Oseltamivir Use in Low-Birth Weight Infants During the 2009 nH1N1 Influenza A Outbreak in the Western Cape, South Africa

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Summary
Before vaccination against nH1N1 influenza was available in South Africa our hospital experienced an outbreak of nH1N1 infection on the maternal and neonatal platform. Oseltamivir was administered to nine low birth weight infants, five for therapy and four for prophylaxis. The median gestational age was 31 (27–37) weeks and the birth weight was 1660 (720–2360) g. Respiratory function improved in those with confirmed disease and none receiving prophylaxis developed worsening respiratory symptoms. One neonate receiving prophylaxis developed self-limiting conjunctivitis; another succumbed from necrotizing enterocolitis (NEC) three days post completion of oseltamivir treatment. A causal relationship between oseltamivir and NEC, although unlikely, cannot be confirmed or excluded.

Key words: oseltamivir, low birth weight, H1N1 influenza.

Introduction
Novel influenza A H1N1 (nH1N1) emerged in Mexico in April 2009, and between 30 August 2009 and 12 June 2010, 279 laboratory-confirmed influenza-associated pediatric deaths were reported, equating to nearly four times the average reported in the previous five influenza seasons. Of these, 226 (81%) were associated with nH1N1 virus and 52 (18.6%) of all influenza cases were aged <2 years [1].

In June 2009, the first case of nH1N1 was confirmed in South Africa, and during August 2009 the epidemic reached its peak. At this time, for a period of 4 weeks, the National Institute for Communicable Diseases reported a rate of >2000 confirmed cases per week [2].

Pregnancy and the early postpartum period were soon identified as a major risk factor for severe nH1N1 disease [3], leading to concerns about the possible risk to neonates. Oseltamivir was recommended for hospitalized patients with severe disease and as prophylaxis for high-risk patients with influenza exposure [4]. However, this drug is not licensed for use in children <1 year of age [5] and limited knowledge existed regarding appropriate dosing for neonates. During the pandemic, once susceptibility to nH1N1 was confirmed, the Food & Drug Administration and the European Medicines Agency authorized emergency use in children <1 year of age [5, 6].

In August 2009, we admitted our first neonatal case of confirmed nH1N1 infection to the neonatal intensive care unit (NICU) and subsequently had documented exposure of hospitalized infants to source cases. We elected to utilize oseltamivir for treatment of suspected and confirmed nH1N1 cases and as prophylaxis in high-risk low birth weight (LBW) infants.

Methods
Tygerberg Hospital (TBH) manages local and referred mothers and infants requiring Levels 2 and 3 obstetric and neonatal care. LBW infants constitute up to 25% of the approximate 7000 infants delivered annually.

The neonatal division at TBH can accommodate 112 babies in 4 locations. Eight infants can be ventilated in the NICU and high care is performed at a ward level. Infants are admitted into large rooms with 4–12 infants per room. They are initially

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nursed on open incubators and once stable are transferred into either closed incubators, cots or kangaroo mother care. Bed occupancy in the wards often reaches 100% with a recommended patient to nurse ratio of 3:1 that is seldom attained. There are no isolation facilities available but during infection outbreaks patients are cohorted.

Due to ongoing staff shortages, personnel are allowed to perform duties in the presence of mild influenza-like symptoms, provided they wear a mask when in contact with patients. Influenza vaccination of staff members is not compulsory and at the time, nH1N1 vaccination was unavailable in South Africa.

We developed an influenza protocol for exposed and symptomatic infants on the neonatal platform. Hospitalized neonates developing signs and symptoms compatible with viral pneumonia (e.g. apnea, worsening respiratory distress) were tested for nH1N1. Nasopharyngeal aspirates or nasal swabs were screened using the shell vial respiratory panel assay, and if positive, were followed by a confirmatory polymerase chain reaction (PCR) assay specific for nH1N1. Infants with suggestive symptoms were initiated on oseltamivir at 2–3 mg/kg/dose twice daily for 5 days as soon as they were identified, without waiting for test results. During the outbreak, laboratory capacity was insufficient, resulting in the turn around time for test results being prolonged. Thus patients with negative results were still exposed to oseltamivir. In addition, infants with co-morbid illness nursed in open incubators and exposed to a source case of nH1N1 were given oseltamivir prophylaxis. A dose of 2–3 mg/kg daily for 10 days was recommended. Seventy-five milligram capsules of oseltamivir were diluted to prepare the paediatric dose, as recommended by the European Medicines Agency [7]. All treatment and prophylaxis was given via an orogastric tube and flushed with sterile water after drug administration.

