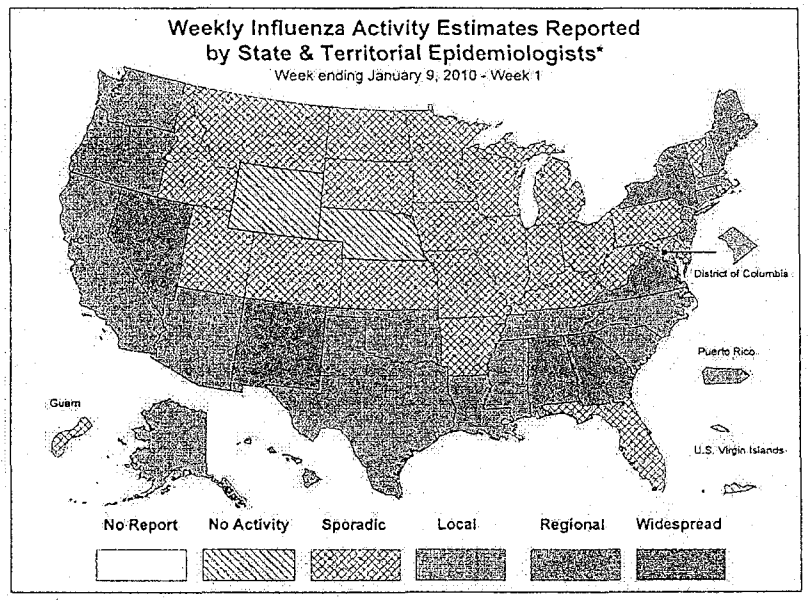
**Geographic Spread of Influenza as Assessed by State and Territorial Epidemiologists:** The influenza activity reported by state and territorial epidemiologists indicates geographic spread of both seasonal influenza and 2009 influenza A (H1N1) viruses and does not measure the severity of influenza activity.

During week 1, the following influenza activity was reported:

- No states reported widespread influenza activity.
- Regional influenza activity was reported by nine states (Alabama, Georgia, Hawaii, Maine, Nevada, New Jersey, New Mexico, New York, and Virginia).
- Local influenza activity was reported by the District of Columbia, Puerto Rico, and 15 states (Alaska, Arizona, California, Connecticut, Louisiana, Massachusetts, Mississippi, New Hampshire, North Carolina, Oklahoma, Oregon, South Carolina, Tennessee, Texas, and Washington).
- Sporadic influenza activity was reported by Guam and 24 states (Arkansas, Colorado, Delaware, Florida, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Michigan, Minnesota, Missouri, Montana, North Dakota, Ohio, Pennsylvania, Rhode Island, South Dakota, Utah, Vermont, West Virginia, and Wisconsin).
- The U.S. Virgin Islands and two states (Nebraska and Wyoming) reported no influenza activity.




* This map indicates geographic spread & does not measure the severity of influenza activity

A description of surveillance methods is available at: http://www.cdc.gov/flu/weekly/fluactivity.htm
Report prepared: January 15, 2010.



別紙様式第2-1

No. 6

# 医薬品 研究報告 調査報告書

| 識別番号・報告回数 | | | 報告日 | 第一報入手日 | 新医薬品等の区分 | 総合機構処理欄 |
|---|---|---|---|---|---|---|
| | | | | 2009. 11. 12 | 該当なし | |
| 一般的名称 | 人血清アルブミン | | 研究報告の公表状況 | ABC Newsletter #38. 2009 Oct 23; 13-14. | 公表国 | |
| 販売名(企業名) | 赤十字アルブミン20(日本赤十字社)<br>赤十字アルブミン25(日本赤十字社)<br>赤十字アルブミン20%静注4g/20mL(日本赤十字社)<br>赤十字アルブミン20%静注10g/50mL(日本赤十字社)<br>赤十字アルブミン25%静注12.5g/50mL(日本赤十字社) | | | | ヨーロッパ | |

| 研究報告の概要 | | | 使用上の注意記載状況・その他参考事項等 |
|---|---|---|---|
| ○EU規制当局はインフルエンザパンデミック時の献血条件緩和を検討<br>欧州連合の血液規制委員会(Blood Regulatory Committee)は、H1N1インフルエンザ・パンデミック時の供給確保のため2つの緩和策を検討していると報告した。ヨーロッパ各国の代表は、パンデミックが深刻化した場合、輸血用血液が10-15%不足するのではと懸念している。血液規制委員会は、ヨーロッパ血液連盟(EBA)や各国の監督官庁に9月末開催の会議への出席を依頼し、血液の安定供給のためにどの基準を緩和するかを検討した。<br>この結果、インフルエンザ様症状回復後の献血延期期間はEU指令では14日間だが、これを7日間に短縮することがドナー確保に大きな効果があると多くの国が評価した。また、ヘモグロビン値を女性12.5g/dL、男性13.5g/dLから女性12g/dL、男性13g/dLにすることについて合意した。 | 報告企業の意見 | 今後の対応 | 赤十字アルブミン20<br>赤十字アルブミン25<br>赤十字アルブミン20%静注4g/20mL<br>赤十字アルブミン20%静注10g/50mL<br>赤十字アルブミン25%静注12.5g/50mL<br>血液を原料とすることに由来する感染症伝播等 |
| 欧州連合の血液規制委員会は、H1N1インフルエンザ・パンデミック時の供給確保のため、インフルエンザ様症状回復後の献血延期期間の短縮とヘモグロビン値の基準の緩和を検討しているとの報告である。<br>インフルエンザは毎年流行をみる最もポピュラーな疾患であるが、本剤によるいかなるインフルエンザウイルス感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれているため、本剤の安全性は確保されていると考える。 | | 日本赤十字社では、問診で発熱などの体調不良者を献血不適としている。更に、平成21年5月18日付薬食血発第0518001号「新型インフルエンザの国内発生に係る血液製剤の安全性確保について」に基づき、新型インフルエンザの患者又は罹患の疑いのある患者と7日以内に濃厚な接触があった人の献血を制限するほか、献血後に新型インフルエンザと診断された場合には当該血漿の使用を禁止している。新型インフルエンザが流行した場合、献血者減少につながることも予想されることから、今後も引き続き情報の収集に努める。 | |

