To summarize the literature regarding 2009 H1N1 influenza A during pregnancy, we conducted a systematic literature review using a PubMed search and other strategies. Studies were included if they reported 2009 H1N1 influenza in pregnant women as original data. In all, 2153 abstracts were reviewed, and a total of 120 studies were included. Data were extracted regarding number of cases, additional risk factors for influenza-associated complications, treatment, and maternal and pregnancy outcomes. Authors were contacted to determine the extent of overlap when it was suspected. Pregnancy was associated with increased risk of hospital and intensive care unit admission and of death. Pregnant women who received delayed treatment with neuraminidase inhibitors or who had additional risk factors were more likely to develop severe disease. Preterm and emergency cesarean deliveries were frequently reported. These results reinforce the importance of early identification and treatment of suspected influenza in this high-risk population.

Key words: H1N1, influenza, pregnancy

On April 15 and 17, 2009, a novel 2009 H1N1 influenza A (2009 H1N1) virus was identified in 2 children in the United States by the Centers for Disease Control and Prevention (CDC). The virus spread rapidly throughout the United States and worldwide, leading the World Health Organization to declare a pandemic on June 11, 2009. As predicted based on experience with seasonal influenza and previous pandemics, pregnant women were quickly identified as a high-risk group for severe complications of 2009 H1N1 influenza, including hospital and intensive care unit (ICU) admissions and death.

Since April 2009, a large number of publications have appeared describing the effects of 2009 H1N1 influenza among pregnant women; however, many of these publications describe small case series and often overlap with other published studies. Therefore, a systematic review of the currently available literature, with an attempt to minimize overlap, is needed to better understand the effects of 2009 H1N1 on the pregnant woman and her fetus to guide optimal management. These data will be helpful to plan for future influenza seasons, during which 2009 H1N1 and seasonal influenza strains are expected to circulate, as well as to plan for future influenza pandemics.

Materials and Methods
A PubMed search was performed (L.G.M.) on May 6, 2010, and Aug. 2, 2010, to identify all publications in the medical literature discussing 2009 H1N1 influenza in pregnancy using the following search terms: (“H1N1” [TiAb] OR “swine” [MeSH terms] OR “swine” [tiab]) AND (“influenza, human” [MeSH terms] OR “influenza” [tiab]) AND (“pregnancy” [MeSH terms] OR “pregnancy” [tiab]). A second PubMed search was performed (L.G.M.) on May 6, 2010, using the same terms as above excluding: (“pregnancy” [MeSH terms] OR “pregnancy” [tiab]). We limited all searches to the English language and did not attempt to identify unpublished articles. The abstracts of all identified papers were examined. When the abstract included clinical or surveillance information, or when no abstract was available, the full paper was examined to determine whether cases of pregnant women with 2009 H1N1 infection were described. Papers that included cases reported as original data (ie, without citing another study as the source of data) were included. We included case-control studies, cohort studies, case reports, and letters and editorials in medical journals that described cases. Policy and practice articles were not included. Additionally, we examined the references of all identified articles for further relevant resources, and we hand-searched the personal files of 2 subject matter experts for the CDC (S.A.R. and D.J.J.) who have authored publications regarding 2009 H1N1 and pregnancy issues.

We contacted authors when possible to determine extent of overlap between studies. If no overlap could be established, we assumed nonoverlap. When overlap was established and cases were described in >1 study (eg, as part of a large report and as a detailed case report), both studies were included in the review, but the pregnant woman was counted toward total cases, hospitaliza-
tions, ICU admissions, and deaths only once.

After accounting for overlap, the proportion of pregnant women among total hospitalizations was calculated by identifying studies that included numbers of hospitalized pregnant women and of total hospitalizations, and summing the total pregnant women hospitalized divided by the total hospitalized in the general population. Proportions of pregnant women admitted to the ICU and who died were calculated in the same manner. Unless otherwise specified, we assumed pregnant women who died had also been admitted to the ICU. When calculating percentages of affected women with additional risk factors for influenza-related complications identified by the Advisory Committee on Immunization Practices (ACIP), only studies with >10 pregnant patients were included in an attempt to avoid bias of data toward more complex patients.

