Association of Antibodies to Hemagglutinin and Neuraminidase with Influenza A Virus Protection in Older Adults: Comparison between Symptomatic and Asymptomatic/ Subclinical Infections

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Background

Hemagglutinin and neuraminidase antibodies are essential for preventing infection and reducing severe illness. Older adults are vulnerable to influenza-related complication. There is a lack of study regarding the relationship between these antibodies and protection against influenza in older adults in the community, particularly in an Asian population with low vaccination coverage.

Objectives

- To estimate the cumulative incidence of influenza virus infection using different methods;
- To compare the association between pre-existing HAI and NAI titers and risk of influenza infection, among those with symptomatic and asymptomatic/ subclinical infections;
- To evaluate the relationship between pre-existing antibody titers and the magnitude of fold change in antibody titer after infection.

Methods

We compared all PCR-confirmed influenza infections and a random subset of 251 participants from a cohort of 1527 adults aged ≥60 years in eastern China in 2015-2017. Nose and throat swabs were collected during acute respiratory illness for influenza type/subtype identifying using polymerase chain reaction (PCR). Sera were collected every 6-12 months using hemagglutination inhibition (HAI) assay and neuraminidase inhibition (NAI) titer using enzyme-linked lectin assay (ELLA).

Results

- **High serological response rates** in **PCR-confirmed infections**;
- Only 2/9 PCR-confirmed infection with data available antibody titer, indicating **potential representation of asymptomatic or subclinical infections**

