Severe maternal morbidity due to respiratory disease and impact of 2009 H1N1 influenza A pandemic in Brazil: results from a national multicenter cross-sectional study

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Abstract

Background: The aim of this study was to assess the burden of respiratory disease, considering the influenza A pandemic season (H1N1pdm09), within the Brazilian Network for Surveillance of Severe Maternal Morbidity, and factors associated with worse maternal outcome.

Methods: A multicenter cross-sectional study, involving 27 referral maternity hospitals in five Brazilian regions. Cases were identified in a prospective surveillance by using the WHO standardized criteria for potentially life-threatening conditions (PLTC) and maternal near miss (MNM). Women with severe complications from respiratory disease identified as suspected or confirmed cases of H1N1 influenza or respiratory failure were compared to those with other causes of severe morbidity. A review of suspected H1N1 influenza cases classified women as non-tested, tested positive and tested negative, comparing their outcomes. Factors associated with severe maternal outcome (SMO = MNM + MD) were assessed in both groups, in comparison to PLTC, using PR and 95 % CI adjusted for design effect of cluster sampling.

Results: Among 9555 cases of severe maternal morbidity, 485 (5 %) had respiratory disease. Respiratory disease occurred in one-quarter of MNM cases and two-thirds of MD. H1N1 virus was suspected in 206 cases with respiratory illness. Around 60 % of these women were tested, yielding 49 confirmed cases. Confirmed H1N1 influenza cases had worse adverse outcomes (MNM:MD ratio < 1 (0.9:1), compared to 12:1 in cases due to other causes), and a mortality index > 50 %, in comparison to 7.4 % in other causes of severe maternal morbidity. Delay in medical care was associated with SMO in all cases considered, with a two-fold increased risk among respiratory disease patients. Perinatal outcome was worse in cases complicated by respiratory disease, with increased prematurity, stillbirth, low birth weight and Apgar score < 7.

Conclusions: Respiratory disease, especially considering the influenza season, is a very severe cause of maternal near miss and death. Increased awareness about this condition, preventative vaccination during pregnancy, early diagnosis and treatment are required to improve maternal health.

Keywords: Maternal morbidity, Maternal mortality, Maternal near miss, H1N1, Respiratory disease

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Background
Improvement in maternal health aiming a reduction in maternal mortality is a priority worldwide, in an attempt to accomplish the established millennium development goals set for 2015 [1–3]. However, the expected reduction in maternal mortality is still far from ideal and varies widely across regions [4, 5]. Most recently, to better comprehend the burden of disease on female health and complement mortality inquiries, an alternative approach has been to study maternal morbidity. Maternal morbidity can have an impact on both low-income and high-income settings.

In 2009, the World Health Organization (WHO) standardized the definitions of potentially life-threatening conditions (PLTC) and maternal near miss (MNM) [6]. PLTC is defined by the number of maternal complications, including hemorrhagic (e.g., abruptio placenta, ruptured uterus, atony and others), hypertensive disorders (e.g., severe preeclampsia, eclampsia, HELLP syndrome), management indicators of severity (e.g., blood transfusion, intubation, intensive care unit admission) and other complications (e.g., pulmonary edema, cardiac disease and sepsis). Maternal near miss (MNM) is any situation in which a woman survives a very severe complication with proven organ dysfunction, during pregnancy or puerperium (42 days after childbirth), with at least one of the following criteria: clinical (e.g., shock or clotting disorder), laboratory (lactate > 5, PaO2/FiO2 < 200 mmHg) or management (hysterectomy due to infection or hemorrhage and blood transfusion ≥ 5 units of packed red blood cells). Severe Maternal Outcome (SMO) accounts for cases of MNM plus Maternal Deaths (MD) [6].

Recently, the concept of “obstetric transition” was incorporated into the study of maternal morbidity and mortality. The concept illustrates a global trend in which a pattern of high maternal mortality rates with predominantly direct obstetric causes (e.g., hemorrhage, preeclampsia or uterine infection) has been replaced by lower maternal mortality rates with an increasing proportion of indirect causes (preexisting disorders or those aggravated by pregnancy, such as cardiac disease, kidney disease or infection due to urinary or pulmonary foci), institutionalization and medicalization of childbirth and increased rate of obstetric interventions [7]. Obstetric transition is important to help understand the occurrence of severe maternal morbidity and provide patients with the appropriate treatment in different settings.

Among the indirect causes of maternal morbidity and mortality, respiratory disease plays a significant role, either due to the presence of severe infection or complications of the underlying conditions, such as asthma and heart disease. Physiological and anatomical changes that occur during pregnancy to provide accommodation for the growing uterus, can affect the known clinical presentation of respiratory signs and symptoms. Adequate diagnosis and treatment of respiratory disease may be delayed [8, 9]. In addition, it is recognized that pregnancy may increase the risk of severe influenza-associated complications [10, 11].