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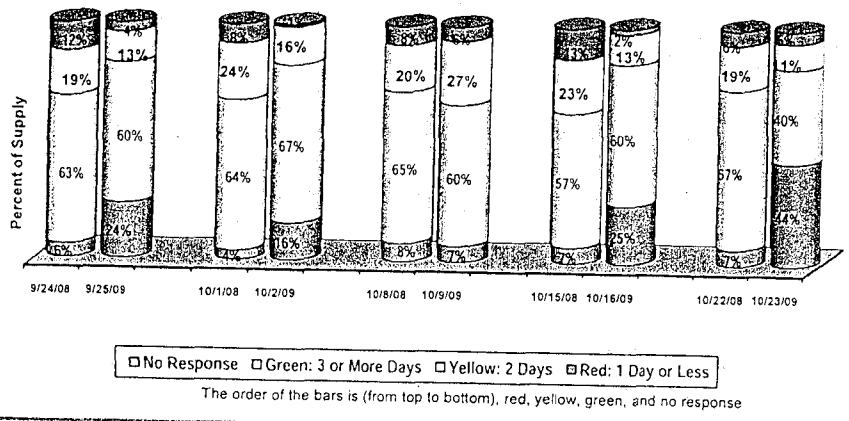
(18)

STOPLIGHT: Status of the ABC Blood Supply, 2008 vs. 2009




The order of the bars is (from top to bottom), red, yellow, green, and no response

## EU Regulator Considers Relaxing Blood Donor Requirements for Flu Pandemic

The Blood Regulatory Committee of DG SANCO, the European regulator for blood requirements, is considering relaxing two of its rules to help assure sufficient blood supplies should an H1N1 flu pandemic create shortages, according to a summary report issued by the committee. Representatives from various European countries and member states are concerned that a severe pandemic could result in a shortage of blood components of up to 10 or 15 percent.

To address this possibility, the committee asked the European Blood Alliance (EBA), the association of national suppliers and regional alliances in Europe, and the national regulators (the so-called "competent authorities" for each European Union [EU] member state or country) to attend a meeting at the end of September to discuss the potential impact of the flu on supply, to consider which rules might be relaxed to maintain an adequate supply, and to gather information from the member states on the measures and contingency plans they are considering in case the blood supply is at risk because an NHIN1 influenza pandemic affects both donors and the staffs of national blood services.

The Blood Regulatory Committee sets standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components. In advance of the meeting, it prepared a working paper providing background information on the following points to be addressed. The paper included:

1. An overview of the potential impact of a pandemic on the blood supply in the EU;
2. Identification of the best ways to correct a potential impact and maintain supply; and
3. An analysis of the potential conflicts between these strategies and the minimum standards for blood and blood components set by the European legislation.

During the meeting, participants were provided with several supporting documents, originating from either member states or the EBA.

(continued on page 14)





EBA Standards (continued from page 13)

Two EU standards were identified as being levers to increase the blood supply on an exceptional and temporary basis in case of a severe shortage. The first involves the deferral period after a potential donor's recovery from a flu-like illness. The EU directive requires that 14 days must elapse between the end of flu-like symptoms in a prospective donor and the donation. Most member states said that reducing this deferral to seven days would have a major effect on accepting donors during a pandemic.

The member states and the committee agreed to request a risk assessment from the European Centre for Disease Control and Prevention on the impact of reducing this deferral period from 14 days to seven or even five days.

In terms of acceptable hemoglobin levels in donors prior to donation, current EU rules state thresholds of 12.5 grams per deciliter (g/dL) for women and 13.5 g/dL for men. There was a consensus among the delegates to the meeting that for a pandemic, these levels could be reduced to 12 and 13 g/dL, respectively, without putting the health of the donors at risk.

**FDA prefers to defer decisions.** When a similar meeting was held earlier this year with officials from the FDA Centers for Biologics Research and Review and representations of various blood organizations, FDA said it prefered not to address "theoretical" questions on donor criteria. It said it would consider such issues as needed. (Source: Blood Regulatory Committee, Summary Report, 9/29/09) ♦

## PEOPLE

**Elizabeth G. Nabel** will be leaving her current position as director of the National Heart Lung and Blood Institute (NHLBI) at the National Institutes of Health to become the next president of Brigham and Women's Hospital and Faulkner Hospital in Boston, the two medical centers announced on Thursday. She will start the new job on January 1, 2010, when the hospitals' current president, **Gary Gottlieb**, becomes president and chief executive of Boston's Partners HealthCare, the parent organization of the two medical centers and Massachusetts General Hospital. He is replacing **James Mongan**, who will be retiring at the end of the year. Nabel, a cardiologist who graduated from Cornell University Medical College, has served at Brigham and Women's before: she completed her internship and residency in internal medicine there, as well as a clinical and research fellowship in cardiovascular medicine. She served on the faculty at the University of Michigan in the 1990s, and she joined NHLBI in 1999.