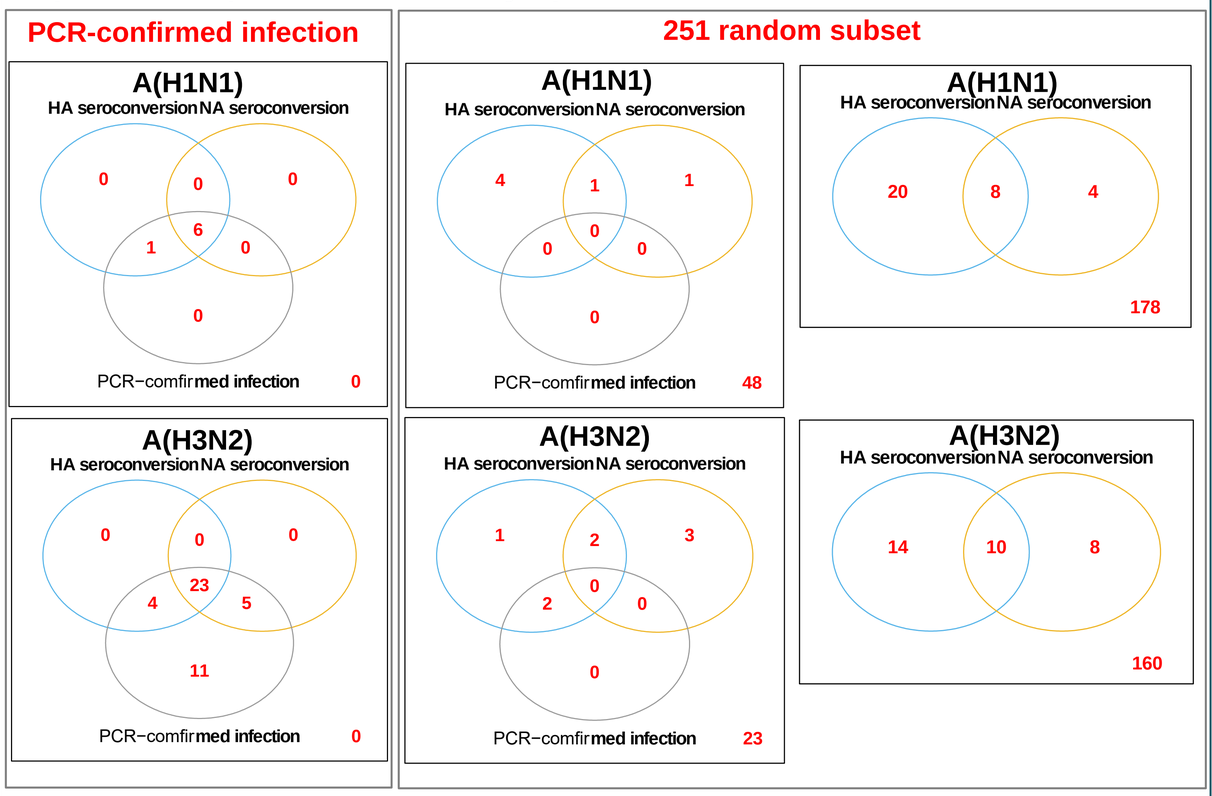

Figure 1. Overlap testing using PCR, HAI and NAI assay among participants with PCR-confirmed influenza A subtype and in a random subset of 251 individuals.

- **HAI method achieves higher** cumulative incidence coverage compared to NAI;
- **Maximum cumulative incidence** can be estimated using different methods

Table 1. Cumulative incidence by PCR or serology with corresponding 95% CI.

	Suzhou (N=108)[a]	Yancheng (N=143)[a]	Overall (N=251)
A(H1N1)			
PCR confirmed infection no. (%)[b]_2015-16	**0 (0)**	**1 (0.70)**	**1 (0.40)**
Seroconversion rate % (95% CI)[c]_2015-16	**(N=108)**	**(N=139)**	**(N=247)**
Anti-H1 % (95% CI)	9.3 (4.5, 16)	16 (10, 23)	13 (9, 18)
Anti-N1 % (95% CI)	7.4 (3.2, 14)	2.9 (0.79, 7.2)	4.9 (2.5, 8.3)
Cumulative incidence by PCR or seroconversion			15 (10, 20)
			17 (14, 19)[a]
A(H3N2)			
PCR confirmed infection no. (%)[b]_2016-17	**0 (0)**	**5 (3.5)**	**5 (2.0)**
Seroconversion rate % (95% CI)[c]_2016-17	**(N=100)**	**(N=126)**	**(N=226)**
Anti-H3 % (95% CI)	12 (6.4, 20)	13 (7.4, 20)	12 (8.4, 17)
Anti-N2 % (95% CI)	9.0 (4.2, 16)	8.7 (4.4, 15)	8.8 (5.5, 13)
Cumulative incidence by PCR or seroconversion			19 (14, 24)
			17 (14, 20)[a]
PCR confirmed infection no. (%)[b]_2017-18	**1 (0.93)**	**2 (1.4)**	**3 (1.2)**
Seroconversion rate % (95% CI)[c]_2017-18	**(N=107)**	**(N=124)**	**(N=231)**
Anti-H3 % (95% CI)	5.6 (2.1, 12)	6.5 (2.8, 12)	6.1 (3.4, 10)
Anti-N2 % (95% CI)	6.5 (2.7, 13)	0.8 (0.02, 4.4)	3.5 (1.5, 6.7)
Cumulative incidence by PCR or seroconversion			12 (7.8, 17)
			12 (10, 13) [a]

[a] Weighted by standardizing to the population age and sex of Jiangsu province, China in 2010.

- **Lower pre-existing HAI and NAI titers** are associated with an increased risk of infection, particularly in relation to **symptomatic infection risk;**
- **HAI** demonstrates **more conservative** in identifying PCR-confirmed infections through the **titer limitation (≤10)** , while in **wide range NAI titers;**
- **Broader protection against strains in anti-NA antibody** with various levels , while **strain-specific in anti-HA antibody** mainly in lower levels