It became clear throughout the 2009 H1N1 influenza pandemic [termed A(H1N1)pdm09] worldwide [12–17] that pregnant women were a highly vulnerable group. From July 2009 to January 2, 2010, 44,544 cases of the disease and 2051 deaths were reported in Brazil, [18]. However, the total number of cases and deaths were likely much higher than the notified number.

We proposed a novel approach to analyzing the burden of 2009 H1N1 influenza virus infection and other respiratory disease among patients with severe maternal morbidity. Cases complicated by severe respiratory disease were compared to cases with morbid conditions due to other causes (such as hemorrhage and hypertension). In addition, factors possibly associated with a higher risk of SMO were evaluated by using the WHO standardized definitions of morbidity in 27 referral maternity hospitals.

Methods
This study is a secondary analysis of the Brazilian Network for Surveillance of Severe Maternal Morbidity including 27 referral maternity hospitals in Brazil. The study evaluated severe maternal morbidity cases, from a prospective surveillance, according to the 2009 WHO newly publicized criteria for these conditions [6].

The methodological details of the original study have already been published elsewhere [19, 20]. Briefly, this multicenter study included 27 referral maternity hospitals distributed among the five Brazilian geographical regions. From July 2009 to June 2010, all women admitted to participating centers, who were identified as having any life-threatening condition, near miss or maternal death, according to the WHO definition, were included in the study. Data collection, by the study team, was acquired through medical chart review after hospital discharge or death of the patient. If any doubt on diagnosis considered, the treating doctors were further contacted for clarifications. Information was entered into the OpenClinica® electronic platform (version 2.5.5 - Waltham, MA, USA) through a structured form completed by the local coordinator from each participating center.

This was not a population based study, however, there was a concern to reduce the impact of nonrandom sampling and an effort to consider representativeness of the national territory (with health facilities from all five macro-regions of the country) and of facilities from public and private sectors, university and non-university hospitals. All selected hospitals had to provide information concerning their characteristics, including location,
complexity of level of care, population covered, number of
maternity beds and availability of resources for severe cases.

Quality control was carried out during various phases of
the study. Initially, training was provided to the entire
team participating in the study, using a detailed operations
manual, with the definition of each variable. Meetings
were held between the local research team and the coor-
dinating team of the study to standardize data. Case review
was conducted by the local investigator. Subsequently, the
coordinating team of the study performed random reviews
of manual and electronic forms for data consistency in
visits to monitor the centers’ performance. Periodically,
review of the electronic system was carried out to check
for data inconsistency, along with systematic case review.
Some reported conditions were delay or substandard care,
which had been previously reported [21]. Reasons for the
delay in treatment were the woman or family member
(including delay in identifying the condition, seeking care
and refusing to accept treatment), health service (difficulties
in obtaining equipment or medical supplies) or health
professional (delays in identifying the correct diagnosis
and providing appropriate patient treatment). Sample size
was determined by the prevalence of about 8 maternal
near miss cases per 1000 births and a maternal mortality
ratio of 140/100,000 live-born infants (95 % confidence
interval). It was predicted that 75,000 births [19] needed
to be monitored.

For the present analysis, we considered severe respira-
tory disease as a suspected or confirmed case of influ-
enza or acute respiratory failure, defined as incapacity of
the respiratory system to promote adequate gas ex-
change, with arterial blood gas parameters: PaO2 <
60 mmHg or peripheral saturation < 90 %, associated or
not with PaCO2 > 50 mmHg. Clinical parameters such as
tachypnea (respiratory rate-RR > 20) or bradypnea
(RR <6), use of accessory respiratory muscles, nasal
flaring, associated with torpor or agitation were also
considered. For suspected or confirmed cases of
A(H1N1)pdm09, the definition of cases considered only
those with severe morbidity, including acute respiratory
insufficiency, sepsis, intensive care admission, intubation
and others. Cases of H1N1 without severe complications
were not included. A review of all H1N1 Influenza cases
was necessary to confirm whether laboratory tests had been
performed and to obtain the results of these tests, since
data in the original study had not been collected in detail.
Case review was requested from each local center and new
data were distributed into three groups: non-tested, positive
and negative cases for H1N1 influenza virus.

