DEFINITION OF A CORRELATE OF PROTECTION FOR INACTIVATED INFLUENZA VACCINES IN CHILDREN LESS THAN FIVE YEARS OF AGE: DIFFERENCE BETWEEN A SEASONAL CORRELATE AND A CHALLENGE MODEL

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BACKGROUND

- The haemagglutination inhibition (HAI) titer of 1:40 which has been recognized as an immunologic correlate corresponding to a 50% reduction in the risk of contracting influenza in adult populations is based largely on challenge studies[1].
- Neither seasonal nor challenge based correlates have been evaluated in children.
- To evaluate potential correlates of protection in children, studies evaluating efficacy against proven influenza infections during the pediatric age are required.

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OBJECTIVES

- To evaluate the relationship between HAI antibody titer and clinical protection from influenza in children between 6 months and six years of age.

METHODS

- 4707 healthy influenza vaccine naive children 6-72 months old were randomized 2:1:1 (year 1) or 2:2:1 (year 2) to receive two doses of MF59®-adjuvanted influenza vaccine (ATIV, Fluad®; Novartis Vaccines), split trivalent influenza vaccine (TIV control, Agrippal®, Novartis Vaccine or Influsplit SSW®, GSK Biologicals), or non-influenza control (tick borne encephalitis vaccine, Encepur® or meningococcus C meningitis vaccine, Menjugate®, Novartis Vaccines) during the 2007-2008 and 2008-2009 influenza seasons.
- The second dose was given 28 days following dose one.
- Clinical cases of influenza-like illness identified were confirmed by RT-PCR testing for influenza. Immunogenicity at day 50 following dose one was evaluated in a subset of 777 children.

METHODS AND RESULTS

- The HI titers, vaccine efficacies, and the corresponding 95% confidence intervals for the three study groups are shown in Table 1. Geometric mean antibody titer attained in the ATIV group was substantially higher (1:746) than in the TIV-control group (1:92).

Table 1. Day 50 Influenza A/Brisbane/2007 (A/H3N2) Geometric Mean Titer (95% CI), Percentages of Subjects with HI Titer ≥ 1:40 and Vaccine Efficacy Against A/H3N2 (95% CI) Subjects 6 to 72 Months of Age for Season 2008/09

	ATIV N=311	TIV N=313	Non-influenza Control N=153
GMT	746 (661-843)	92 (74-115)	12 (9.0-15.4)
Percent ≥1:40	98.7%	65.2%	20.9%
Vaccine Efficacy	89% (77-94%)	43% (15-61%)	

- The titer of 1:92 in the TIV-control group was associated with less than 50% protection in contrast to what would have been expected if the 1:40 adult correlate held for children.
- Immunogenicity and efficacy results for H3N2 were evaluated using the Prentice criterion[2] which indicated that Day 50 antibody titers mediated most of the vaccine effect on incidence of infection, thus warranting estimation of an immunologic correlate (Table 2).

Table 2. Logistic Regression Models to Explain Influenza Infection in Subjects 6 to <72 Months of Age for Season 2008/09

Parameter	Estimated Coefficient (SE)	p-value
Intercept	-3.77 (0.29)	<0.01
Vaccination		0.0328
Influenza control	0.71 (0.33)	
ATIV	-1.27 (0.50)	
Intercept	-2.00 (0.66)	0.0023
Log_2 titer	0.30 (0.11)	0.0071
Vaccination		0.1372
Influenza control	0.61 (0.34)	
ATIV	-0.31 (0.62)	

- We then used the Dunning model[3] (Table 3) fitting the H3N2 antibody levels at day 50 and the influenza cases observed in the immunogenicity subset. The fitted curve from the model including 95% confidence intervals is shown in Figure 1.

Table 3. Parameter Estimates of Dunning's Model

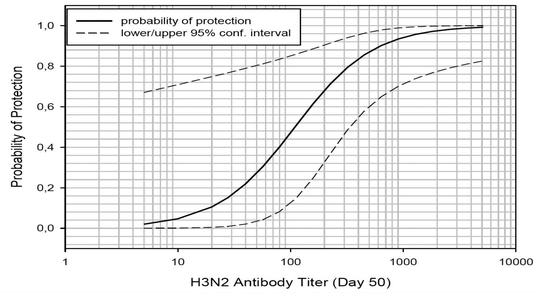
Parameter Estimated	Coefficient (SE)	p-value
Lambda	0.065 (0.017)	0.0002
Alpha	-3.88 (2.340)	0.0972
Beta	0.87 (0.374)	0.0198

- A cut-off HAI titer of 1:110 was associated with the conventional 50% clinical protection rate and titers of 1:215, 1:330 and 1:629 predicated protection rates of 70%, 80% and 90% respectively (Table 4).
- The conventional adult 1:40 HAI titer was associated with 22% protection (Figure 1).
- Although the titer measured at a fixed time (50 days) following initial vaccination was used to estimate these correlates, it was recognized that the titer at the time of the child was exposed to influenza was more likely to be the important biologic phenomenon.

Table 4. Estimated Antibody Titers at Day 50 Needed to Provide Various Levels of Protection in Subjects 6 to <72 Months of Age for Season 2008/09

Probability of Protection	H3N2 Antibody Titer Level
50%	1:110
60%	1:151
70%	1:215
80%	1:330
90%	1:629

Figure 1. Probability of Protection by A/Brisbane/2007 (A/H3N2) Titers at Day 50 in 6 to <72 Months Age Group derived from the Dunning model



- Therefore we estimated that a titer of 1:85 (95% confidence interval 35.6-137.9) at the time of exposure was associated with 50% protection in this model and a titer of 1:302 (95% confidence interval 176.9-439.2) was associated with 80% protection at the time of exposure.

CONCLUSIONS

- **The use of the 1:40 HAI adult correlate of protection is not appropriate when evaluating influenza vaccines in children.**
- **Although a cut-off of 1:110 may be used to predict the conventional 50% clinical protection rate, a titer of 1:330 would predict an 80% protective level which would seem to be more desirable from a public health perspective.**

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