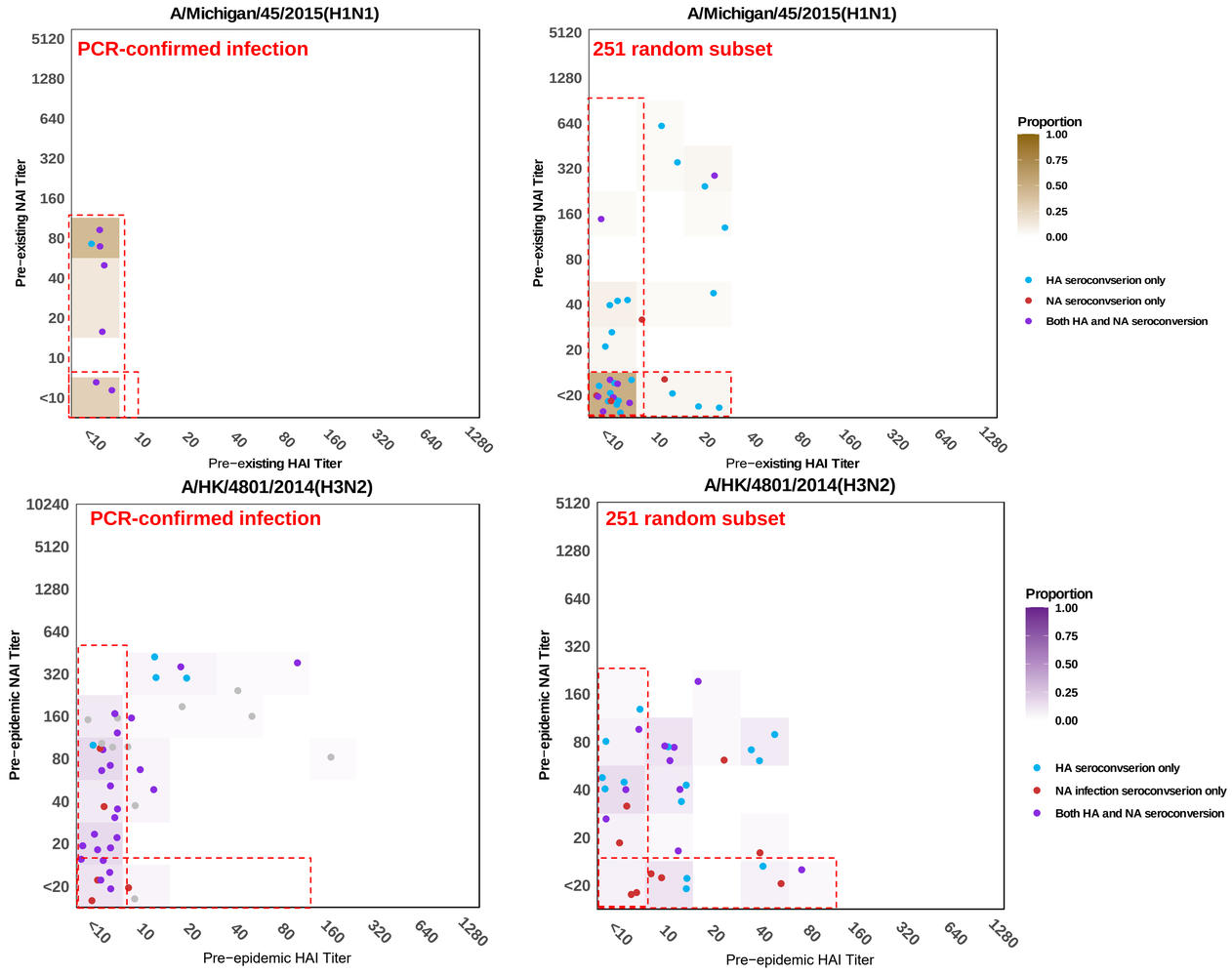

Figure 2. Correlation of pre-existing HAI and NAI titer against influenza A virus infection. Points indicated pre-existing/pre-epidemic antibody titer among different seroconversion, and arrows indicated pre- and post- HAI and NAI antibody trends and fold change.