Initially, the prevalence of PLTC, MNM and MD was
calculated per group, as well as the respective health in-
dicators related to maternal morbidity and mortality:
maternal near miss ratio, severe maternal outcome ratio,
mortality index and maternal mortality ratio, according
to the WHO definition [6]. To evaluate the progression
of severe maternal morbidity in cases complicated by res-
piratory disease throughout the study, maternal out-
comes (PLTC, MNM and MD) were measured for each
month studied. The risk of SMO associated with proce-
dures used to manage the severity of conditions was esti-
mated for the group with severe respiratory disease and
other causes of severe maternal morbidity, using Preva-
ience Ratios plus their respective 95 % CI adjusted for
the design effect of cluster sampling.

Subsequently, we performed an analysis considering
the total number of cases with severe respiratory disease
versus cases with other causes of severe maternal mor-
bidity. In each group, PLTC (less severe cases) and Se-
vere Maternal Outcome (SMO: MNM + MD) cases were
compared to evaluate the factors potentially associated
with more severe disease, including delay in obstetric
care, also using the Prevalence Ratios plus their respect-
ive 95 % CI adjusted for the design effect of cluster sam-
ping. The prevalence of sociodemographic, obstetric
and perinatal factors were evaluated between the two
groups using Chi-square tests. Values statistically signif-
cant were considered those with a p-value under 0.05.
The statistical procedures for analysis were performed
with SPSS and Stata.

Results

During the 12-month study period, 82,388 women were
screened. Of these, 9555 had criteria for severe maternal
morbidity. Among these 9555 women, only 485 (5 %)
had severe respiratory disease. However, in this group
with respiratory illness, symptom severity progressed
more rapidly, if compared to other causes of severe mor-
bidity (Fig. 1), such as bleeding or hypertensive disor-
ders, and may be 40 times more lethal.

Among the total number of women with respiratory
disease, patients with suspected H1N1 influenza A virus
infection had more severe disease (55.2 % MNM and
23.3 % MD) than those without suspected H1N1 influ-
enza A virus (prevalence of MNM: 21.3 %, MD: 14.1 %)
(Fig. 1). About 60 % of cases of suspected H1N1influen-
a A were tested. Women who tested positive (49 cases)
for H1N1 had more severe disease, with a higher
prevalence of SMO.

Figure 2 shows the distribution of cases with severe re-
spiratory disease, according to progression of severity
during the study period, based on date of admission in
participating centers. There was a higher incidence of
cases in the first months considered, especially July,
August and September 2009. National guidelines and avail-
ability of vaccination during pregnancy were instituted
in March/2010.

Considering health indicators, disease was more severe
among cases tested and positive for H1N1 (Table 1).
Mortality rate was higher than 50% among positive cases for A(H1N1)pdm09. The death rate was about 36% in cases testing negative for H1N1 and 27.5% in non-tested cases. In contrast, the mortality rate was only 7.4% in morbid disorders due to other causes. The maternal near miss to mortality ratio was 0.93:1, 1.80:1 and 2.39:1, among positive, negative and non-tested groups for A(H1N1)pdm09, respectively, compared to a value of 12.43:1 for other causes of severe maternal morbidity.

More than 55% of patients with severe respiratory disease had three diagnostic criteria for near miss: laboratory, clinical and management, while for the remaining causes of severe maternal morbidity, around 24% of patients only had criteria for laboratory or management diagnosis (Table 2). All procedures for management of severity were associated with a worse outcome in both groups, women with severe respiratory disease and those with severe maternal morbidity due to other causes (Table 3).

Analysis of sociodemographic and obstetric characteristics (Table 4) compared cases of PLTC and SMO for both groups: with severe respiratory disease and other causes of morbidity. For the respiratory complications,
there was an association to SMO and non-white color, history of diabetes, low weight and substance abuse (use of psychoactive substances, including alcohol and illicit drugs), in addition to delay in care. In contrast, the group of cases due to other causes of morbidity, low maternal age, first pregnancy, history of maternal obesity and lack of a partner were identified as having lower association to SMO, while hospitalization in a non-public institution, parity, history of caesarian section, drug abuse, complication occurrence at an earlier gestational age and mainly in the postpartum period, in addition to any type of delay in obstetric care, were associated with SMO.

Concerning characteristics of pregnancy and perinatal results (Table 5), the group with severe respiratory disease had a higher rate of early preterm births, between 22 and 33 weeks of gestation, low birthweight (<2500 g), Apgar < 7 at five minutes of life, stillborn and the need for hospital admission/transference of the newborn infant, compared to the group with severe maternal morbidity due to other causes. Neonatal death increased threefold in women with severe respiratory disease. A statistically significant difference was observed in the groups compared, when the mode of delivery and onset of labor were taken into consideration (p < 0.001). The number of women who did not undergo pregnancy resolution and remained pregnant during the severe morbid event was much higher in the respiratory disease group. Around 35 % were “still pregnant” compared to 5 % in the group with severe maternal morbidity due to other causes.