CORRECTION: An article in the Oct. 16, 2009, *ABC Newsletter* misstated the relationship between Tom and Sue Zuck. She is his wife. We apologize for the mistake. ♦

### Save the Date: FDA Workshop on Emerging Arboviruses

The blood banking community has learned that the Food and Drug Administration will be holding a workshop on emerging arboviruses and recipient safety on Dec. 14-15, 2009 at the National Institutes of Health in Bethesda, Md. The official announcement will be made in the next few weeks. Pre-registration for this free workshop will be required, and forms will be available at the time of the announcement.

別紙様式第2-1
番号11

医薬品
医薬部外品　研究報告　調査報告書
化粧品

| 識別番号・報告回数 | | | 報告日 | 第一報入手日<br>2010年3月8日 | 新医薬品等の区分<br>該当なし | 厚生労働省処理欄 |
|---|---|---|---|---|---|---|
| 一般的名称 | 乾燥濃縮人アンチトロンビンIII | | 研究報告の公表状況 | Clinical Infectious Diseases 2010; 50(5): 672-678 | 公表国<br>オーストラリア | |
| 販売名<br>(企業名) | ①ノイアート静注用500単位（ベネシス）<br>②ノイアート静注用1500単位（ベネシス）<br>③ノイアート（ベネシス） | | | | | |

**研究報告の概要**

背景
パンデミック2009インフルエンザA型ウイルス(H1N1)の重症感染は、妊娠、肥満、および免疫抑制を含むリスクファクターと関連している。重症の1例で免疫グロブリンG2(IgG2)欠損が同定されたことを受けて、我々はH1N1感染患者のコホートでのIgGサブクラスのレベルを調べた。
方法
H1N1の急性で重症の感染患者(集中治療室での呼吸のサポートを必要とする感染と定義した)、中等度のH1N1感染患者(入院患者だが集中治療室へは収容されていない患者と定義した)、および健康な妊娠女性からランダムにサンプリングした被験者を対照として、患者および対照の血清IgGおよびIgGサブクラスのレベルを含む特性を調べた。
結果
H1N1感染した39例の患者(重症感染が19例、そのうち7例が妊娠中；中等度感染が20例でそのうち2例が妊娠中)のうちで、低アルブミン血症(P<0.001)、貧血(P<0.001)、および総IgG(P=0.01)、IgG1(P=0.022)、IgG2(19例中15例 vs. 20例中5例；P=0.001；平均値±標準偏差[SD]，1.8±1.7 g/L vs. 3.4±1.4 g/L；P=0.003)が低レベルであったことは、統計学的に有意に重症H1N1感染と関連していたが、多変量解析で統計学的に有意であったのは低アルブミン血症(P=0.02)と平均のIgG2レベルが低値であったこと(P=0.043)のみであった。IgG2欠損患者で生存していた15例(79%)のフォローアップを急性期の最初の検体採取後、平均(±SD)で90±23日目(範囲は38-126日目)に行ったところ、低アルブミン血症は大多数の症例で解消していたが、15例中11例(73%)の患者ではIgG2欠損はそのままであった。対照の健康な妊娠女性17例では、10例で軽度のIgG1および/またはIgG2レベルの低値が認められたが、H1N1感染のあった妊娠患者ではIgG2レベルが有意に低かった(P=0.001)。
結論
重症H1N1感染はIgG2の欠損と関連し、それは患者の多くで持続性となるものと考えられる。IgG2レベルの妊娠に関連した低下が、妊娠女性の全てとは言えないまでもいくらかの比率でH1N1感染の重症度が増加することを説明するものかもしれない。H1N1感染の発症機序におけるIgG2欠損の役割を知るにはさらに研究が必要であるが、それはこのことが治療上意義を有する可能性があるからである。

使用上の注意記載状況・その他参考事項等

代表としてノイアート静注用500単位の記載を示す。
2. 重要な基本的注意
(1)本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-I抗体陰性で、かつALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohnの低温エタノール分画で得た画分から人アンチトロンビンIIIを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

| 報告企業の意見 | 今後の対応 |
|---|---|
| パンデミック2009インフルエンザA型ウイルス(H1N1)重症感染と血清中のIgG2低値は関連しているとの報告である。<br>インフルエンザA(H1N1)はオルソミクソウイルス科に属し、ビリオンは球形で、直径80～120nmの脂質エンベロープを有する比較的大きなRNAウイルスである。万一、インフルエンザA(H1N1)が原料血漿に混入したとしてもBVDをモデルウイルスとしたウイルスバリデーション試験成績から、製造工程にて十分に不活化・除去されると考えている。 | 本報告は本剤の安全性に影響を与えないものと考えるので、特段の措置はとらない。 |

(19)

アンチトロンビンIII





# Association between Severe Pandemic 2009 Influenza A (H1N1) Virus Infection and Immunoglobulin $G_2$ Subclass Deficiency

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*Background.* Severe pandemic 2009 influenza A virus (H1N1) infection is associated with risk factors that include pregnancy, obesity, and immunosuppression. After identification of immunoglobulin $G_2$ ($IgG_2$) deficiency in 1 severe case, we assessed IgG subclass levels in a cohort of patients with H1N1 infection.

*Methods.* Patient features, including levels of serum IgG and IgG subclasses, were assessed in patients with acute severe H1N1 infection (defined as infection requiring respiratory support in an intensive care unit), patients with moderate H1N1 infection (defined as inpatients not hospitalized in an intensive care unit), and a random sample of healthy pregnant women.