We reviewed the records until discharge from hospital, of all the infants receiving oseltamivir. Approval was obtained from the Stellenbosch University Ethics Review board (NO9/09/252).

**Results**

A total of nine LBW infants exposed to nH1N1 while hospitalized received oseltamivir; five were symptomatic and thus received therapy; four received prophylaxis. The median gestational age (GA) for all infants was 31 (27–37) weeks and birth weight was 1660 (720–2360) g.

The five infants receiving therapeutic oseltamivir had a median GA of 28 (27–36) weeks and birth weight of 1130 (720–1660) g. The median duration of hospitalization at the time of screening for influenza was 20 (8–52) days. Three of the five had confirmed nH1N1. All three required increased respiratory support; one had increased oxygen requirement while on nasal continuous positive airway pressure (nCPAP); one needed to be placed on nCPAP from nasal prong oxygen and one required intubation and ventilation (Table 1). Two of the three confirmed cases had new changes on chest radiography compatible with viral pneumonia. All nH1N1 positive infants improved on oseltamivir. In Case 1, the positive nH1N1 PCR persisted after 5 days of treatment. We elected to prolong therapy because of the need for ongoing ventilator support. The course of illness in this infant was complicated by concomitant respiratory syncytial virus infection and ventilator associated pneumonia. The two infants without positive PCR confirmation had worsening respiratory symptoms, coinciding with exposure to nH1N1, thus early oseltamivir therapy was initiated.

Case 5 died from necrotising enterocolitis (NEC) three days after completion of therapeutic oseltamivir. Risk factors for NEC included prematurity, respiratory distress syndrome and a patent ductus arteriosus requiring ibuprofen treatment (completed 4 days before the initiation of oseltamivir). No gastrointestinal complications or raised inflammatory markers were observed during oseltamivir use in this patient. At diagnosis of NEC, the infant had a raised C-reactive protein, thrombocytopenia, hyponatremia (sodium 123 mmol/l) and renal impairment (urea 5.3 mmol/l, creatinine 111 μmol/l).

The exposure to nH1N1 influenza in Cases 1 and 4 was thought to be from the mother; in Case 1 the mother was symptomatic but never tested and in Case 4 the mother had a positive nH1N1 test. The parents of Cases 2, 3 and 5 were asymptomatic so nosocomial transmission was postulated. It was discovered that a nurse who tested nH1N1 positive had nursed Case 2 and 5.

Four infants in contact with proven nH1N1 cases received prophylactic oseltamivir and none suffered respiratory deterioration (Table 2). The median GA was 36 (30–37) weeks and the median birth weight was 1988 (1660–2360) g. Infants were hospitalized for a median of 10 (5–12) days prior to exposure. One patient (Case 6) developed self-limiting conjunctivitis.

The first nH1N1 PCR positive case was in NICU ventilated with high-frequency oscillation. This method of ventilation allows air to escape from the circuit, potentially disseminating airborne viruses. All NICU patients are nursed on open incubators and as the remaining 3 patients in that room were requiring mechanical ventilation they were considered high-risk contacts and given oseltamivir prophylaxis. The fourth patient required mechanical ventilation following abdominal surgery and the mother was confirmed to have nH1N1 infection.

We noted significant incorrect prescribing practices among clinicians caring for infants on
oseltamivir. Although the correct dose was always given; in the preventative group, two patients did not receive the medication for the required duration. Oseltamivir was administered for longer than was indicated in two of the five infants receiving therapy. None of the nine LBW infants showed any central nervous system abnormalities potentially related to oseltamivir, nor was any deterioration noted in their renal function.