Discussion
Our study presents the burden of severe respiratory diseases among cases of severe maternal morbidity and results of the 2009 H1N1 influenza pandemic, considering 27 referral maternity hospitals in Brazil. Overall, the prevalence of respiratory disease was rare (5 %). Nevertheless, respiratory disease accounted for one-quarter of MNM cases and two-thirds of MD. Worse adverse outcomes occurred among cases of confirmed A(H1N1)pdm09, with an impressive MNM:MD ratio below one, meaning that there were more deaths than near miss cases in this group.

The mortality index (MI) was over 50 % in the H1N1 group, compared to 7.4 % for other causes of severe maternal morbidity. The MI is known to correlate to quality of care and when the index is above 20 %, it represents substandard care [22]. Numbers of MI over 50 % were “still pregnant” compared to 5 % in the group with severe maternal morbidity due to other causes.

Table 1: Women with severe respiratory disease: cases non-tested for influenza A(H1N1)pdm09, influenza A(H1N1)pdm09 positive, influenza A(H1N1)pdm09 negative and other causes of morbidity according to severity of outcome (PLTC, MNM, MD) and their correspondent health indicators

| Conditions | PLTC | MNM | MD | Total | Health indicators |
|------------|------|-----|----|-------|-------------------|
|            |      |     |    |       | MNMR/ 1000LB | SMOR/ 1000LB | MNM:MD ratio | Mortality index % | MWR/ 100000LB |
| Influenza A(H1N1)pdm09 positive | 22   | 13  | 14 | 49    | 0.16  | 0.33  | 0.93:1  | 51.8  | 17.0  |
| Influenza A(H1N1)pdm09 negative | 55   | 18  | 10 | 83    | 0.22  | 0.34  | 1.80:1  | 35.7  | 12.2  |
| Non-tested for influenza A(H1N1)pdm09 | 116  | 167 | 70 | 353a  | 2.03  | 2.89  | 2.39:1  | 29.5  | 85.2  |
| Total Respiratory disease | 193  | 198 | 94 | 485   | 2.41  | 3.55  | 2.11:1  | 32.2  | 114.4 |
| Other causes | 8452 | 572 | 46 | 9070  | 6.96  | 7.52  | 12.43:1 | 7.4   | 56.0  |

LB: live births; PLTC: potentially life-threatening condition; MNM: maternal near miss; MD: maternal death; MNMR: maternal near mits ratio; SMOR: severe maternal outcome ratio = (MNM + MD)/LB X 1000; MNM:MD ratio = MNM:1MD; Mortality index = MD/(MNM + MD); MMR: maternal mortality ratio = MD/LB X 100.000
*a Non-tested for influenza A(H1N1)pdm09 = includes suspected Influenza (74) + without suspected Influenza (279)

Table 2: Prevalence of maternal near miss criteria in women with severe respiratory disease or other causes of severe maternal morbidity

| Maternal Near Miss criteria | Respiratory | Other causes | p* |
|-----------------------------|-------------|--------------|----|
|                            | n | % | N | % |
| Clinical only              | 20 | 6.8 | 93 | 15.0 |
| Laboratory only            | 21 | 7.2 | 151 | 24.4 |
| Management only            | 22 | 7.5 | 153 | 24.8 |
| Clinical + Laboratory      | 15 | 5.1 | 23 | 3.7 |
| Clinical + Management      | 41 | 14.0 | 82 | 13.3 |
| Laboratory + Management    | 12 | 4.1 | 30 | 4.9 |
| Clinical + Laboratory + Management | 161 | 55.1 | 86 | 13.9 |

*p* Adjusted for design effect of cluster sampling

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therapy, as soon as possible in case of suspected disease [10]. Brazil followed these recommendations and launched a national vaccination campaign before the winter of 2010, targeted at high-risk groups, including pregnancy. The vaccine was available in all public health facilities, at no cost for the patient and reached very high coverage (around 80 %), most likely due to the long term experience in the National Immunization Program for Children and due to the awareness about the severity of the disease, among health professionals and among the society [23]. We cannot evaluate the impact of those preventive measures in our study, since we lack information on the total number of cases and specific data on individual history of vaccination or treatment, however, from our Fig. 2, we can see on the linear traces that there is a trend towards decrease in numbers of severe cases, through time, especially after vaccination.