*Results.* Among the 39 patients with H1N1 infection (19 with severe infection, 7 of whom were pregnant; 20 with moderate infection, 2 of whom were pregnant), hypoalbuminemia ($P < .001$), anemia ($P < .001$), and low levels of total IgG ($P = .01$), $IgG_1$ ($P = .022$), and $IgG_2$ (15 of 19 vs 5 of 20; $P = .001$; mean value ± standard deviation [SD], 1.8 ± 1.7 g/L vs 3.4 ± 1.4 g/L; $P = .003$) were all statistically significantly associated with severe H1N1 infection, but only hypoalbuminemia ($P = .02$) and low mean $IgG_2$ levels ($P = .043$) remained significant after multivariate analysis. Follow-up of 15 (79%) surviving $IgG_2$-deficient patients at a mean (± SD) of 90 ± 23 days (R, 38–126) after the initial acute specimen was obtained found that hypoalbuminemia had resolved in most cases, but 11 (73%) of 15 patients remained $IgG_2$ deficient. Among 17 healthy pregnant control subjects, mildly low $IgG_1$ and/or $IgG_2$ levels were noted in 10, but pregnant patients with H1N1 infection had significantly lower levels of $IgG_2$ ($P = .001$).

*Conclusions.* Severe H1N1 infection is associated with $IgG_2$ deficiency, which appears to persist in a majority of patients. Pregnancy-related reductions in $IgG_1$ level may explain the increased severity of H1N1 infection in some but not all pregnant patients. The role of $IgG_2$ deficiency in the pathogenesis of H1N1 infection requires further investigation, because it may have therapeutic implications.

Since the onset of the current novel influenza A (H1N1) virus pandemic, it has been recognized that certain risk factors, such as pregnancy, obesity, and immunosuppression, are associated with severe disease [1, 2]. In Victoria, Australia, which was one of the key regions for the H1N1 pandemic in the Southern Hemisphere [3, 4], such risk factors have been frequently observed in our sickest patients, but the explanation for this association has remained elusive [5].

We identified immunoglobulin $G_2$ ($IgG_2$) subclass deficiency in 1 young pregnant patient who had an unusual presentation with severe H1N1 infection that required intensive care unit (ICU) admission. Because of this observation, we systematically assessed total IgG and IgG subclasses in all patients with H1N1 infection requiring ICU care (many of whom were pregnant) and

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DOI: 10.1086/650462

compared these results with those obtained from all inpatients with less severe H1N1 infection (ie, those patients who did not require ICU admission), as well as a random sample of healthy pregnant women who presented for routine antenatal care.

## METHODS

The study was initially undertaken at Austin Health (AH), a tertiary university teaching hospital in Melbourne, Australia. After the observation of $IgG_3$ deficiency in a patient with H1N1 infection, all patients with polymerase chain reaction (PCR)–proven H1N1 infection who were sufficiently unwell to require admission to AH underwent routine hematological and biochemical assessment, had their serum immunoglobulin levels and subclasses determined, and were reviewed for their clinical features, demographic characteristics, and treatment outcome. Acute-phase serum samples were either assessed prospectively or were retrieved from storage for analysis; patients for whom there were no appropriate stored serum samples were noted but not included in the study. Because of the potential therapeutic implications of our initial findings, and after discussions with the Department of Human Health Victoria, we subsequently broadened recruitment to 2 other hospitals in Victoria (Royal Melbourne Hospital [RMH] and Bendigo Health [BH]), which were actively managing patients with severe H1N1 infection and had ICU admission criteria that were similar to those at AH, to obtain similar acute-phase serum specimens and clinical details.

The following definitions were used for the study: patients with severe H1N1 infection were defined as those with confirmed H1N1 infection who required admission to the ICU for respiratory (invasive or noninvasive mechanical ventilation) and/or vasopressor support, whereas patients with moderate H1N1 infection were defined as those who required hospital inpatient (but not ICU) care. Community-acquired pneumonia was defined according to the Infectious Diseases Society of America guidelines [6].

The clinical and laboratory features of patients with severe H1N1 infection at the 3 recruitment sites (AH, RMH, and BH) were compared with those of patients with moderate H1N1 infection (AH). All patients who were found to be IgG subclass deficient during their acute illness were followed up to obtain convalescent immunoglobulin and IgG subclass levels to assess whether the identified deficiency was transitory or persistent.

Because a large number of our patients with severe H1N1 infection were pregnant, we investigated the immunological status of a random sample of healthy pregnant women to compare these results with those observed among pregnant women with moderate and severe H1N1 infection. Thus, we obtained serum samples from 15–20 healthy pregnant women who had antenatal outpatient visits at the Mercy Hospital for Women (Melbourne, Australia) on 19 or 20 July 2009.

All data were summarized and analyzed according to H1N1 infection severity (severe vs moderate), presence of pregnancy, and, if the patient was pregnant, presence of H1N1 illness (patients with H1N1 infection vs healthy control subjects). Ethics committee approval was obtained at all 4 participating centers that undertook the study.

*Laboratory assays.* The presence of H1N1 infection was confirmed by strain-specific PCR at the Victorian Infectious Diseases Reference Laboratory and World Health Organization Influenza Reference Laboratory (Melbourne, Australia) using standard H1N1 assays.