Results

The PubMed search that included “pregnant OR pregnancy” in the search terms yielded 151 publications, 106 of which were published on or after April 1, 2009, 93 of which were English-language papers. Among these 93, 42 provided clinical information on pregnant women with confirmed, probable, or suspected 2009 H1N1 and were thus included in our review.3,5-34 This search was repeated on Aug. 2, 2010, and yielded an additional 26 papers, of which 14 included cases of pregnant women affected by 2009 H1N1.45-58

The PubMed search that excluded the pregnancy terms yielded 2494 publications, 2032 of which were published in English, on or after April 1, 2009. Of these, 116 provided clinical information on pregnant women with 2009 H1N1 influenza and thus were included in our review.3,5,34,59-106,110-135 All 42 studies from the initial pregnancy-specific PubMed search were included in this collection of 116. One paper was unavailable through CDC and Emory University library systems as of Aug. 10, 2010, and so was not included in this review.107

Review of personal collections of papers of 2 CDC subject matter experts (D.J.J. and S.A.R.) yielded an additional 2 papers to be included in the review.108,109 Review of reference lists of included publications yielded no new studies fitting our criteria.

Overall, 332 papers reported clinical information on pregnant women with 2009 H1N1 (Figure).2,3,5-106,108-135 Of these, 12 papers were excluded because they did not meet our eligibility criteria: one was published as a policy and practice paper,17 and other papers reported only cases and information described in previous studies.33,37,60,71,77,79,95,114,119,121,124

All papers were evaluated for overlap if they reported cases from the same geographic location during the same time period. Overlap was suspected and was found to varying degrees in reports from the following regions: Argentina,58,59,83,134 Australia,8,11,14,15,20,24,27,28,36,44,52,61,68,110 Brazil,75,81,90 Canada,56,70,94,106,112,115,123 Chile,85,89,98,101 China,50,53,78,82 France,16,23,62 Hong Kong,97,125 Iran,47,67 Israel,95,86,118 Mexico,66,113,131,135 New Zealand,8,14,44,103,130,134 Reunion Island,97,125,127 Singapore,34,42,48 South Africa,9,29,32 United Kingdom,12,17,20,54,69,80,104,105,132 and United States.4,2,3,5-7,10,13,18,19,21,22,25,26,30,31,35,39,41,49,51,63,72-74,92,99,109,116,127,129

The 120 papers that were included in the review reported 3110 pregnant women from 29 countries with 2009 H1N1 influenza infection, including 1625 (52.3%) who were hospitalized with 2009 H1N1, of whom 378 (23.3%) were admitted to an ICU and 130 (8%) died.

Hospitalization and severe disease in pregnancy

Several studies demonstrated that pregnant women, when compared to non-pregnant women of similar age, or when compared to the general population, have an increased risk of hospitalization, ICU admission, death, and other severe outcomes due to 2009 H1N1 infection (Table 1). Pregnancy was found to be significantly associated with hospitalization (P = .015).100 A study from California identified an association between pregnancy and ICU admission that was not statistically significant (P = .07).35 One study of severely ill patients found that pregnant women were more likely to develop acute renal failure (P < .05).58

Pregnant women were disproportionately represented among hospitalizations, ICU admissions, and deaths. While approximately 1% of the population is pregnant at any given time in both the United States and Australia,3,28,136 pregnant women accounted for 6.3% of hospitalizations (835/13,322), 5.9% of ICU admissions (236/3989), and 5.7% of deaths (188/3295) due to 2009 H1N1 in pooled data from all studies included in this review.

Relation between antiviral treatment and severe disease

Five studies demonstrated that neuraminidase inhibitors administered within 48 hours of symptom onset conferred decreased risk of severe disease.13,35,41,46,54 No study reached the conclusion that antivirals did not confer benefit. Siston et al11 also found that antivirals 3-4 days after symptom onset still conferred benefit when compared to antiviral treatment >4 days after symptom onset.11

