

# Serological studies for influenza in Norway

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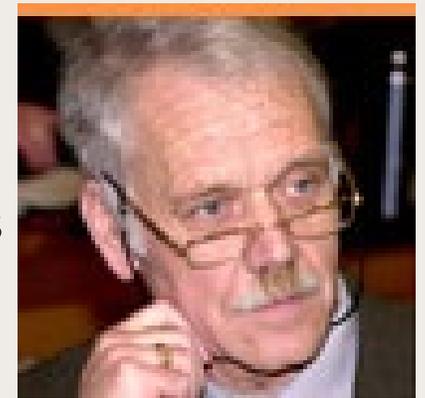


# Experiences from four decades of annual serosurveys for influenza viruses in Norway

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Prof. Lars R Haaheim  
1945-2011

## Background:

# Influenza serosurveys in Norway

- Norwegian annual influenza serosurveys have been carried out since the late 1970s
  - Established just in time to record the previous H1N1 "Russian pandemic" reemergence in 1977-78
- Residual, anonymised sera from hospital labs
  - all country coverage
  - age representative
  - Anonymised; only sex, age, sampling time (approx.) and county of residence (not vaccination status)
  - Collected annually in August
  - Approx 120 per county; 19 (old) counties -> 2000-2400 sera
  - Antigens: Vaccine strains (old and new) & other relevant antigenic variants (typically 4-6 antigens)

Haaheim LR. Surveillance of the antibody status to current influenza strains in the Norwegian population.

1: Method of serum sampling and evaluation of the A/USSR/77 (H1N1) impact in various age groups in 1978.  
NIPH Ann. 1979 Dec;2(2):45-54.

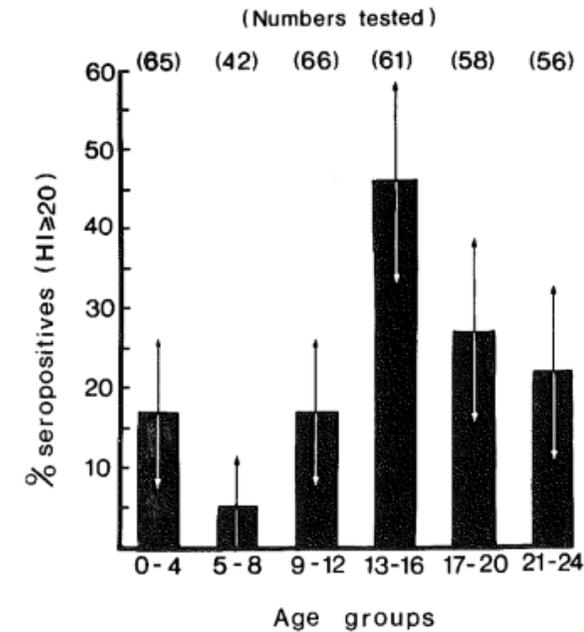
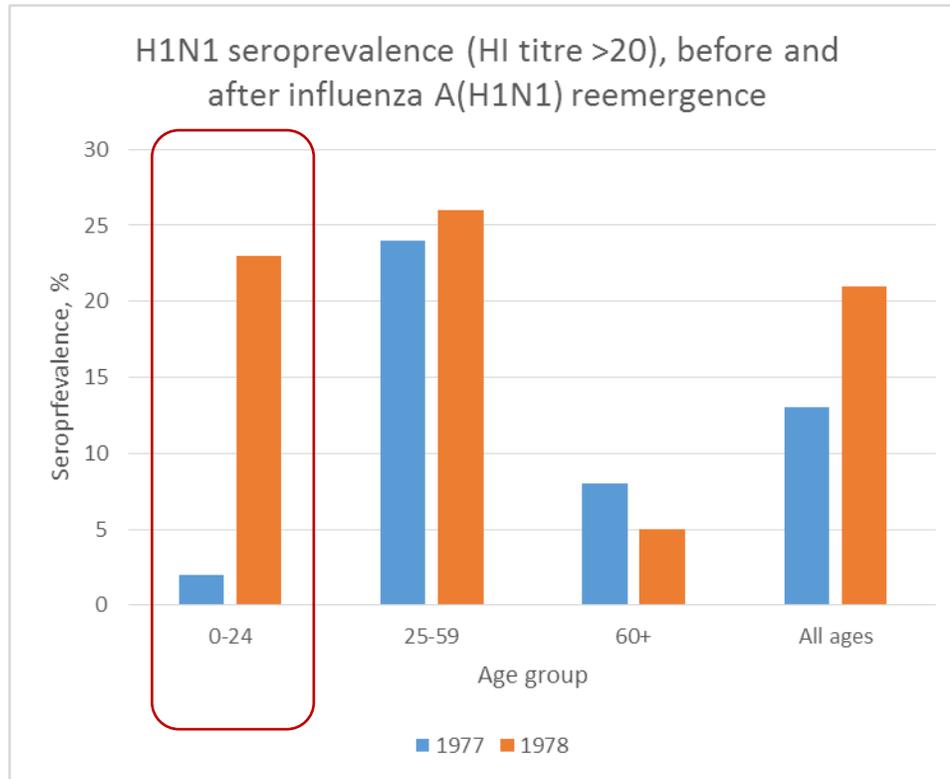
2: Antibodies to the A/USSR/90/77 (H1N1) virus in various age groups after the second epidemic wave.  
NIPH Ann. 1980 May;3(1):49-56.



