ARTICLE DETAILS

TITLE (PROVISIONAL)	Advanced age and asthma are associated with severe disease in children with pandemic H1N1 influenza; a retrospective cross sectional study of risk factors for severe pandemic H1N1 influenza in children
AUTHORS	Shaun Morris, Patricia Parkin, Michelle Bridge, Padmaja Subbarao, Yvonne Yau, Sean O'Riordan, Michelle Barton, Upton Allen, Dat Tran

VERSION 1 - REVIEW

REVIEWER	Romina P. Libster Vanderbilt University
REVIEW RETURNED	07/11/2011

THE STUDY	ABSTRACT: 1) Admission criteria and age range for inclusion were not clearly defined in the design section. Please revise. 2) Would be important to include the p value for the reported comparisons. INTRODUCTION: 1) I found the following sentence not very accurate: " It is not known if pandemic H1N1 influenza has differing risk factors…" . I encourage the authors to add an exhaustive literature revision in order to support this statement. Some examples are: Increased extent of and risk factors for pandemic (H1N1) 2009 and seasonal influenza among children, Israel. Engelhard D, Bromberg M, Averbuch D, Tenenbaum A, Goldmann D, Kunin M, Shmueli E, Yatsiv I, Weintraub M, Mandelboim M, Strauss-Liviatan N, Anis E, Mendelson E, Shohat T, Wolf DG, Shapiro M, Grotto I. Emerg Infect Dis. 2011 Sep;17(9):1740-3. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis.Van Kerkhove MD, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, Carlino LO, Owen R, Paterson B, Pelletier L, Vachon J, Gonzalez C, Hongjie Y, Zijian F, Chuang SK, Au A, Buda S, Krause G, Haas W, Bonmarin I, Taniguichi K, Nakajima K, Shobayashi T, Takayama Y, Sunagawa T, Heraud JM, Orelle A, Palacios E, van der Sande MA, Wielders CC, Hunt D, Cutter J, Lee VJ, Thomas J, Santa-Olalla P, Sierra-Moros MJ, Hanshaoworakul W, Ungchusak K, Pebody R, Jain S, Mounts AW; WHO Working Group for Risk Factors for Severe H1N1pdm Infection. PLoS Med. 2011 Jul;8(7):e1001053. Epub 2011 Jul 5.
RESULTS & CONCLUSIONS	1) If data are available, would be very interesting to show a comparison of the clinical symptoms by age category and the laboratory values between the H1N1 and seasonal influenza infection. 2) Would be interesting also to show unadjusted and adjusted OR in

	the table 5 for both H1N1 and seasonal influenza analysis.
GENERAL COMMENTS	The current article seeks to describe the characteristics and risk factors associated with severe disease of children admitted with laboratory confirmed 2009 pandemic H1N1 influenza and compare them to historic controls admitted with seasonal influenza. I found this article very interesting, however, some points should be described in more detail. ABSTRACT: 1) Admission criteria and age range for inclusion were not clearly defined in the design section. Please revise. 2) Would be important to include the p value for the reported comparisons. INTRODUCTION: 1) I found the following sentence not very accurate: " It is not known if pandemic H1N1 influenza has differing risk factors…" . I encourage the authors to add an exhaustive literature revision in order to support this statement. Some examples are: Increased extent of and risk factors for pandemic (H1N) 2009 and seasonal influenza among children, Israel. Engelhard D, Bromberg M, Averbuch D, Tenenbaum A, Goldmann D, Kunin M, Shmueli E, Yatsiv I, Weintraub M, Mandelboim M, Strauss-Liviatan N, Anis E, Mendelson E, Shohat T, Wolf DG, Shapiro M, Grotto I. Emerg Infect Dis. 2011 Sep;17(9):1740-3. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis.Van Kerkhove MD, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, Carlino LO, Owen R, Paterson B, Pelletier L, Vachon J, Gonzalez C, Hongjie Y, Zijian F, Chuang SK, Au A, Buda S, Krause G, Haas W, Bonmarin I, Taniguichi K, Nakajima K, Shobayashi T, Takayama Y, Sunagawa T, Heraud JM, Orelle A, Palacios E, van der Sande MA, Wielders CC, Hunt D, Cutter J, Lee VJ, Thomas J, Santa-Olalla P, Sierra-Moros MJ, Hanshaoworakul W, Ungchusak K, Pebody R, Jain S, Mounts AW; WHO Working Group for Risk Factors for Severe H1N1pdm Infection. PLoS Med. 2011 Jul;8(7):e1001053. Epub 2011 Jul 5. DESIGN 1) Admission criteria and age range for inclusion were not clearly defined in the design section. Please revise as requested for the abstract. TABLES 1) If data are available, would be very interesting to show a comparison of the clinical symptoms by age category and the laboratory values between the H1N1 and seasonal influenza infection. 2) Would be interesting also to show unadjusted and adjusted OR in the table 5 for both H1N1 and seasonal influenza analysis.

REVIEWER	Natasha Halasa, MD, MPH Assistant Professor Vanderbilt University Medical Center Nashville, TN USA
REVIEW RETURNED	02/12/2011

THE STUDY	This is a retrospective study - that compares seasonal and H1N1 flu - however, the methods of detection differ between the viruses - therefore, there may be an underdetection of seasonal influenza. As stated, this is not populaiton-based. The comparisons are

	convenient sampling.
	Only those with positive flu within 3 days of admision were included. Not sure exactly how they found their patients - through micro lab, database, etc... Are the author sure they located all patients with flu? Why only 4 seasons of influenza compared to 1 season of flu - not sure of the rationale. Please provide. More details are needed.
RESULTS & CONCLUSIONS	More details are needed about the clinical presentation of sesaonal influenza - there is nothing about this.
	In addition - lab values should be presented as well for seasonal flu.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Romina P. Libster
Vanderbilt University

If you have any further comments for the authors please enter them below.
The current article seeks to describe the characteristics and risk factors associated with severe disease of children admitted with laboratory confirmed 2009 pandemic H1N1 influenza and compare them to historic controls admitted with seasonal influenza. I found this article very interesting, however, some points should be described in more detail.