In severely ill women, other treatment modalities were sometimes offered. A number of studies described the use of extracorporeal membrane oxygenation (ECMO) in pregnant women. Twenty-two peripartum women were placed on ECMO; 4 were pregnant,20,40,52,92 3 were postpartum,7,14,22 and 15 were not clearly identified as prepartum or postpartum.8,24,51,56 Of pregnant women treated with ECMO, 2 survived, 1 died, and 1 outcome was not reported.20,40,52,92 Of those treated with ECMO in whom delivery status was unclear, 7 survived,5 3 died,8 and 5 have no reported outcome information.24,51,56 Additionally, 1 postpartum woman who survived was treated with intravenous peramivir after delivery,7 and 1 postpartum woman treated with intravenous zanamivir subsequently died.92

Presence of additional risk factors for severe disease

Although many pregnant women without additional ACIP risk factors became very ill, additional ACIP risk factors con-
Abstracts and papers reviewed, and papers accepted, for systematic review of 2009 H1N1 influenza and pregnancy.

SME, subject matter expert.

ferred increased risk for severe disease. The proportion of patients with additional risk factors was calculated using all studies reporting this information on >10 pregnant women; 30.3% of pregnant patients had additional ACIP risk factors (or unspecified comorbidities) for severe disease other than pregnancy.2,3,6,9,13,20,22,24,26,29,31,32,34,35,39,41,43,45–49,54,56,57,62,63,72,74,80,81,86,92,99,116,128,129,132,133,135

The most common additional risk factor reported was asthma, followed by diabetes mellitus of any type. Obesity was also commonly reported.

Mode of delivery and neonatal outcomes
Preterm delivery, whether spontaneous or iatrogenic, was commonly reported, particularly with severe maternal illness (Table 2). In 3 of 4 series reporting >50 pregnancy outcomes, preterm birth rates approximated or exceeded 30%.8,41,54; the 1 exception is a study from the French island of La Reunion, which found a preterm birth rate of 15%.16 This can be compared to a baseline rate of preterm birth of 9.6% worldwide.137 Yates et al54 found that when pregnant women with 2009 H1N1 were compared to uninfected pregnant women, they had increased odds of preterm birth (odds ratio, 5.5; 95% confidence interval, 3.5–8.3) and of very preterm birth at <32 weeks (odds ratio, 4.3; 95% confidence interval, 2.1–8.9).

Cesarean delivery was also commonly reported among mothers with 2009 H1N1 (Table 2), often as an attempt to improve worsening maternal status. Siston et al41 reported 109 cesarean deliveries (58.0%) vs 79 vaginal deliveries (42.0%) in pregnant women with 2009 H1N1 in the United States, compared to the baseline cesarean delivery rate of 30.5%.138 In all studies discussing indication for cesarean delivery, maternal hypoxemia or maternal decompensation was more frequently listed as an indication (N = 30) than infant considerations (N = 15). Emergency cesarean deliveries were frequently reported, with 19 designated as urgent or emergent. Often, deliveries occurred outside of labor and delivery wards or a controlled operating room setting, including 15 cesarean and 4 vaginal deliveries that occurred in an ICU or emergency department.8,10,13,19,25,31,35

While many neonates required neonatal ICU admission and extended hospital stays, these were largely for preterm birth rather than neonatal influenza. Very few infants of ill mothers tested positive for 2009 H1N1 influenza. Among 20 infants in the Australia and New Zealand cohort tested, 2 tested positive for 2009 H1N1.8 In a series from California, no placental infection was reported among 3 women with 2009 H1N1.25 In a series from La Reunion, of 22 placent and 7 amniotic fluid samples tested for 2009 H1N1, none were positive.46 In this study, an infant delivered by cesarean was positive for 2009 H1N1, but was asymptomatic and postnatal transmission was suspected.46 The possibility of vertical transmission was raised in 2 infants delivered by cesarean delivery that were not exposed to their ill mothers, but testing for 2009 H1N1 was unspecified in 1 paper and limited to a throat swab in another; conclusive testing was not