Serum immunoglobulins (IgG, IgM, and IgA) were assessed using both a Beckman IMMAGE 800 analyzer (Beckman Coulter) and an Abbott Architect ci8200 analyzer (Abbott Laboratories, Abbott Park) in accordance with the manufacturers' instructions. Similarly, immunoglobulin subclasses ($IgG_1$, $IgG_2$, $IgG_3$, and $IgG_4$) were measured using Binding Site Human IgG Subclass kits on a Beckman IMMAGE 800 analyzer in accordance with the manufacturer's instructions. The reference ranges for normal adults according to the manufacturer were as follows: total IgG, 7.0–16.5 g/L; $IgG_1$, 3.8–9.3 g/L; $IgG_2$, 2.4–7.0 g/L; $IgG_3$, 0.22–1.76 g/L; $IgG_4$, 0.04–0.86 g/L. Routine hematological and biochemical analyses were performed in the Pathology Departments at contributing hospitals.

*Statistical analysis.* Univariate analysis was undertaken using Fisher's exact test, Student's $t$ test, or the Wilcoxon rank-sum test (as appropriate) with Stata software, version 8.2 (Stata Corporation), to identify features associated with H1N1 infection severity. Variables that were potentially associated ($P < .2$) on univariate analysis were included in a multivariate analysis to identify features statistically associated with severe H1N1 infection. Similarly, a univariate analysis of the clinical and laboratory features of healthy vs H1N1-infected pregnant participants was undertaken to assess for any associations with the presence of H1N1 infection. A $P$ value of $\leq .05$ was considered to be statistically significant.

## RESULTS

*Severe versus moderate H1N1 infection.* A total of 47 patients with acute H1N1 infection (19 with severe infection and 28 with moderate infection) were assessed from 30 May through 16 August 2009. Appropriate serum specimens were available for 39 patients (19 with severe infection and 20 with moderate infection), and results are shown in Table 1. Among the 8 patients for whom no serum samples were available, no special features were noted to explain the lack of stored serum samples.

Patient demographic data and comorbidities for the 39 participants were similar between the severe and moderate H1N1

**Table 1. Comparison of Results for Immunoglobulin (Ig) Levels for Patients with Severe versus Moderate H1N1 Infection**

| Variable | Severe H1N1 infection ($n$ = 19) | Moderate H1N1 infection ($n$ = 20) | $P$ |
|---|---|---|---|
| Age, mean years ± SD (range) | 36 ± 19 (16–79) | 41 ± 16 (19–76) | .32 |
| Male sex | 7 | 11 | .34 |
| Pregnant[a] | 7 | 2 | .065 |
| Comorbidity | | | |
| Hematological malignancy[b] | 1 | 2 | >.99 |
| Solid-organ transplantation | 0 | 2 | .49 |
| Asthma (requiring inhaled corticosteroids only) | 3[c] | 6[d] | .45 |
| Obesity | 1[c] | 3[d] | .60 |
| Diabetes mellitus | 3[c] | 5[d] | .70 |
| Influenza-related myocarditis | 1 | 0 | ... |
| Pneumonia present[e] | 16 | 4 | <.001 |
| ICU management[f] | | | |
| Endotracheal intubation/ventilation alone | 12 | ... | ... |
| Endotracheal intubation/ventilation plus ECMO | 2 | ... | ... |
| Noninvasive ventilation/high-flow oxygen | 5 | ... | ... |
| Mortality | 2 | 0 | .23 |
| Laboratory results | | | |
| Hemoglobin level, mean g/L (±SD) | 104 ± 23 | 133 ± 21 | <.001 |
| Leukocyte count, mean cells × $10^9$/L (±SD) | 10.4 ± 10.5 | 8.7 ± 8.3 | .56 |
| Lymphocyte count, mean cells × $10^9$/L (±SD) | 0.94 ± 0.5 | 3.0 ± 8.8 | .31 |
| Renal impairment (creatine level >110 μmol/L) | 4 | 3 | .70 |
| Abnormal liver function | 16 | 11 | .08 |
| Serum albumin level, mean g/L ± SD (range)[g] | 23 ± 5 (16–34) | 35 ± 5 (23–42) | <.001 |
| Immunoglobulin data | | | |
| Mean day (±SD) of H1N1 illness when serum immunoglobulins assessed (range) | 6.2 ± 2.4 (3–11) | 6.9 ± 6.1 (1–23) | .67 |
| Low IgA | 3[h] | 2[h] | .66 |
| Low IgM | 2[h] | 4[h] | .66 |
| Low total IgG | 12[i] | 4 | .01 |
| Total IgG levels, mean g/L (±SD) | 7.2 ± 5.5 | 9.7 ± 2.4 | .069 |
| Patients with low $IgG_3$ | 11 | 4 | .022 |
| $IgG_3$ levels, mean g/L (±SD) | 4.2 ± 3.9 | 5.2 ± 1.9 | .31 |
| Patients with low $IgG_2$ | 15[i] | 5 | .001 |
| $IgG_2$ levels, mean g/L (±SD) | 1.8 ± 1.7 | 3.4 ± 1.4 | .003 |

NOTE. Data are no. of patients, unless otherwise indicated. Severe H1N1 infection was defined as requiring intensive care unit (ICU) admission and respiratory support. Moderate H1N1 infection was defined as requiring hospital admission but not ICU admission. ECMO, extra-corporeal membrane oxygenation; SD, standard deviation.

[a] Of the 7 pregnant women with severe H1N1 infection, 2 had mild asthma (not using inhaled corticosteroids), whereas 1 pregnant woman with moderate H1N1 infection had both type 2 diabetes mellitus and obesity.

[b] One patient in each group had chronic lymphocytic leukemia.