Clinical evaluation should determine treatment, in order to ensure timely and effective interventions. In our study, around 60 % of suspected cases of H1N1 influenza A virus were tested. In accordance with previous reports, symptoms were more severe in positive cases [24]. The majority of cases in Brazil occurred during cold weather (July, August and September), period of increased infections by respiratory viruses and influenza outbreak in the country (Brazil declared a pandemic in mid-July 2009).

Over half of the reported cases of severe respiratory disease were not due to suspected influenza infection. Acute respiratory failure was the cause, including a broad number of conditions, as follows: pulmonary edema, cardiac disease community-acquired pneumonia, aspiration, pulmonary embolism, asthma exacerbation or venous embolism. Unfortunately we do not have detailed information on each of the mentioned causes.

Nevertheless, these complications include mostly indirect causes of maternal morbidity and mortality, which represent novel or preexisting health problems unrelated to pregnancy, such as cardiac disease and asthma. Asthma is the most common medical condition that may worsen during pregnancy and it is often underdiagnosed and under-treated [9]. Direct causes of maternal morbidity and mortality can also lead to respiratory failure, such as systemic consequences of sepsis due to uterine infection and severe preeclampsia and eclampsia, complicated by pulmonary edema [25, 26].

It is very important to understand all differential diagnosis, since timely and adequate interventions can potentially improve maternal outcome. Future studies focusing on the specific differences in diagnosis and management of causes of acute respiratory failure should consider the main aspects on diagnosis and management of these conditions. Pneumonia in pregnancy and postpartum, for example, is the leading cause of fatal non obstetric infection and can be caused by bacteria, virus (at risk of secondary bacterial infection), fungus and mycobacteria and the clinical features include fever, cough, dyspnea and hypoxia [9].

Another important cause of severe complications is pulmonary edema, which can be consequence of left ventricular systolic or diastolic dysfunction, or due to the use of tocolytic agent, fluid overload, severe hypertension or severe renal disease. The clinical presentation of pulmonary edema is normally dyspnea, tachypnea, tachycardia, chest pain and diffuse crackles. There can be evidence of cardiac dysfunction, specific alterations in the electrocardiogram and radiographic abnormalities [27].

### Table 3 Estimated risk of severe maternal outcome (SMO) among women with severe respiratory disease or other causes of severe maternal morbidity according to management procedures used for severity

| Procedures associated with severity | Respiratory SMO | PR | 95 % CI* | Other causes SMO | PR | 95 % CI* |
|-----------------------------------|----------------|----|----------|-----------------|----|----------|
| Blood transfusion                  | 146            | 13 | 2.05     | 1.38–3.05       | 397 | 1010     |
| Central venous access              | 190            | 11 | 2.63     | 1.71–4.06       | 125 | 37       |
| ICU admission                      | 262            | 75 | 3.84     | 1.94–7.59       | 364 | 1414     |
| Hospital stay >7 days              | 211            | 65 | 1.97     | 1.32–2.95       | 322 | 2270     |
| Invasive mechanical ventilation    | 204            | 1  | 3.17     | 2.08–4.81       | 86  | 5        |
| Use of vasoactive drug             | 148            | 0  | 2.34     | 1.60–3.43       | 96  | 0        |
| Transfusion of ≥5U packed red blood cells | 60  | 0  | 1.83     | 1.37–2.45       | 189 | 0        |
| Intubation and ventilation ≥60 min not related with anesthesia | 210  | 0  | 3.35     | 2.23–5.05       | 85  | 0        |
| Dialysis for acute renal insufficiency | 34  | 0  | 1.75     | 1.35–2.26       | 29  | 0        |
| CPR                               | 84             | 0  | 1.93     | 1.46–2.55       | 36  | 0        |

Values in bold mean they are statistically significant (p < 0.05)

SMO severe maternal outcome (maternal near miss plus maternal death); PLTC potentially life-threatening condition; PR prevalence ratio adjusted for cluster design effect; CI confidence interval; ICU intensive care unit; CPR cardiopulmonary resuscitation

*Adjusted for design effect of cluster sampling
Table 4 Estimated risk of severe maternal outcome (SMO) among women with severe respiratory disease or other causes of severe maternal morbidity according to sociodemographic and obstetric characteristics, medical history and delay in care