- Pre-epidemic HAI and NAI titer were slightly higher in **no seroconversion** group but without statistically significant;
- **More pronounced increase** in antibody levels in seroconversion **in both HAI and NAI assay,** and **NAI seroconversion may contribute to higher HAI titers**

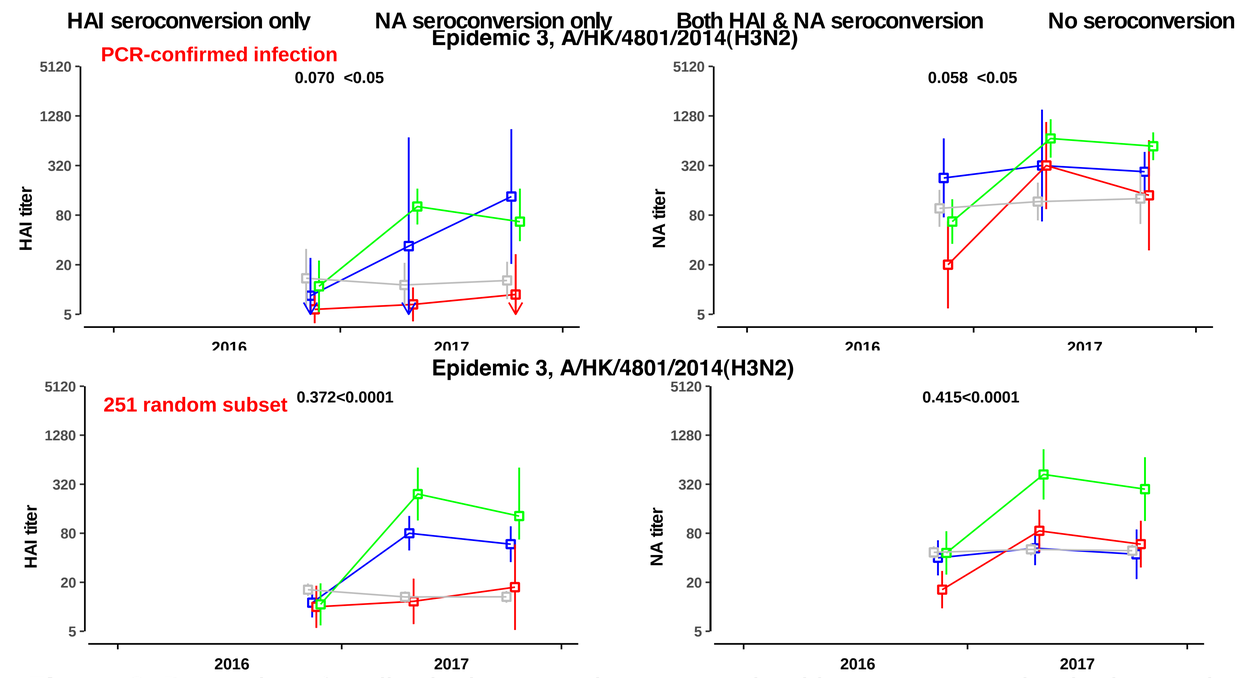

Figure 3. Dynamics of antibody titer over time categorized by seroconversion in the random subset. Rectangles indicate geometric mean titer with arrow segments representing 95% confidence intervals at each timepoint.

Conclusion

HAI testing is more effective in capturing a broader range of infections, and NAI can take as a supplementary method. Lower pre-existing HAI and NAI titers are associated with an increased risk of infection, particular for symptomatic infections. Our findings emphasize the potential value of incorporating pre-existing HAI testing into surveillance and risk assessment strategies, as well as considering the impact of NAI seroconversion on HAI antibody levels in vaccine development.

References

[1] Cowling, BJ., et al., Cohort profile: the China Ageing REespiratory infection Study (CARES), a prospective cohort study in older adults in Eastern China. BMJ Open 2017; 7(10): e017503.

Acknowledgements

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