者の確認

シナリオ 2.

国内での第 1 例目の患者が発生して 10 日目。すでにあなたの医療機関の地域でも新型インフルエンザの流行が報告され、すでに第三段階のまん延期に入ったと都道府県も政府も発表した。人口の 5%程度が感染しているという報告もある。

現在、医療機関の病床の 20%が、新型インフルエンザに感染した患者である。

医師も看護師も、そして事務職員も人数は普段の数の 70%程度である。職員の中にも感染した疑いのある者がいるようである。社会はパニックの様相を呈しており、医療機関にも相談の電話が継続してかかっている。死者も数名でており、安置する場所の確保が難しくなっている。（社会の状況は 6 ページのまん延期を参照いただきたい）。

このような状況の中で医療機関が現段階から検討しておくことについて討論せよ。

討論すべきことの例

1．医療機関での意思決定の体制
2．診療継続のための人員確保
3．発熱外来の運営
4．重症患者の治療
5．保健所や発熱相談センターとの連携
6．地域の医療機関との連携
7．職員やその他の患者の感染管理
8．物品の確保
9．関連業者の確保

チェックポイント

☐ 机上または実地演習の実施
☐ さらなる課題の抽出を行い継続して検討する

⑤・おわりに

ワークブックを用いて医療機関での診療継続計画作りを始めることができたであろうか。検討するうちにワークブックで取り上げられなかった項目が課題として多数あがったと思われる。それらについてもさらに今後も継続して検討する。

本ワークブックにおいて取り上げられなかった側面の代表的な面である財務面、倫理的側面、法的側面について簡単に触れる。

財務面については、流行による社会影響によって未収金が多発する可能性がある。職員に対する給与の支払いや医療機関の財務面での影響についても考慮し、キャッシュフローなども確認が必要である。

倫理的側面については、難しい点が多い。特にまん延期においては、限られた医療資源の分配にあたって様々な判断が求められる。WHOの報告書では、「より多くの生命を守るためにはどうしたらよいか」を考え方の基本とすることが示されている。しかしながら、子供と高齢者とどちらを救うかといった選択においては、現段階では十分に示されていない。わが国でもこうした側面について、今後専門家の間で議論を進めることが求められる。

法的側面についても多岐にわたる課題がある。入院患者を可能な限り自宅療養にするような方向性があるが、それによって起こりうる医療過誤の責任や、電話によるトリアージの責任のあり方などが挙げられる。また、その他に労働時間に関しては労働基準法がある。また場合によっては就業規則の見直しも必要である。こうした法的な側面についても今後検討が求められる。

本ワークブックにより、より多くの医療機関が備えを行い、国民の危機ともいえる新型インフルエンザの流行に対して一丸となって対応することで被害を最小限にすることが可能になる。そのためにもこうした備えが必要である。

なお、冒頭に示したようにこうした計画は新型インフルエンザに限らず、その他の新興・再興感染症に関しても適用できるものである。

平成20年度厚生労働科学研究費補助金
「新型インフルエンザ大流行時の公衆衛生対策に関する研究」
（主任研究者：東北大学大学院医学系研究科微生物学分野教授　押谷仁）

編集／和田耕治（北里大学医学部衛生学公衆衛生学）

⑥ 付録 チェックリスト一覧

未対策	対策中	対策済	チェックポイント	担当者又は進行状況
□	□	□	1. 医療機関としての方針と担当組織を設置する □ 医療機関の方針を明記する □ 準備期と流行期の意思決定組織を設置し、メンバーの役割を明確にする	
□	□	□	2. 迅速かつ的確な情報を確保する □ 新型インフルエンザの最新情報を収集する人を選任する □ 関連情報を収集する □ 医療機関で情報を周知する方法を検討する	
□	□	□	3. 受け入れ病床の確認と患者の動線の確保をする □ 全体の病床の10%から20%を新型インフルエンザの重症患者に対応させた場合の病床を確保する □ 確保した病床での人工呼吸器管理の可能性について検討する □ 医療機関の地図に発熱外来の場所や病床までの患者の動線を書き込む	
□	□	□	4. 受け入れ能力を調整する □ 確保できる職員数を推定する □ 新型インフルエンザに関連する医療ニーズをできるだけ少なくする □ 待機可能な医療の提供を一時的に減少させる □ 診療業務以外の部署の運営を確保する □ 診療継続のために確保できる職員数と必要な職員数の差について検討する □ 倫理的側面や法的側面を検討する	
□	□	□	5. 職員の健康を管理する □ 職員に対して感染やストレスの影響から自分を守れるよう教育する □ 流行時の職員の健康管理ができる職員を選任または育成する	