| Variables                      | Respiratory SMO | PR  | 95 % CI* | Other causes SMO | PR  | 95 % CI* |
|-------------------------------|----------------|-----|----------|------------------|-----|----------|
|                               | Respiratory PLTC |     |          | Other causes PLTC |     |          |
|                               | SMO             | PLTC |          | SMO             | PLTC |          |
| Age (years)                   |                 |      |          |                  |      |          |
| ≤ 19                          | 59              | 33   | 1.11     | 0.90–1.38        | 80  | 1541     | 0.73 | 0.59–0.89 |
| 20–34                         | 176             | 130  | 1.00     |                  | 401 | 5513     | 1.00 |
| ≥ 35                          | 57              | 30   | 1.14     | 0.97–1.34        | 137 | 1398     | 1.32 | 1.05–1.64 |
| Marital statusa               |                 |      |          |                  |      |          |
| With partner                  | 152             | 100  | 1.00     |                  | 317 | 3704     | 1.00 |
| Without partner               | 84              | 57   | 0.99     | 0.76–1.28        | 159 | 3466     | 0.56 | 0.40–0.78 |
| Educationb                    |                 |      |          |                  |      |          |
| Elementary                    | 91              | 62   | 1.00     |                  | 192 | 2871     | 1.00 |
| > Elementary                  | 89              | 62   | 0.99     | 0.77–1.28        | 188 | 3368     | 0.84 | 0.66–1.08 |
| Skin Colorc                   |                 |      |          |                  |      |          |
| White                         | 133             | 112  | 1.00     |                  | 247 | 2539     | 1.00 |
| Non white                     | 115             | 62   | 1.20     | 1.01–1.41        | 229 | 3702     | 0.66 | 0.43–1.01 |
| Number of pregnanciesd        |                 |      |          |                  |      |          |
| 1                             | 117             | 65   | 1.12     | 0.92–1.38        | 194 | 3599     | 0.65 | 0.56–0.75 |
| 2 or more                     | 170             | 127  | 1.00     |                  | 411 | 4810     | 1.00 |
| Number of childbirthsd        |                 |      |          |                  |      |          |
| 0                             | 132             | 74   | 1.00     |                  | 210 | 4160     | 1.00 |
| 1 or more                     | 155             | 118  | 0.89     | 0.73–1.08        | 395 | 4249     | 1.77 | 1.55–2.02 |
| Previous C-sectionse         |                 |      |          |                  |      |          |
| 0                             | 217             | 129  | 1.00     |                  | 402 | 6363     | 1.00 |
| 1 or more                     | 61              | 63   | 0.78     | 0.59–1.04        | 184 | 1940     | 1.46 | 1.22–1.74 |
| Medical historyf              |                 |      |          |                  |      |          |
| Chronic hypertension          | 30              | 17   | 1.11     | 0.88–1.41        | 84  | 1325     | 0.90 | 0.66–1.23 |
| Diabetes                      | 12              | 3    | 1.39     | 1.04–1.86        | 21  | 173      | 1.69 | 0.94–3.07 |
| Smoking                       | 21              | 23   | 0.80     | 0.58–1.12        | 32  | 390      | 1.18 | 0.68–2.04 |
| Obesity                       | 39              | 36   | 0.88     | 0.68–1.12        | 66  | 1848     | 0.46 | 0.30–0.70 |
| Low weight                    | 5               | 0    | 1.73     | 1.33–2.27        | 1   | 21       | 0.70 | 0.09–5.30 |
| Respiratory disease           | 26              | 31   | 0.76     | 0.48–1.20        | 11  | 166      | 0.96 | 0.62–1.46 |
| HIV/AIDS                      | 9               | 9    | 0.85     | 0.51–1.44        | 6   | 67       | 1.27 | 0.56–2.88 |
| Substance abuse               | 14              | 4    | 1.36     | 1.06–1.74        | 11  | 71       | 2.09 | 1.20–3.63 |
| Prenatal coverageg            |                 |      |          |                  |      |          |
| Public                        | 206             | 134  | 1.00     |                  | 430 | 5890     | 1.00 |
| Other                         | 34              | 15   | 1.15     | 0.85–1.54        | 69  | 746      | 1.24 | 0.82–1.88 |
| Prenatal adequacyh            |                 |      |          |                  |      |          |
| No                            | 56              | 36   | 1.00     | 0.81–1.22        | 109 | 1925     | 0.75 | 0.60–0.94 |
| Yes                           | 212             | 135  | 1.00     |                  | 476 | 6197     | 1.00 |
| Hospitalization coveragei     |                 |      |          |                  |      |          |
| Public                        | 285             | 187  | 1.00     |                  | 602 | 8366     | 1.00 |
| Other                         | 6               | 6    | 0.83     | 0.44–1.54        | 16  | 78       | 2.54 | 1.43–4.50 |
During labor or immediate postpartum, a rare and feared complication is the aspiration of gastric contents, if needed intubation for general anesthesia, due to increased intraabdominal pressure and predisposing physiological changes of pregnancy such as relaxation of the lower esophageal sphincter and delayed gastric emptying. However, in the last decades, the incidence of aspiration significantly declined, even with food intake during labor [28].