Discussion

During the nH1N1 outbreak at our hospital, LBW infants were thought to be at high risk for disease. In busy units such as ours there is potential for nosocomial infection. Complicating factors for severe disease in neonates are their immature immune system and often pre-existing lung disease. The lack of prior maternal exposure to novel influenza viruses and therefore the absence of protective antibodies further increase the risk. In addition, there is a lack of licensed medication available for use in these patients. Following a report on mortality in juvenile rats receiving a single high dose of 1000 mg of oseltamivir, the manufacturers warned against its use in children <1 year of age. Mortality in the animal model was thought to be partly due to an immature blood brain barrier [8]. The dose was far in excess of the recommended 2–3 mg/kg/dose. Despite this, oseltamivir was safely used in Japanese children <1 year of age. Reports indicate that these children (mean age of 7.5 months) had no significant adverse events [9]. Subsequent to the pandemic, data released from the Collaborative Antiviral Study Group supports a dose of 3 mg/kg in children <9 months of age [10]. It is not clear whether these doses were assessed sufficiently in preterm LBW infants. The WHO recommends that lower doses can be considered in patients who are not receiving regular oral feeds or where concomitant medication is likely to significantly reduce renal function [11]. Acosta et al. [12] have done a pharmacokinetic analysis in premature infants, finding that in order to achieve adequate plasma levels of oseltamivir, a dose of 3 mg/kg in children >9 months of age with influenza encephalitis. Their study showed that 10 mg/kg twice daily in premature babies produces oseltamivir carboxylate (the active metabolite) exposures similar to those in older children, although with the advantage of less frequent dosing. This is most likely due to the immature hepatic function and diminished renal capacity of the premature infant.

Known adverse effects of oseltamivir include abdominal pain, nausea, vomiting, epistaxis, ear disorders, conjunctivitis, neuropsychiatric changes and encephalopathy [3]. Kimberlan et al. [14] found that the frequency of adverse neurological events in children under 12 months of age who received oseltamivir were not increased compared with those who received adamantanes. However, only 18% of those who received oseltamivir were not so treated.

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<th>TABLE 1</th>
<th>Clinical characteristics of 5 neonates who received therapeutic oseltamivir</th>
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<td>Case</td>
<td>Presumed contact</td>
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<td>1</td>
<td>Mother—suspected</td>
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<td>2</td>
<td>Health care worker—confirmed</td>
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<td>3</td>
<td>Health care worker—suspected</td>
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<td>4</td>
<td>Mother—confirmed</td>
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<td>5</td>
<td>Health care worker—confirmed</td>
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<sup>a</sup>Intermittent positive pressure ventilation.  
<sup>b</sup>High-frequency oscillation ventilation.  
<sup>c</sup>Nasal continuous positive airway pressure.  
<sup>d</sup>Necrotising Enterocolitis.
subjects were <2 months and the oseltamivir recipients were more likely to be full term at birth.

Subsequent to this outbreak there have been two articles citing oseltamivir use in very low birth weight (VLBW) infants. The first is a case report of a VLBW infant in Israel who received oseltamivir and suffered no adverse events [15]. The second is a case series of term and preterm infants treated with oseltamivir in Portugal [16]. Again, no adverse events were reported.

Two adverse events were noted in our patients, but only the self-limiting conjunctivitis can be linked to oseltamivir. NEC is multifactorial in origin and cannot be directly attributed to the oseltamivir; however caution should be used when prescribing off label medications. In this regard preterm infants have highly altered physiology and pharmacokinetic properties that may vary significantly from term infants and older children.

It is difficult to comment on the efficacy of oseltamivir treatment and prophylaxis due to the small sample size of our cohort and retrospective nature of the study. The three confirmed nH1N1 cases, all of whom developed significant respiratory disease, improved with the early use of oseltamivir. Two of the positive cases required only nCPAP, suggesting possible arrest in disease progression. These two infants returned to their baseline oxygen requirement after treatment with oseltamivir.

Prior to the nH1N1 pandemic, oseltamivir was not in routine use at TBH. Although the drug was initiated for appropriate indications and at the correct dose, the duration of use was inconsistent. Information was made available and protocols provided but further training will be needed in subsequent influenza seasons.

There is uncertainty regarding the exact dose of oseltamivir for LBW infants. A dose of 3 mg/kg twice daily has been used without adverse events [16] however possible side effects were seen in our small study. The WHO makes the provision to give only one dose a day to infants younger than 2 weeks or to reduce the dose in high-risk infants [11]. Acosta et al. [12] showed that lower doses are needed in preterm infants. From this information we feel that 1–3 mg/kg/dose of oseltamivir, daily for 10 days as prophylaxis or twice daily for 5 days as treatment, is acceptable. However, the use of oseltamivir, as well as other antivirals, in the very young and preterm infants requires further investigation.

### References