未対策	対策中	対策済	チェックポイント	担当者又は進行状況
□	□	□	6. 職員、関連機関、地域住民との緊急連絡体制を整備する □ 緊急連絡先のリストを作成する □ だれがどの情報を発信し、受信するかを決める。また院内での情報を集約する担当者を決める □ 地域への情報発信のあり方を検討する	
□	□	□	7. 地域の医療機関と行政機関との連携を始める □ 地域の医療機関、診療所、長期療養施設などで話題にして連携を始める □ 保健所などでの地域の会合の場があるかを確認する	
□	□	□	8. 医薬品や必要物品を確保できるか確認する □ 流行時に必要となる物品とその量の推定を行う □ 流行時に確保できるよう業者との連携を始める	
□	□	□	9. 職員の行動を明確にする □ 行動計画をもとにした医療機関の部署や職種の具体的な行動を決める □ マニュアルの作成を行い、周知させる	
□	□	□	10. 訓練を実施する □ 机上または実地演習の実施 □ さらなる課題の抽出を行い継続して検討する	

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Address for correspondence: Peter J.M. Rottier, Virology Division, Department of Infectious Diseases and Immunology, Veterinary Faculty, Utrecht University, Yalelaan 1, 3584 CL Utrecht, the Netherlands; email: p.rottier@uu.nl

Effects of Vaccination against Pandemic (H1N1) 2009 among Japanese Children

To the Editor: We report findings from a household-based study on the protective effects of vaccination against pandemic (H1N1) 2009 among Japanese children. In Japan, prioritized vaccination started in October 2009, focusing on health care workers, pregnant women, persons with underlying diseases, and children 1–9 years of age. Only nonadjuvant split vaccines (inactivated) produced by 4 manufacturers (Denka Seiken, Tokyo, Japan; Kaketsuken, Kumamoto-shi, Japan; Kitasato, Tokyo, Japan; and Biken, Suita-shi, Japan) were used by the end of January 2010 (*1*). Because the protective effects of vaccination at the individual level are best measured by household data (*2*), we conducted a retrospective household survey involving 1,614 nonrandomly sampled households (i.e., based on area sampling of households across Japan, according to the regional population size, with a total of 6,356 household members), in which the earliest cases were diagnosed from October 2009 to mid-February 2010. Our study aimed to assess vaccine-induced reductions in susceptibility and infectiousness among children by using the household secondary attack rate.

Influenza cases were defined as confirmed cases (i.e., diagnosed by real-time PCR) or influenza-like illness (ILI) cases (i.e., in febrile patients [≥37.5°C] with cough and/or sore throat). The cases had to meet the following inclusion criteria for analyses: 1) index case-patient and exposed persons in households were healthy children 1–9 years of age (households with <2 children were excluded), because age-specific susceptibility and infectiousness can greatly influence the frequency of household transmission (*3–6*); b) all exposed persons shared the same household with index case-patients for at least 1 of 7 days after illness onset of the index case-patient; c) index case-patient did not receive treatment with antiviral agents (e.g., zanamivir or oseltamivir) within 2 days after illness onset; d) time interval from illness onset of the index case-patient to that of subsequent case-patients was ≤7 days (*7,8*); and e) vaccinated persons received their first vaccination >28 days before illness onset (if index case-patient) or exposure (if not index case- patient).

In total, 251 children met the above criteria, comprising 109 index case-patients and 133 unvaccinated and 9 vaccinated exposed persons. The mean age was 6.4 ± 2.1 SD years. Among the 251 children, 15 (6.0%) had been vaccinated, and 169 (67.3%) had received a diagnosis of influenza. Confirmed cases accounted for 17.8% (30/169) of cases; 21 patients were the index case-patients in individual households. The mean age of patients with confirmed diagnoses was 6.5 ± 2.0 SD years and did not differ significantly from the ILI patients.

Let SAR_{ij} represent the household secondary attack rate (SAR) with vaccination statuses of the index patient j and exposed persons i (where i or j is 0 or 1 for unvaccinated or vaccinated, respectively), and let b represent both groups. Among 133 exposed unvaccinated children, ILI developed in 59, yielding an SAR_{0b} of 44.4%. Among 9 exposed vaccinated children, ILI developed in 1 child, yielding an SAR_{1b} of 11.1%. The difference between these SARs was marginally significant ($p = 0.08$ by Fisher exact test), and the susceptibility reduction was $1 - SAR_{1b}/SAR_{0b}$ = 75.0% (95% confidence interval [CI] –60.5% to 96.1%). Considering only exposures caused by unvaccinated first patients, SAR_{00} and SAR_{10} were 44.7% (59/132) and 0% (0/4), respectively.