ABSTRACT:
1) Admission criteria and age range for inclusion were not clearly defined in the design section. Please revise.

Authors' response: The 'Participants' section of the newly structured abstract now lists the admission criteria (ie all laboratory identified cases), age range (children under 18), and exclusion criteria (those with onset of symptoms >3 days after date of admission).

2) Would be important to include the p value for the reported comparisons.

Authors' response: P values have now been added to the comparisons of proportions in the results section of the abstract.

INTRODUCTION:
1) I found the following sentence not very accurate: " It is not known if pandemic H1N1 influenza has differing risk factors…" . I encourage the authors to add an exhaustive literature revision in order to support this statement. Some examples are:
Increased extent of and risk factors for pandemic (H1N1) 2009 and seasonal influenza among children, Israel. Engelhard D, Bromberg M, Averbuch D, Tenenbaum A, Goldmann D, Kunin M, Shmueli E, Yatsiv I, Weintraub M, Mandelboim M, Strauss-Liviatan N, Anis E, Mendelson E, Shohat T, Wolf DG, Shapiro M, Grotto I. Emerg Infect Dis. 2011 Sep;17(9):1740-3.
Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis.Van Kerkhove MD, Vandemaele KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, Carlino LO, Owen R, Paterson B, Pelletier L, Vachon J, Gonzalez C, Hongjie Y, Zijian F, Chuang SK, Au A, Buda S, Krause G, Haas W, Bonmarin I, Taniguichi K, Nakajima K, Shobayashi T, Takayama Y, Sunagawa T, Heraud JM, Orelle A, Palacios E, van der Sande MA, Wielders CC, Hunt D, Cutter J, Lee VJ, Thomas J, Santa-Olalla P, Sierra-Moros MJ, Hanshaoworakul W, Ungchusak K, Pebody R, Jain S, Mounts AW; WHO Working Group for Risk Factors for Severe H1N1pdm Infection. PLoS Med. 2011 Jul;8(7):e1001053. Epub 2011 Jul 5.

DESIGN

Authors' response: The sentence noted above has been deleted from the text and the initial paragraph of the introduction has been edited to include the first two of the above suggested references.

1) Admission criteria and age range for inclusion were not clearly defined in the design section. Please revise as requested for the abstract.

Authors' response: The design section has now been amended to more clearly state that admission criteria in this study include all children who tested positive for influenza in the 2004-05 to 2008-09 seasonal influenza seasons and the 2009 pH1N1 influenza season, that the age range for admission includes all children to 18 years, and the major exclusion criterion was development of symptoms on or after the third day of admission.

TABLES
1) If data are available, would be very interesting to show a comparison of the clinical symptoms by age category and the laboratory values between the H1N1 and seasonal influenza infection.

Authors' response: The table of clinical symptoms has now been edited to show both seasonal and pH1N1 influenza.

2) Would be interesting also to show unadjusted and adjusted OR in the table 5 for both H1N1 and seasonal influenza analysis.

Authors' response: We have added the unadjusted (univariate) odds ratios to the footnote to table 5. We have placed this information in the footnote rather than expand the table itself because it is the more important adjusted numbers that we wish to draw the reader's attention to.

Reviewer: Natasha Halasa, MD, MPH
Assistant Professor
Vanderbilt University Medical Center
Nashville, TN USA

This is a retrospective study - that compares seasonal and H1N1 flu - however, the methods of detection differ between the viruses -therefore, there may be an underdetection of seasonal influenza. As stated, this is not population-based. The comparisons are convenient sampling.

Only those with positive flu within 3 days of admission were included. Not sure exactly how they found their patients - through micro lab, database, etc... Are the author sure they located all patients with flu? Why only 4 seasons of influenza compared to 1 season of flu - not sure of the rationale. Please provide. More details are needed.

Authors' response: The design section has been edited to state that cases were found via a review of microbiology laboratory records. Through this method we are certain that we located all patients at the hospital with influenza with the exception of any cases that had a false negative result or were tested at an outside hospital with no repeat test at our institution. However, we expect both of these numbers to be very small, particularly for the pH1N1 season when testing of any and all children with any respiratory symptoms was very widespread. The limitations section of the discussion has been edited to reflect the above. We included 5 years of data on seasonal influenza A in order to obtain a sample

size comparable to pH1N1 from waves 1 and 2 of the pandemic for improved statistical power.

More details are needed about the clinical presentation of seasonal influenza - there is nothing about this.

Authors' response: The clinical symptoms table has been edited to now show clinical symptoms for both seasonal and pH1N1 influenza.

In addition - lab values should be presented as well for seasonal flu.

Authors' response: This has now been done.

Additional note: The surname of Dr. Michelle Bridge has changed and is now Dr. Michelle Science.

VERSION 2 – REVIEW

REVIEWER	Natasha Halasa, MD, MPH Assistant Professor Vanderbilt University Medical Center Nashville, TN USA
REVIEW RETURNED	26/01/2012

THE STUDY	the authors did a good job of addressing the concerns of the reviewers.