[c] One patient had obesity and diabetes, and 1 patient had asthma and diabetes. All 3 patients had type 2 diabetes.

[d] One patient had asthma, obesity, and diabetes; 2 patients had obesity and diabetes; 3 patients had asthma and diabetes; 1 patient had obesity and asthma. Two of 5 patients had type 1 diabetes, and 3 of 5 patients had type 2 diabetes.

[e] Community-acquired pneumonia was defined according to Infectious Diseases Society of America guidelines [6].

[f] Among patients who required endotracheal intubation/ventilation alone, ECMO, and noninvasive ventilation/high-flow oxygen, pregnancy was present in 4, 1, and 2 patients, respectively.

[g] Serum albumin level on same day that immunoglobulin levels were measured.

[h] Deficiencies in IgM and IgA were all mild.

[i] An additional patient who was 16 years and 11 months of age was not reported to have deficient immunoglobulin levels, because her immunoglobulin levels were within the pediatric range; however, these values would have been considered to be deficient if the adult (defined as ≥17 years of age) normal range values had been used.

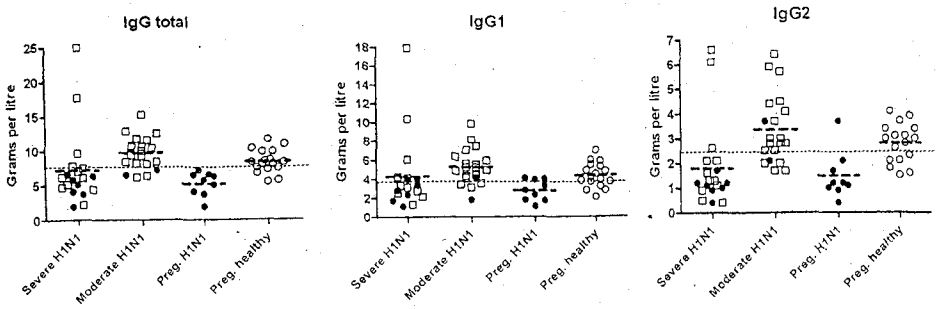


**Figure 1.** Serum immunoglobulin G (IgG) (total), $IgG_1$, and $IgG_2$ levels for patients with acute H1N1 infection stratified according to disease severity (severe vs moderate) and compared with healthy pregnant (Preg) patients. Data are shown for pregnant patients with H1N1 infection (●), nonpregnant patients with H1N1 infection (□), and healthy pregnant control patients (○). *Dashed line*, mean value of each grouping; *dotted line*, lower limit of normal adult range for the relevant immunoglobulin.

infection groups, except that pregnancy was more common among patients in the severe H1N1 infection group (7 of 19 vs 2 of 20); however, this difference did not achieve statistical significance ($P = .065$; Table 1).

Hypoalbuminemia and anemia were more common among patients with severe H1N1 infection ($P < .001$ for both; Table 1). Similarly, the presence of severe H1N1 infection was significantly associated with low levels of total IgG (12 of 19 vs 4 of 20 patients; $P = .01$), $IgG_1$ (11 of 19 vs 4 of 20 patients; $P = .022$) and $IgG_2$ (15 of 19 vs 5 of 20 patients; $P = .001$; Table 1 and Figure 1), compared with patients with moderate H1N1 infection. Furthermore, 1 patient with severe H1N1 infection (patient A) was a pregnant woman at 21 weeks gestation (age, 16 years and 11 months) who had an $IgG_2$ level of 1.1 g/L, which was reported as normal on the basis of the $IgG_2$ reference ranges used for children (age ≤16 years: 0.6–5.0 g/L) but would have been considered to be deficient if the adult reference ranges (age ≥17 years: 2.4–7.0 g/L) had been applied.

Assessment of the mean (± standard deviation [SD]) concentrations of total IgG and IgG subclasses demonstrated that patients with severe H1N1 infection had significantly lower levels of $IgG_2$ (and therefore lower levels of total IgG) than did patients with moderate H1N1 infection (Table 1). However, the mean (±SD) levels of $IgG_1$ (4.2 ± 3.9 vs 5.2 ± 1.9 g/L; $P = .31$), $IgG_3$ (0.50 ± 0.28 vs 0.77 ± 0.55 g/L; $P = .07$) and $IgG_4$ (0.28 ± 0.43 vs 0.24 ± 0.24; $P = .68$) were not significantly different between patients with severe and patients with moderate H1N1 infection (Figure 1).

The association between pregnancy, hypoalbuminemia, anemia, and low levels of $IgG_2$ with severe H1N1 infection were assessed in a multivariate model. The results are shown in Table 2. Abnormal liver function test results were not included in this analysis, because they were correlated with hypoalbuminemia ($P = .024$). After this analysis, only low mean serum concentrations of $IgG_2$ and albumin remained statistically significantly associated with severe H1N1 infection, compared with moderate H1N1 infection ($P = .043$ and $P = .02$, respectively; Table 2).