When the first patients with ILI in households were unvaccinated, ILI was observed in 59 of 136 children, yielding an SAR_{b0} of 43.4%. Among 6 exposures caused by vaccinated first patients, ILI developed in 1 person, yielding an SAR_{b1} of 16.7%. Although not significant (p = 0.40), the reduction in infectiousness by vaccination was estimated to be $1 - SAR_{b1}/SAR_{b0}$ = 61.6% (95% CI –132.3% to 93.6%). The SAR_{01} was 0% (i.e., 1 exposure to an unvaccinated person caused by a vaccinated first patient did not result in influenza). Limiting the definition of influenza to confirmed cases, all 8 exposures to vaccinated persons did not result in influenza, and SAR_{0b} and SAR_{1b} were 10.8% and 0%, respectively. Similarly, all 5 exposures caused by vaccinated first patients did not result in confirmed cases, and SAR_{b0} and SAR_{b1} were 10.5% and 0%, respectively.

Although the CIs of the estimates included zero because of the small sample size, the expected reductions in susceptibility and infectiousness were 75.0% and 61.6%, respectively, which is consistent with findings from a meta-analysis of vaccine efficacy against seasonal influenza (*9*). Two limitations must be noted, namely, estimates based on nonrandom samples and a case definition that relied on symptoms of case-patients. The former point cannot be explicitly addressed by a retrospective study design, but we enforced strict inclusion criteria for analyses and limited our study to healthy children. Accounting for the latter point (e.g., serologic diagnosis to capture symptomatic and asymptomatic cases) could yield slightly higher estimates than ours, provided that vaccination reduces the probability of clinical illness if infection occurs. Thus, despite these limitations and a critical need for further studies that include estimations of effectiveness (*10*), our results provide insight into the effects of vaccination in reducing risks for infection and clinical attack among children exposed to pandemic (H1N1) 2009 virus in their households.

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Hiroshi Nishiura and Hitoshi Oshitani

Author affiliations: Japan Science and Technology Agency, Saitama, Japan (H. Nishiura); University of Utrecht, Utrecht, the Netherlands (H. Nishiura); and Tohoku University Graduate School of Medicine, Sendai, Japan (H. Oshitani)

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Address for correspondence: Hiroshi Nishiura, University of Utrecht, Yalelaan 7, Utrecht, 3584 CL, the Netherlands; email: nishiura@hku.hk

Pandemic (H1N1) 2009 Virus in 3 Wildlife Species, San Diego, California, USA

To the Editor: The influenza A pandemic (H1N1) 2009 virus rapidly created a global pandemic among humans and also appears to have strong infectivity for a broad range of animal species (*1–3*). The virus has been found repeatedly in swine and has been detected in a dog, cats, turkeys, and domestic ferrets and in nondomestic animals, including skunks, cheetahs, and giant anteaters (*2–4*). In some cases, animal-to-animal transmission may have occurred, raising concern about the development of new wildlife reservoirs (*2*).

In 2009, the first recognized occurrence of pandemic (H1N1)

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Household Transmission of Influenza (H1N1-2009) in Japan: Age-specificity and Reduction of Household Transmission Risk by Zanamivir Treatment

H Nishiura[1,2] and H Oshitani[3]

[1]PRESTO, Japan Science and Technology Agency, Saitama, Japan; [2]Theoretical Epidemiology, University of Utrecht, Utrecht, The Netherlands; [3]Department of Virology, Tohoku University Graduate School of Medicine, Sendai, Japan

This study investigated household transmission data for influenza (H1N1-2009) in Japan in order to quantify the age-specific risk of infection and estimate the impact of antiviral treatment on the risk of household transmission. Among a total of 1547 households, involving 4609 household contacts, the secondary attack ratio (SAR) was estimated to be 11.4%. School children aged 5 – 18 years dominated the index cases. Age-specific infectiousness and susceptibility were highest among 0 – 4-year olds, with SAR estimated at 19.4% and 29.6%, respectively. Zanamivir treatment within 24 and 24 – 48 h of illness onset in index cases, respectively, reduced the risk of household transmission to 0.57 (95% CI 0.44, 0.73) and 0.58 (95% CI 0.38, 0.86) times that among those receiving the same treatment at > 48 h and those not receiving treatment. The preventive performance of antiviral treatment and prophylaxis should be further examined in randomized controlled trials.