The definitions of severe respiratory complications that are usually reported can be rather confusing and sometimes difficult to incorporate [29]. Recent onset of fever and respiratory symptoms, including cough is the clinical definition of Severe Acute Respiratory Syndrome. In the setting of an epidemic, this definition is very useful to raise awareness and ensure prompt treatment, as soon as a suspected case is identified [30]. ARDS is another acronym for Acute Respiratory Distress Syndrome, a different condition that represents hypoxemic respiratory failure and bilateral radiographic opacities, without congestive heart failure. This diagnosis depends on oxygenation deficit measurements and chest imaging [31, 32].

In the current study, we couldn’t accurately establish any of the above conditions, since we did not collect data on clinical symptoms (fever, cough) neither obtained the results of those specific laboratory findings or imaging. The diagnosis of H1N1 influenza was also not standardized through all hospitals included. We understand that timing of sample collection, quality of sample and laboratory procedures are key for the accurate diagnosis and unfortunately we do not have data on details regarding these procedures.

Another limitation was the lack of data on the use of antiviral therapy or vaccination. For cases of SMO, complicated by documented organ dysfunction, ARDS would probably be the diagnosis of respiratory disease. Nevertheless, confirmation was lacking for all cases. In addition, we do not have a control group, with no underlying complication, what would be key to access risk factors. We only have data on severe maternal morbidity cases, comparing less severe (PLTC) to more severe cases (SMO).

Factors associated with SMO, included non-white color, history of diabetes, low weight and substance abuse, along with delay in care, were reported for the majority of conditions under study. Substance abuse associated with increased risk of severity in cases of respiratory disease, is in agreement with previous reports [33, 34]. Drug-related severe respiratory complications can occur, resulting from parenchymal (infectious and non-infectious pneumonitis, aspiration-related events, hemorrhage, pulmonary edema and pneumothorax), pulmonary vascular insults (endovascular infection, hemorrhage, and vasoconstriction) or airway (bronchospasm and hemorrhage) abnormalities. Diabetes was also associated with an increased risk of SMO among cases complicated by severe respiratory disease. Previous studies had demonstrated this fact, even in the Brazilian population. Diabetes is one of the main risk factors for death from H1N1 influenza A [35] virus infection. Medical history, including known factors related to worse outcomes should be highlighted and the awareness among patients and health professionals towards targeted cases could impact in the final outcome.

Pregnancy characteristics and perinatal outcomes according to the main cause of severe morbidity showed that pregnancies complicated by respiratory disease present an increased rate of preterm delivery and worse perinatal outcomes. This finding had already been demonstrated [10, 36]. Studies have shown that vaccination
Characteristics of pregnancy and perinatal results according to cause of morbidity: severe respiratory disease or other causes

| Variables                              | Respiratory   | Other causes   | p*       |
|----------------------------------------|---------------|---------------|----------|
|                                        | n  | %  | n  | %  |          |
| Gestational age at delivery (weeks)a   |     |     |     |     | <0.001  |
| < 22                                   | 20  | 4.5 | 307 | 3.6 |          |
| 22–27                                  | 23  | 5.2 | 259 | 3.0 |          |
| 28–33                                  | 83  | 18.8| 1341| 15.6|          |
| 34–36                                  | 56  | 12.7| 1724| 20.1|          |
| ≥ 37                                   | 95  | 21.5| 4427| 51.7|          |
| Still pregnant                         | 164 | 37.2| 511 | 6.0 |          |
| Mode of deliveryb                      |     |     |     |     | <0.001  |
| Vaginal                                | 58  | 12.1| 2080| 23.0|          |
| C-section                              | 233 | 48.5| 5921| 65.5|          |
| Abortion/ ectopic pregnancy            | 24  | 5.0 | 521 | 5.8 |          |
| Still pregnant                         | 165 | 34.4| 512 | 5.7 |          |
| Onset of laborc                        |     |     |     |     | <0.001  |
| Spontaneous                            | 66  | 14.1| 2652| 29.6|          |
| Induction                              | 33  | 7.1 | 792 | 8.8 |          |
| No labor                               | 179 | 38.3| 4477| 50.0|          |
| Abortion                               | 24  | 5.1 | 521 | 5.8 |          |
| Still pregnant                         | 165 | 35.3| 513 | 5.7 |          |
| Perinatal results                      |     |     |     |     |          |
| Apgar at 5 min <7d                     | 38  | 17.7| 258 | 3.5 | <0.001  |
| Apgar at 5 min ≥7                      | 177 | 82.3| 7152| 96.5|          |
| Birth weight <2500 g o                 | 142 | 58.9| 3007| 39.1| <0.001  |
| Birth weight ≥2500 g                   | 99  | 41.1| 4675| 60.9|          |
| Still birthf                            | 36  | 13.6| 352 | 4.5 | <0.001  |
| Live birth                             | 229 | 86.4| 7504| 95.5|          |
| Perinatal outcomeg                     |     |     |     |     | <0.001  |
| Neonatal death                         | 15  | 7.0 | 178 | 2.5 |          |
| Admitted/ transferred                  | 83  | 38.6| 1547| 21.4|          |
| Hospital discharge                     | 117 | 54.4| 5506| 76.1|          |