Among the 21 patients identified as $IgG_2$ deficient during the acute stage of H1N1 infection (16 with severe infection, including patient A; 5 with moderate infection), convalescent serum samples was obtained from 15 patients (71%; 11 with severe infection, 6 of whom were pregnant; 4 with moderate infection, 1 of whom was pregnant) a mean (±SD) of 90 ± 23 days (range, 38–126 days) after the initial acute-phase specimen was obtained. Convalescent-phase serum samples were not available for 6 patients, because 2 had died, 3 were not contactable, and 1 refused testing. Serum $IgG_2$ results are shown in Figure 2. Among the 11 patients with previous severe H1N1 infection, serum $IgG_2$ levels remained in the deficient range for 8 (73%; 3 postpartum, one pregnant, and 4 nonpregnant; Figure 2). Two of the 3 patients with severe H1N1 infection with normal convalescent serum $IgG_2$ levels were postpartum women; 1 of these 2 women had received intravenous pooled immunoglobulin as a component of her therapy for severe

**Table 2. Multivariate Analysis of Features Potentially Associated with Severe versus Moderate H1N1 Infection**

| Variable | Odds ratio (95% confidence interval) | *P* |
|---|---|---|
| Pregnancy | 8.9 (0.32–248.2) | .20 |
| Mean hemoglobin per g/L | 1.01 (0.94–1.08) | .80 |
| Mean serum albumin per g/L | 1.6 (1.08–2.3) | .02 |
| Mean immunoglobulin $G_2$ level per g/L | 2.25 (1.03–4.92) | .043 |



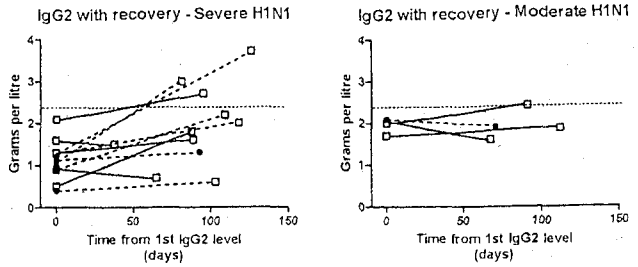


***Figure 2.*** *Comparison of serum immunoglobulin G subclass 2 ($IgG_2$) levels among patients with $IgG_2$ deficiency during severe H1N1 infection and with recovery (nonpregnant and pregnant women). Data are shown for pregnant patients with H1N1 infection (●) and nonpregnant patients with H1N1 infection (□). Dashed line, pregnant patient at time of initial $IgG_2$ sample; dotted line, lower limit of normal adult range for $IgG_2$.*

*H1N1 infection, but this was 77 days before testing of convalescent-phase serum samples.* Notably, the only patient with severe H1N1 infection with normal convalescent-phase $IgG_2$ levels who was nonpregnant was only mildly deficient during the acute phase of illness (acute-phase $IgG_2$ level, 2.1 g/L; convalescent-phase $IgG_2$ level, 2.6 g/L; normal range, ≥2.4 g/L). Of the 4 patients with moderate H1N1 infection who were assessed at follow-up, 3 remained $IgG_2$ deficient, including 1 woman who was still pregnant at this time (Figure 2).

Persistence of immunoglobulin deficiency was less prominent for non-$IgG_2$ subclasses. Among the 8 patients with severe *H1N1 infection who were initially deficient in* $IgG_1$, 6 had normal $IgG_1$ levels on testing of convalescent-phase serum samples (data not shown). Similarly, hypoalbuminemia had resolved in most patients (9 of 14 assessable patients); however, of the other 5 patients, 2 remained pregnant at the time of follow-up.

***Immunoglobulin levels and pregnancy.*** A total of 9 patients with H1N1 infection were pregnant (23%; Table 1). Serum immunoglobulin levels for these patients were compared with levels for 17 healthy pregnant control subjects, and results are shown in Figure 1 and Table 3. The healthy pregnant women were slightly older than those with H1N1 infection, but both groups were similar with regard to mean gestation period (Table 3). Among the 17 healthy patients, 10 had mildly low $IgG_1$ and/or $IgG_2$ levels, compared with the standard reference range for nonpregnant women ($IgG_1$ alone, 4 patients; $IgG_2$ alone, 4 patients; $IgG_1$ and $IgG_2$, 2 patients). However, pregnant women with H1N1 infection had significantly lower mean levels of total IgG ($P < .001$), $IgG_1$ ($P = .005$), and $IgG_2$ ($P = .001$) than did the 17 control subjects (Table 3 and Figure 1).

**Table 3. Comparison of Results for Pregnant Women with H1N1 Infection versus Healthy Control Subjects**

| Variable | Patients with H1N1 infection[a] (*n* = 9) | Healthy control subjects[b] (*n* = 17) | *P* |
|---|---|---|---|
| Age, mean years ± SD (range) | 24 ± 6.2 (16–37) | 30 ± 3.9 (20–36) | .008 |
| Gestation, mean weeks ± SD (range) | 32 ± 6.0 (21–38) | 35 ± 2.9 (29–40) | .16 |
| Low total IgG | 7[c] | 3 | .009 |
| Total IgG level, mean g/L (±SD) | 5.2 ± 1.7 | 8.5 ± 1.7 | <.001 |
| Low $IgG_1$ | 6 | 6 | .22 |
| Mean (±SD) $IgG_1$ level, mean g/L (±SD) | 2.8 ± 1.1 | 4.4 ± 1.3 | .005 |
| Low $IgG_2$ | 7[c] | 6 | .097 |
| $IgG_2$ level, mean g/L (±SD) | 1.5 ± 1.0 | 2.8 ± 0.8 | .001 |

**NOTE.** Data are no. of patients, unless otherwise indicated. IgG, immunoglobulin G.

[a] Including 7 patients with severe H1N1 infection and 2 patients with moderate H1N1 infection.

[b] Two healthy pregnant patients had gestational diabetes.

[c] An additional patient who was 16 years and 11 months of age was not reported to have deficient immunoglobulin levels, because her immunoglobulin levels were within the pediatric range; however, these values would have been considered to be deficient if the adult (defined as ≥17 years of age) normal range values had been used.