KEY WORDS: Influenza; H1N1-2009; Epidemiology; Pandemic; Antiviral drugs; Neuraminidase inhibitors; Prophylaxis; Oseltamivir; Zanamivir

Introduction

Influenza A (H1N1-2009) virus caused the first pandemic of the 21st Century. Confirmed cases were most frequent among children and adolescents,[1,2] which is believed to reflect age-specificity of transmission and pre-existing immunity in the elderly.[3,4] Although the virulence of this particular strain of the influenza virus appeared to be low, especially among adolescents and young adults,[5] a full understanding of the epidemiological risks of infection and an estimation of the treatment effects are crucial for elucidating the most effective countermeasure strategies to use in the future.

Epidemiological analysis of the specific risk of infection by H1N1-2009, together with statistical estimation of antiviral effects on secondary transmission, present two major

technical challenges. The first is concerned with the difficulty of ascertaining all influenza cases. Although paediatric influenza cases were the most frequently reported, children may be more likely to be tested than adults, and such a biased diagnosis could arise from the frequent formation of school clusters.[6,7] The second challenge is associated with 'dependent happening': because H1N1-2009 is transmitted from human to human, the risk of infection in a single individual is not independent of other individuals in the same population unit.[8] Accordingly, widely used epidemiological measurements of risk (e.g. odds ratio and risk ratio) are not strictly applicable to aggregate population data (e.g. population-based surveillance data).[9] Nevertheless, both these technical problems have been addressed by examining household transmission that conditions the risk of infection on exposure to a household index case and minimizes case ascertainment bias.[10,11]

Several household studies of H1N1-2009 – which identified the younger age groups as having a higher risk of infection than the older age groups, and estimated the preventive effects of antiviral treatment and prophylaxis on household transmission – have been published.[10,12 - 16] Although individuals in younger age groups were shown to be at a higher risk of infection in the early studies of H1N1-2009,[10,14] the sample sizes were small and the age-grouping tended to be crude (e.g. dichotomized into children and adults). Postexposure prophylaxis in households was highly effective in Japan during the early stages of the pandemic;[12] however, these early stages have various confounding factors, such as the containment effort and dramatic variations in contact behaviours within households (e.g. reduced contact with index cases on diagnosis). Antiviral treatment of index cases was demonstrated to be effective, but most published studies focused on oseltamivir treatment, for which the estimated risk reductions of household transmission were only marginally significant.[13 - 15] Findings of the published household studies need to be validated in different population settings and with larger sample sizes.

To provide practical insights into the household transmission of H1N1-2009, the present study aimed to validate the age-specificity of infection and evaluate the effects of antiviral therapy on the risk of household transmission, with particular emphasis on zanamivir treatment among Japanese teenagers.

Patients and methods

CASE DEFINITION

In the present study, influenza cases of H1N1-2009 were defined as either medically diagnosed cases (inclusive of those diagnosed by rapid diagnostic testing and reverse transcription–polymerase chain reaction) or influenza-like illness cases (febrile patients [body temperature ≥ 37.5 °C] with a cough and/or sore throat). Because of the retrospective nature of the household survey, medically diagnosed cases were only allegedly diagnosed at a medical facility. All cases were, therefore, dealt with as a single group of cases throughout the following analyses.

DATA COLLECTION

A retrospective household survey of 1614 non-randomly sampled households in Japan was conducted between May 2009 and February 2010. The household respondents were invited from a Japanese community of research monitors that is used for multiple study purposes. The community has been

formed by respondent-driven sampling and maintained by a commercial research company located in Tokyo. The size of the community varies with time, but always involves more than 10 000 monitors from different households across Japan. The primary conditions for invitation to the survey were that: (i) the household size (total number of household members) was two or more; and (ii) one or more household member(s) experienced symptomatic H1N1-2009 infection between May 2009 and mid-February 2010. Enrolment was based on area sampling of households (one respondent per household) across Japan, according to the regional population sizes. That is, voluntary participation was invited until the number of participants in each region reached a predetermined maximum number proportional to the regional population size. Initially 1614 households with a total of 6536 household members were enrolled. All participants were contacted by the investigators at least twice; additional contact was made when participants had questions or when clarification was required from participants regarding the household transmission status. The respondent from each household received remuneration based on the organizing company's point system. The survey was conducted in real-time during the course of the pandemic, to minimize recall bias, and was completed by the end of February 2010.