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### Table 1

<table>
<thead>
<tr>
<th>Paper</th>
<th>Risk of hospitalization</th>
<th>Risk of ICU admission</th>
<th>Risk of death</th>
<th>Risk of severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>New South Wales Public Health Network110</td>
<td>RR, 5.8a</td>
<td>RR, 10.2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANZIC9</td>
<td>RR, 7.4a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campbell et al123</td>
<td>RR, 0.7 (0.4–1.2)a</td>
<td>RR, 1.1 (0.3–4.1)a</td>
<td>RR, 0.7 (0.4–1.3)</td>
<td></td>
</tr>
<tr>
<td>Creanga et al13</td>
<td>RR, 7.2a</td>
<td></td>
<td>RR, 4.3a</td>
<td></td>
</tr>
<tr>
<td>Fuhrman et al42</td>
<td>RR</td>
<td>OR, 0.4 (0–2.6)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gérardin et al46</td>
<td>RR</td>
<td>OR, 5.2 (4.0–6.9)</td>
<td>OR, 1.4 (0.3–4.2)</td>
<td></td>
</tr>
<tr>
<td>Hanslik et al23</td>
<td>RR, 4.3 (2.3–7.8)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jamieson et al8</td>
<td>RR, 5.2 (4.6–5.8)b</td>
<td>RR, 6.5 (4.8–8.8)b</td>
<td>RR, 1.4 (0.4–4.5)b</td>
<td></td>
</tr>
<tr>
<td>Kelly et al28</td>
<td>RR, 5.2 (4.6–5.8)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koegelenberg et al29</td>
<td>OR, 1.13 (0.14–8.88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliveira et al81</td>
<td>RR, 1.07 (.82–1.41)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al83</td>
<td>OR, 0.8 (0.2–3.5)</td>
<td>OR, 0.4 (0.2–3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zarychanski et al106</td>
<td>OR, 3.64 (0.86–15.4)b,c</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANZIC, ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System; aOR, adjusted odds ratio; ICU, intensive care unit; OR, odds ratio; RR, relative risk.

* Compared to nonpregnant women of reproductive age; † Compared to general population; ‡ This number reports increased odds that pregnant women would require ICU admission over that they would require only outpatient treatment.

done. Among all infants tested for 2009 H1N1 using varying methods, 39 negative and 6 positive tests were reported.\footnote{8,19,24,25,27,36,40,80,84,108}

**Comment**

Based on this systematic review, pregnant women were disproportionately affected by 2009 H1N1 influenza, and were at increased risk for hospitalization, ICU admission, and death. Treatment up to 4 days after symptom onset, ideally within 48 hours, confers decreased risk of severe disease and death. Although safety of oseltamivir in pregnancy has not been clearly established, the benefits of treatment appear to outweigh the risks.\footnote{139} The best way to prevent influenza is through use of influenza vaccine\footnote{140}; increasing influenza vaccine uptake in pregnant women should be an important goal for health care providers.

While it is likely that cesarean deliveries were overreported, given that severely affected women were more likely to be reported, cesarean deliveries were commonly described. Cesarean delivery outside of a controlled operating room setting was frequently described, indicating the urgent nature of these deliveries and the critical status of the parturients.

Also, although infants of affected women generally did well, they were more likely to be born preterm, which is associated with neonatal and long-term morbidity and mortality.\footnote{141} Vertical