*aAdjusted for design effect of cluster sampling

Missing information for: * 545; # 41; $ 133; % 1930; & 1632; @ 1434; ¥ 2109 cases

Conclusion

Severe respiratory disease, especially considering the influenza season, is one of the most serious causes of maternal near miss and death. Increased awareness of this condition, preventive vaccination during pregnancy, early diagnosis and treatment are required to improve maternal health.

Table 5

**Abbreviations**

SMM: severe maternal morbidity; ICU: intensive care unit; CPR: cardiopulmonary resuscitation; PR: prevalence ratio; A(H1N1)pdm09: H1N1 influenza pandemic; ARDS: acute respiratory distress syndrome; CI: confidence interval; MD: maternal deaths; MI: mortality index; MNM: maternal near miss; PLTC: potentially life-threatening conditions; RR: respiratory rate; SMO: severe maternal outcome; WHO: World Health Organization.

**Competing interests**

The authors declare that they have no competing interests.

**Ethics and consent to participate**

The study complied with ethical principles guiding human research described in the Declaration of Helsinki and was approved by the Institutional Review Board of each local center and research coordinating center (CONEP, Brazilian Ministry of Health: 097/2009). The Informed Consent Form was waived, since data were obtained from hospital records after patient discharge, without any contact with research subjects.

**Availability of data and materials**

All the data supporting the presented findings is contained within the manuscript.

**Authors’ contributions**

The idea for the study and this specific analytical approach arose in a group discussion among all the authors. Analyses were planned by LCP, MLC and JGC. The first version of the manuscript was drafted by LCP and MLC. Subsequently, all remaining authors complemented with suggestions. All authors contributed to the development of the study protocol and approved the final version of the manuscript.

**Acknowledgements**

Brazilian Network for Surveillance of Severe Maternal Morbidity Group: João L. Pinto Silva, Maria H. Sousa, Rodrigo S. Camargo, Wina Zotareli, Lúcio T. Gurgel, Eliana M Amaral, Lale Say, Robert C. Pattinson, Maritza V Rudge, Isacema M Calderon, Maria V Bahamondes, Danielly S Santana, Simone P Gonçalves, Olímpio B Moraes Filho, Simone A Carvalho, Francisco E Feitosa, George N Chaves, Ione R Brum, Gloria C Saint’Yves, Carlos A Menezes, Patrícia N Santos, Everardo M Guanabara, Elton J Almeida Jr, Joaquim L. Moreira, Maria R Sousa,

During the first trimester of pregnancy can improve those outcomes and decrease stillbirth rates without increasing the risk of malformations, which is a common concern among health practitioners and pregnant women [37].
Federico A Peret, Liv B Paula, Luiza E Schmaltz, Cleire Pessoni, Leila Katz, Adriana Bione, Antonino C Barbosa Lima, Edilberto A Rocha Filho, Melânia A Amorim, Debrah Leite, Ivelyne Radaci, Marília G Martins, Frederico Barroso, Fernando C Oliveira Jr, Denis J Nascimento, Cláudio S Paiva, Moines D Lima, Djacir M Freire, Roger D Ruhloff, Simone M Rodrigues, Sergio M Costa, Adriana G Lutz, Daniela Guimarães, Gustavo Lobato, Marcos Nakamura-Pereira, Eduardo Cardioli, Alessandra Petersson, Cynthia D Perez, Jose C Peraçoli, Roberto A Costa, Nelson L Maia Filho, Jacinta P Matias, Elaine C Moises, Fátima A Lotufo, Luiz E Carvalho, Carla B Andreucci, Elvira A Zanette, Márcia M Aquino, Maria H Ohnuma, Rosiane Mattar and Felipe F Campanharo.

Funding
This study was funded by CNPq/DECIT (The National Research Council and the Department of Science and Technology of the Brazilian Ministry of Health), grant number 402702/2008-5. The authors are solely responsible for the content, which does not necessarily represent the official views of CNPq, nor influence manuscript content.

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Received: 6 July 2015 Accepted: 26 April 2016
Published online: 21 May 2016

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