In addition to the presence of at least one H1N1-2009 case in the household, eligible households in the present study had to meet the following inclusion criteria: (i) the earliest case was diagnosed between October 2009 and mid-February 2010, to avoid confounding effects of containment efforts during the earlier time period and the summer school holiday in 2009; (ii) all exposed individuals (i.e. household contacts) shared the household with the first (index) case for at least one of the 7 days following illness onset in the index case; (iii) the time interval from illness onset of the index case to that of subsequent cases was ≤ 7 days,[10,16] however, no adjustment of co-primary cases was imposed (i.e. two or more cases infected in the community[17]); and (iv) both the index case and the household contacts were unvaccinated (or vaccinated within 14 days of illness onset in the index case). The protective effect of vaccination among child participants has been assessed and reported elsewhere.[18]

Information on the household size, and age and gender of each household member, was collected. When a participant met the definition of an H1N1-2009 case, they were asked for their earliest date of symptom onset. When an index case underwent antiviral treatment, the name of the antiviral agent and the time from illness onset to the date of first treatment was queried. Similarly, when a household contact undertook antiviral prophylaxis, the time from illness onset in the index case to the first date of prophylaxis was recorded. Following published studies,[13,15] the time delay from illness onset in the index case to prophylaxis or treatment was categorized into one of three groups: (i) within 24 h of illness onset; (ii) 24 – 48 h after illness onset; and (iii) $>$ 48 h after illness onset and those without treatment. Prior to the pandemic, the Japanese government issued a warning that oseltamivir should not be given to teenagers because of reported irrational behaviour among the administered patients (see Discussion).[19] Although this instruction did not restrict the use of oseltamivir among teenagers at high risk of severe disease and although oseltamivir was available in the form of dry syrup for those aged $<$ 10 years, a substantial fraction of school-aged subjects

aged ≥ 10 years undertook treatment and prophylaxis with the alternative antiviral agent, zanamivir.

ETHICAL CONSIDERATIONS

It was explained that enrolment in this study was voluntary and participants were given the explicit right to withdraw at any time. For each household, adult participants were informed of how the information would be used and assured of confidentiality of the responses. Written informed consent was obtained from all adult respondents. No names (only ID numbers) were assigned to each response. Because the survey did not directly impose prevention or treatment and only collected existing information, recorded in such a manner that the subjects could not be identified, the study did not formally involve human subjects and did not, therefore, require approval by a human research ethics committee.

STATISTICAL ANALYSES

The demographic and epidemiological characteristics of the index cases and their household contacts were documented. The secondary attack ratio (SAR), defined as the proportion of infected individuals among household contacts,[20] was analysed in relation to covariates measured at the index case and household contact levels using the univariate Fisher's exact test or the χ^2-test. The 95% confidence interval (CI) of the SAR was computed using the Wilson score method. Subjects were stratified into four discrete age groups: (i) preschool (≤ 4 years old); (ii) school-aged (5 – 18 years); (iii) 19 – 50 years; and (iv) aged ≥ 51 years. Household size was also categorized as (i) ≤ 3, (ii) 4, and (iii) ≥ 5 members.[15] To estimate the univariate and multivariate odds ratio (OR) of infection for each variable among household contacts, a logistic model with a generalized estimating equation was used to account for clustering in households.[21] The serial interval (i.e. the time from symptom onset in an index case to symptom onset in secondary cases[22,23]) was estimated from all index and secondary case pairs. The level of statistical significance was set at $P = 0.05$. All statistical data were analysed using JMP statistical software, version 9.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 1614 households surveyed, 1547 (95.8%) met all of the above criteria to be eligible for inclusion in the analysis, giving a dataset of 1547 index cases and 4609 household contacts. Of the 1547 index cases, 387 (25.0%) were allegedly diagnosed at a medical facility. Of the 4609 household contacts, 524 developed influenza in the household, so the SAR for the entire dataset was estimated to be 11.4% (95% CI 10.5, 12.3). A total of 96 secondary cases (18.3% of all secondary cases) were diagnosed at a medical facility. A comparison of the demographic and epidemiological characteristics between index cases and household contacts is shown in Table 1. Children aged 5 – 18 years dominated the index cases, and the age of the household contacts was significantly older than the age of index cases ($P < 0.01$ for the difference of age distributions, χ^2-test).

The SAR by age group of the index cases reflects the age-specific infectiousness of the index cases and shows a clear age-dependent gradation, with the highest estimate among those aged 0 – 4 years (Fig. 1A). The SAR in this age group was estimated at 19.4% (95% CI 15.4, 24.2). Similarly, the SAR by age group of household contacts, reflecting age-specific susceptibility of the household contacts, was also highest among those aged 0 – 4 years, with the SAR being 29.6% (95% CI 24.8, 34.9) (Fig. 1B). In addition to the

TABLE 1:
Characteristics of the index cases and their household contacts for household transmission of influenza (H1N1-2009) in Japan