## DISCUSSION

Although a number of authors have described the clinical features of H1N1 infection [7–9], including those of pregnancy as a risk factor for severe H1N1 infection [10], this is, to our knowledge, the first report to identify a potential association between H1N1 disease severity and the presence of immunoglobulin subclass deficiency. Patients with severe H1N1 infection were significantly more likely to be deficient in $IgG_2$ than were patients with moderate H1N1 infection ($P = .001$). $IgG_2$ deficiency was not necessarily noticeable if only total IgG levels were assessed. Furthermore, our findings suggest that, for the majority of such patients (11 of 15 patients; 73%), $IgG_2$ deficiency persists after recovery from H1N1 infection, regardless of whether the illness was associated with possible risk factors, such as pregnancy. Low $IgG_2$ levels are therefore less likely to be simply related to a severe inflammatory response, as is sometimes noted for acute-phase reactants, such as albumin, creatine kinase, and lactate dehydrogenase [8, 11].

IgG subclass deficiency is usually asymptomatic, and low levels of 1 or more IgG subclasses can be found in 2%–20% of healthy individuals [12, 13]. If symptomatic, patients with IgG subclass deficiency tend to have recurrent sinopulmonary bacterial infections [13]. However, to our knowledge, IgG subclass deficiency has not been studied in detail in humans with influenza infection, although in mouse models, anti-influenza antibody (and specifically IgG) has a key role in virus control in the lower respiratory tract, compared with the upper respiratory tract [14, 15]. In humans, Logtenberg et al [16] described a single patient with severe transitory hypogammaglobulinemia associated with acute influenza A virus infection. However, in this case, all immunoglobulin classes (IgG, IgM, and IgA) were affected. Other than this report, we can find no other association between influenza and immunoglobulin deficiency.

Thus, it is uncertain whether we have simply identified a cohort of patients with H1N1 infection with underlying unrecognized $IgG_2$ deficiency, or whether there is an interaction between the H1N1 virus and the host that leads to such deficiency. Given that the half-life of $IgG_2$ is ~3 weeks [17], a potent and specific interaction between H1N1 virus and host B cells would need to occur to lead to such a precipitous decrease in serum $IgG_2$. Bone marrow apoptosis of B cells by influenza virus has been demonstrated in mice [18], but how this relates to disease in humans remains unclear. However, the fact that the $IgG_2$ deficiency that we identified appears to persist in most cases long after disease resolution (convalescent serum samples were collected a mean ($\pm$ SD) of 90 $\pm$ 23 days after the acute phase of illness) suggests the possibility of potential long-term implications for these patients and that follow-up of moderate and severe cases of H1N1 infection may be warranted.

Because of our findings, we hypothesize that $IgG_2$ deficiency may be associated with an inability to mount an early effective immune response to influenza and may therefore be linked to severe disease. Furthermore, if the $IgG_2$ deficiency that we observed is long-lasting or permanent, will this affect the patients' likely response to influenza vaccination? Response to influenza vaccination is measured by specific neutralization assays, rather than by total immunoglobulin concentrations, and it is not known whether response to influenza vaccination by individuals who are $IgG_2$ subclass deficient is diminished.

Pregnancy is a known risk factor for increased severity of both seasonal and pandemic influenza infections [19–23], which is thought to be attributable to pregnancy-related physiologic and immunologic changes, such as decreased lung capacity and increased cardiovascular demand, as well as a shift away from cell-mediated immunity to humoral immunity [24]. Our finding that a substantial number (10 of 17) of our healthy pregnant cohort had mildly low $IgG_1$ and/or $IgG_2$ levels is consistent with the known decrease in immunoglobulin levels that occurs during normal pregnancy and resolves after delivery [25, 26]. Low $IgG_2$ levels in pregnant women could therefore potentially explain why pregnancy appears to be a risk factor for severe H1N1 infection [2–4]. However, this alone does not appear to explain the significantly lower levels of $IgG_2$ observed among pregnant patients with H1N1 infection, compared with levels among our healthy pregnant control subjects ($P = .001$), nor the fact that $IgG_2$ deficiency persisted postpartum in some women with severe H1N1 infection.

Although $IgG_2$ deficiency appears to be associated with H1N1 infection severity, it remains uncertain whether administration of immunoglobulin to patients who are $IgG_2$ deficient is likely to be therapeutically beneficial. We administered pooled immunoglobulin to some of our patients with severe H1N1 infection who had $IgG_2$ deficiency, but our observations were uncontrolled. Nevertheless, convalescent blood products were administered during the Spanish influenza pandemic with a reduction in mortality [27], and more recently, convalescent-phase plasma samples obtained from a patient who recovered from H5N1 influenza infection was used successfully [28]. Further investigation of the use of convalescent-phase blood products in severe pandemic H1N1 infection is needed.

Our study has a number of important limitations, including being of relatively limited size and lacking suitable specimens to analyze patient cellular immunity or to assess influenza virus neutralization, and we have not compared our findings with those that might be expected among healthy nonpregnant control subjects. Furthermore, with the number of cases of H1N1 infection now decreasing in Australia, our findings need to be confirmed in other geographical locations (although the H1N1 strain circulating in Victoria appears to be the same as that isolated in the Northern Hemisphere) [4].

Nevertheless, we considered our finding of a statistically significant association between $IgG_2$ deficiency and H1N1 infection severity to be sufficiently notable and hypothesis-generating in terms of potential clinical therapeutic importance that prompt notification of these data to clinicians managing cases of H1N1 infection was warranted.


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