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**TABLE 2**

<table>
<thead>
<tr>
<th>Paper</th>
<th>No. of deliveries\textsuperscript{*}</th>
<th>Proportion of preterm deliveries</th>
<th>Proportion of cesarean deliveries</th>
<th>Fetal/neonatal survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC\textsuperscript{7}</td>
<td>9</td>
<td>5/9</td>
<td>At least 2/9</td>
<td>1 stillbirth; 1 neonatal death</td>
</tr>
<tr>
<td>Creanga et al\textsuperscript{13}</td>
<td>22 while ill 22 after recovery</td>
<td>While ill: 3/22 (2 in women with severe disease) After recovery: 3/22</td>
<td>While ill: 11/22 After recovery: 7/22</td>
<td>2 neonatal deaths</td>
</tr>
<tr>
<td>Jamieson et al\textsuperscript{3}</td>
<td>6</td>
<td>6/6</td>
<td>6 (5 in cases with maternal death)</td>
<td></td>
</tr>
<tr>
<td>Louie et al\textsuperscript{14}</td>
<td>35</td>
<td>25-28 wks: 3 &gt;28 wks: 32 Of severe maternal illness: 10/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al\textsuperscript{49}</td>
<td>6</td>
<td>4/6</td>
<td>5/6</td>
<td>1 neonatal death</td>
</tr>
<tr>
<td>Siston et al\textsuperscript{41}</td>
<td>169</td>
<td>30.2%</td>
<td>109/188</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANZIC\textsuperscript{8}</td>
<td>59</td>
<td>36%</td>
<td>While ill: 14/22 After recovery: 6/23</td>
<td>4 stillbirths; 2 neonatal deaths; 1 postneonatal death</td>
</tr>
<tr>
<td>Hewagama et al\textsuperscript{24}</td>
<td>15</td>
<td>40%</td>
<td></td>
<td>2 stillbirths; 1 neonatal death</td>
</tr>
<tr>
<td>France (La Reunion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gérardin et al\textsuperscript{46}</td>
<td>115</td>
<td>17/115; 5 precipitated by flu</td>
<td>21/114</td>
<td>No adverse neonatal outcome</td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yates et al\textsuperscript{24}</td>
<td>153</td>
<td>45/153</td>
<td></td>
<td>6 stillbirths</td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lim et al\textsuperscript{48}</td>
<td>42</td>
<td>13/42</td>
<td>6/42</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honarvar et al\textsuperscript{47}</td>
<td>6</td>
<td>1/6</td>
<td>5/6</td>
<td>1 neonatal death due to H1N1 infection</td>
</tr>
</tbody>
</table>

\textsuperscript{ANZIC, ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System; CDC, Centers for Disease Control and Prevention.}

\textsuperscript{*} Number of deliveries of fetuses of potentially viable gestational age (definition varied by study).

\textsuperscript{Mosby. 2009 H1N1 and pregnancy. Am J Obstet Gynecol 2011.}
transmission of 2009 H1N1 was not conclusively established, although it was suspected in 1 case and seems possible in a second.\textsuperscript{84,108} Although infants of affected mothers were rarely affected by 2009 H1N1 influenza, many infants were born preterm due to maternal illness, experienced adverse outcomes, or died due to complications with delivery or preterm birth. Maternal vaccine administration could prevent maternal infection and may thereby decrease the risk of preterm birth, as well as help decrease neonatal morbidity and mortality due to influenza.\textsuperscript{142}

Strengths of this analysis include a thorough literature search and large total numbers of reports of pregnant women with 2009 H1N1. We also attempted to control for overlap between studies.\textsuperscript{2,3,5-37,39-58,63,66-87,89-107,109,110,112-119,121-125,129-135}

Limitations include that underreporting was likely substantial in all populations. Many studies reported only severely affected women. The numbers of patients included in many of these studies were small, follow-up times were short, and few of these cases were proven by viral culture.

The cases described here represent a fraction of cases of 2009 H1N1 in pregnant women. In the United States, for example, total hospitalizations were only reported through Aug. 21, 2009, and ICU admissions and deaths were reported through Dec. 31, 2009.\textsuperscript{31} Only 1 paper included surveillance from 2010.\textsuperscript{45} Many studies reported only ICU admissions and deaths, or only deaths, skewing our data toward women with more severe disease. Additionally, in contrast to the majority of reports, some studies reported odds ratios of <1 for ICU admission, death, and severe disease, suggesting a lower risk among pregnant women. However, only one of these findings was statistically significant, and the authors of this study maintained that pregnancy should be considered a risk factor for severe disease.\textsuperscript{62}

Additionally, pregnant and postpartum women were often reported together, without specifying how many women belonged to each group, and we were unable to resolve all situations with potential overlap, resulting in a possible increase in our overall numbers.

Relative risk data regarding antiviral treatment were limited. Additionally, pregnancy outcome data were often not reported, and studies often used different parameters to describe pregnancy outcomes, limiting our ability to pool these data. Finally, all studies included here were observational.

This review highlights the need for additional research regarding 2009 H1N1 influenza in pregnancy. Additional data regarding safety of antiviral medications and of vaccines in pregnancy may help to increase uptake of these crucial tools against disease in this high-risk population. Increased monitoring of pregnant women with influenza is critical in understanding the increased risk of severe complications of influenza (both seasonal and pandemic) in pregnancy and the optimal treatment of these women.

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