Characteristic	Index cases (n = 1547)	Household contacts (n = 4609)
Age, years		
Mean ± SD	16.3 ± 12.3	33.6 ± 18.8
Range	1 – 91	0 – 102
Age group		
0 – 4 years	101 (6.5)	311 (6.7)
5 – 18 years	1045 (67.6)	989 (21.5)
19 – 50 years	369 (23.9)	2690 (58.4)
≥ 51 years	32 (2.1)	619 (13.4)
Gender (male)	798 (51.6)	2196 (47.6)
Diagnosis		
Diagnosed at medical facility[a]	387 (25.0)	96 (18.3)[b]
Influenza-like illness	1160 (75.0)	428 (81.7)[b]
Antivirals[c]	1293 (83.6)	397 (8.6)

Data presented as n (%) unless otherwise stated.
[a]Allegedly diagnosed at a medical facility, inclusive of those diagnosed by rapid diagnostic testing and confirmed by reverse transcription–polymerase chain reaction.
[b]Diagnosis of household contacts counted only those medically diagnosed or those with influenza-like illness (percentage calculations based on n = 524).
[c]For index cases, refers to treatment using antivirals; for household contacts, refers to prophylactic antiviral use.

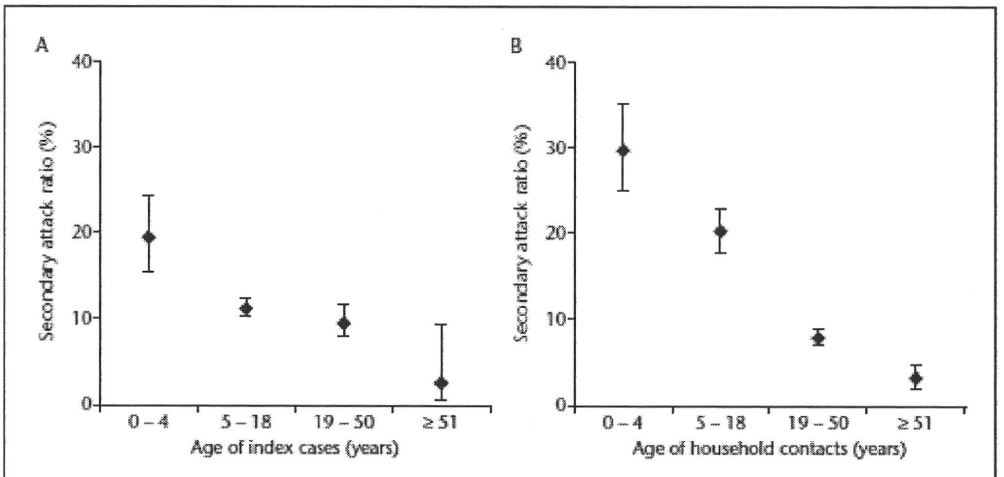

FIGURE 1: (A) Secondary attack ratios (SAR) by age group of index cases indicating age-specific infectiousness of the index cases. (B) Secondary attack ratios by age group of household contacts reflecting age-specific susceptibility of exposed household members. Diamonds represent the sample proportions (mean values) of cases among the total of household contacts; whiskers show lower and upper 95% confidence intervals derived using the Wilson score method

univariate association between age and the risk of household transmission, the 0 – 4 years age group remained the most significant risk factor for infection when multivariate analysis was carried out (Table 2). Household size was not significantly associated with the risk of household secondary transmission (Table 2). Gender was also not significantly associated with infection among all subjects (data not shown), but adult females aged 19 – 50 years were significantly more likely to be infected

TABLE 2:
Secondary attack ratios (SAR) and univariate and multivariate odds ratios (OR) for influenza (H1N1-2009) in household contacts (n = 4609) in Japan

	SAR (95% CI)	Univariate OR[a] (95% CI)	Multivariate OR (95% CI)
Age of index case (years)			
0 – 4	19.4 (15.4, 24.2)	8.55 (2.59, 52.76)	4.00 (1.13, 25.49)
5 – 18	11.3 (10.3, 12.4)	4.53 (1.42, 27.54)	2.39 (0.70, 15.03)
19 – 50	9.6 (7.9, 11.7)	3.77 (1.16, 23.10)	1.99 (0.60, 12.34)
≥ 51	2.7 (0.8, 9.5)	–	–
Age of household contacts (years)			
0 – 4	29.6 (24.8, 34.9)	12.58 (7.73, 21.45)	10.88 (6.63, 18.69)
5 – 18	20.1 (17.7, 22.7)	7.54 (4.83, 12.46)	7.74 (4.90, 12.90)
19 – 50	7.9 (7.0, 9.0)	2.58 (1.66, 4.24)	2.24 (1.49, 3.88)
≥ 51	3.2 (2.1, 4.9)	–	–
Household size			
≤ 3	10.2 (8.3, 12.4)	–	–
4	12.2 (10.9, 13.7)	1.23 (0.96, 1.60)	1.01 (0.84, 1.22)
≥ 5	10.8 (9.4, 12.5)	1.07 (0.82, 1.42)	0.84 (0.68, 1.03)
Oseltamivir prophylaxis[b]			
Within 24 h	10.3 (6.1, 16.9)	1.55 (0.82, 2.70)	1.46 (0.76, 2.57)
24 – 48 h	11.9 (5.2, 25.0)	1.82 (0.62, 4.28)	1.66 (0.56, 3.94)
> 48 h/no usage	6.9 (6.1, 7.8)	–	–
Zanamivir prophylaxis[c]			
Within 24 h	18.5 (8.2, 36.7)	0.81 (0.27, 2.00)	1.06 (0.35, 2.68)
24 – 48 h	20.0 (3.6, 62.4)	0.89 (0.05, 6.06)	1.36 (0.07, 9.40)
> 48 h/no usage	21.9 (19.7, 24.2)	–	–
Oseltamivir treatment[b]			
Within 24 h	5.1 (3.1, 8.2)	0.56 (0.38, 0.82)	0.62 (0.37, 1.02)
24 – 48 h	12.7 (7.6, 20.6)	0.98 (0.54, 1.66)	1.10 (0.56, 2.05)
> 48 h/no usage	7.1 (6.2, 8.1)	–	–
Zanamivir treatment[c]			
Within 24 h	17.3 (13.9, 21.4)	0.57 (0.45, 0.72)	0.57 (0.44, 0.73)
24 – 48 h	17.8 (11.7, 26.1)	0.60 (0.40, 0.87)	0.58 (0.38, 0.86)
> 48 h/no usage	24.4 (21.6, 27.4)	–	–

The 95% confidence interval (CI) of the SAR was derived using the Wilson score method and the 95% CI of OR was computed employing a logistic model involving a generalized estimating equation. Where OR is not shown the variables were used as the baseline.
[a]Univariate OR of antiviral prophylaxis and treatment are age-adjusted.
[b]Prophylaxis and treatment with oseltamivir was mainly among adults (68.9% and 71.7% among total of cases with oseltamivir prophylaxis and treatment, respectively).
[c]Zanamivir was almost exclusively used for teenagers (100% and 96.5% among the total of cases with zanamivir prophylaxis and treatment, respectively).

than adult males in the same age group in households ($P < 0.01$; OR of female to male adults, 2.01; 95% CI 1.49, 2.72).

The SAR was also compared by antiviral prophylaxis and treatment (Table 2). The proportions of subjects aged < 20 years with oseltamivir or zanamivir prophylaxis, among the total household contacts with this prophylaxis (across all age groups), were 31.1% and 100%, respectively. Prophylaxis using oseltamivir or zanamivir did not yield a significant reduction in the risk of household transmission. Only a few per cent of the household contacts taking oseltamivir and zanamivir implemented prophylactic treatment within 24 h of illness onset. The proportions of those aged < 20 years treated with oseltamivir and zanamivir were 28.3% and 96.5%, respectively, among the total household contacts with these treatments (across all age groups). The risk of household transmission among households in which the index cases received oseltamivir treatment within 24 h of illness onset was 0.62 (95% CI 0.37, 1.02) times that among those with the same treatment at > 48 h and those without the treatment. Oseltamivir treatment at 24 – 48 h after illness onset in the index case did not yield a significant reduction in the risk of household transmission. Zanamivir treatment within 24 and 24 – 48 h of illness onset in index cases, respectively, significantly reduced the risk of household transmission to 0.57 (95% CI 0.44, 0.73) and 0.58 (95% CI 0.38, 0.86) times that among those receiving the same treatment at > 48 h and those without the treatment.

The mean ± SD serial interval was estimated as 3.1 ± 1.9 days and the sample serial interval ranged from 0 to 7 days after illness onset in the index case (Fig. 2). The median (lower and upper quartiles) was 3.0 (2.0, 4.0) days. There was no positive correlation or association between the serial interval and the SAR (Pearson's correlation coefficient, –0.04; not statistically significant).

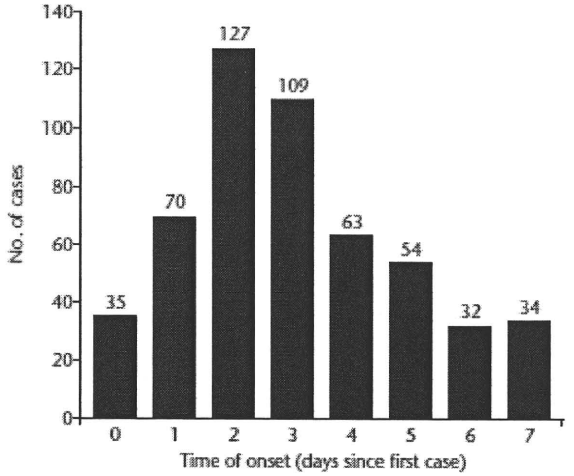

FIGURE 2: Distribution showing the time from illness onset in the index case (day 0) to illness onset in secondary cases in the households ($n = 524$; the potential presence of coprimary cases [first and second cases in the households who were infected in the community[17]] has not been adjusted for)

Discussion

The present study investigated the household transmission data of influenza (H1N1-2009) in 1547 eligible households in Japan. Although the efficacy and effectiveness of antiviral treatment with respect to clinical outcomes have been relatively well assessed among severe cases,[24 - 26] the present survey was conducted because the household study is well suited to assess treatment-induced risk reduction in secondary transmission, explicitly. In agreement with published studies,[10,14] clear age specificities in infectiousness and susceptibility were seen, and both infectiousness and susceptibility were highest among preschool children. The overall SAR was estimated at 11.4% (95% CI 10.5, 12.3), consistent with earlier findings for H1N1-2009 in other countries.[15,16] The finding that early zanamivir treatment among teenage index cases significantly reduced the risk of secondary transmission within households was novel. Zanamivir treatment within 48 h of illness onset in the index case led to a risk reduction of approximately 10 – 60% relative to delayed, or an absence of, zanamivir treatment. Because no estimate of zanamivir-induced risk reduction in household transmission of H1N1-2009 is available,[11,26] the present study gives an important insight into the treatment-driven prevention of household transmission arising from school-aged index cases. The mean serial interval of 3.1 days was consistent with other published estimates.[10]

The present dataset is specific because teenage cases in Japan were almost exclusively administered zanamivir (for treatment), whereas oseltamivir was given to children and adults for either prophylaxis or treatment. Although oseltamivir is available for children aged < 10 years in the form of a dry syrup, and despite the fact that the use of half a capsule of oseltamivir was permitted by the government for school-age children in the midst of the pandemic, there were concerns that oseltamivir treatment in teenagers may cause psychological and neuropsychiatric side-effects that include self-harm in some adolescent patients. Thus, before the pandemic, the Japanese government issued a warning that oseltamivir should not be given to teenagers.[19] This policy offered a unique opportunity to assess the treatment effect of zanamivir only among teenage index cases. The sample size of zanamivir treatment was sufficiently large because of the domination of school-age children among the index cases, permitting the conclusion that zanamivir treatment among teenagers significantly reduced the risk of household transmission.

Although no significant risk reduction of household transmission by antiviral prophylaxis was observed in the present study, caution is required in the interpretation of these results. First, although other studies showed oseltamivir prophylaxis to be efficacious in preventing household transmission,[11,26] it should be noted that, in the present study, oseltamivir prophylaxis was generally only given to adults. Secondly, although prophylaxis, including zanamivir use, was highly effective in Japan during the early phase of the pandemic,[12] this previous study included data from the early pandemic period that involved various disease-control efforts and a school holiday. Thus, such confounding factors might have led to an overestimation of the efficacy of zanamivir. Indeed, the unclear preventive effect of zanamivir prophylaxis is consistent with a systematic review in which the sample size was underpowered.[11] Thirdly, the present study was underpowered to determine significant reductions in the risk of household transmission during antiviral prophylaxis, therefore the findings on the

effects of prophylaxis are limited. Oseltamivir treatment within 24 h was, however, shown to yield an odds ratio of 0.62, which was not statistically significant, but is broadly consistent with published studies.[13,15]

The simple adjustment of the age-effect in the statistical model may not have been enough to correct for confounding factors. This is also a problem when an age-specific treatment strategy is employed. Ideally, in future, study design and sample size estimations of relevant household surveys should account for age-specific strategies of antiviral treatment in addition to age-dependent infectiousness and susceptibility. Two other limitations of the present study were that estimates were based on non-random samples and the case definition relied on symptoms of cases. The former cannot be addressed by retrospective study design, but strict inclusion criteria were enforced for the analysis. Future randomized trials that account for the above-mentioned issues, with an appropriate sample size, are called for.

In conclusion, the present study demonstrated the presence of clear age-specificity in infectiousness and susceptibility in the transmission of influenza (H1N1-2009), and showed that early zanamivir treatment among teenage index cases induced a significant reduction in the risk of household transmission.

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Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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Author's address for correspondence
Dr Hiroshi Nishiura
Theoretical Epidemiology, University of Utrecht, Yalelaan 7, Utrecht 3584 CL, The Netherlands.
E-mail: nishiurah@gmail.com