# Use of influenza seroepidemiology in the Norwegian National Influenza Centre: main objectives

- Retrospective assessment of virus circulation
  - By strain, age groups, by region
- Assessment of epidemic potential
  - Annual early-season risk assessments for Norway
  - Special cases; pandemic risk assessment
- Informing WHO Vaccine Composition Meetings
  - Pattern of human antibody reactivity to different virus strains may be different from ferret antibodies

# Age specific attack rates during re-emergence of A(H1N1), Norway 1977-78



The distribution of antibodies (HI titres  $\geq 20$ ) to the A/USSR/77 (H1N1) strain in people under the age of 25 years. The histograms represent per cent seropositives with arrows indicating  $\pm 2$  SE. The numbers of sera tested in each age group are in brackets.

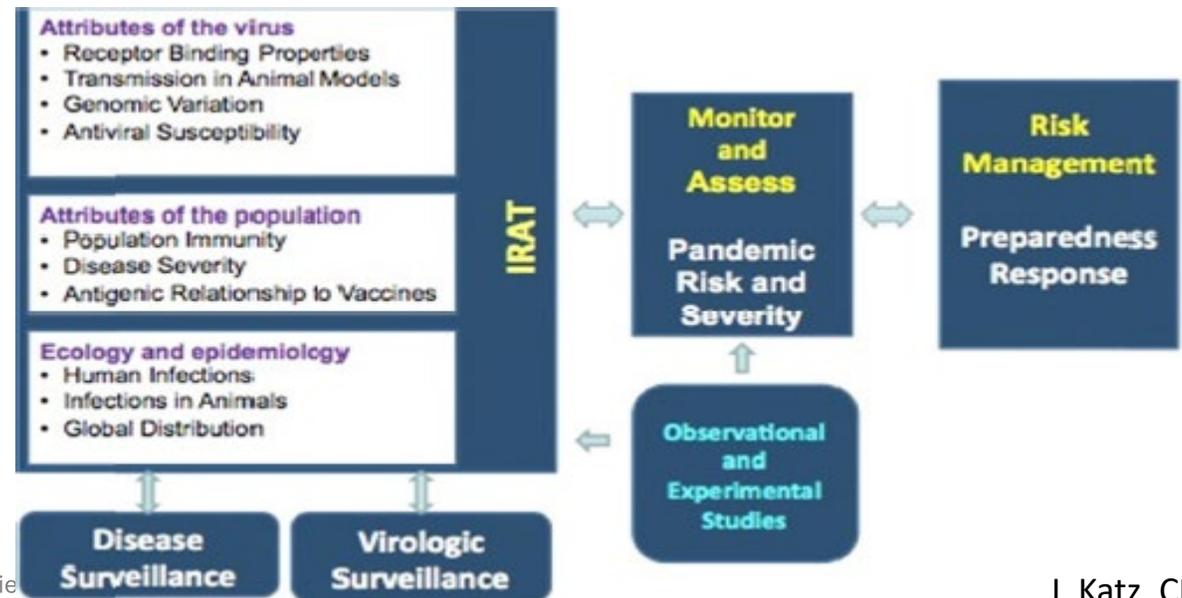
- Re-emerging A(H1N1) primarily affected the young, born after A(H1N1) elimination by the 1957 A(H2N2) pandemic

# Influenza seroepidemiology: assessing pandemic risk

- Zoonotic swine-derived A(H3N2)v infections in USA, 2011 onwards
- Can this virus spark a pandemic?
- A reassortant virus, with H3 HA from human virus in the mid-1990s

Detected U.S. Human Infections with H3N2v by State since August 2011

States Reporting H3N2v Cases	Cases in 2011	Cases in 2012	Cases in 2013	Cases in 2014	Cases in 2015
Total	12	309	19	3	3

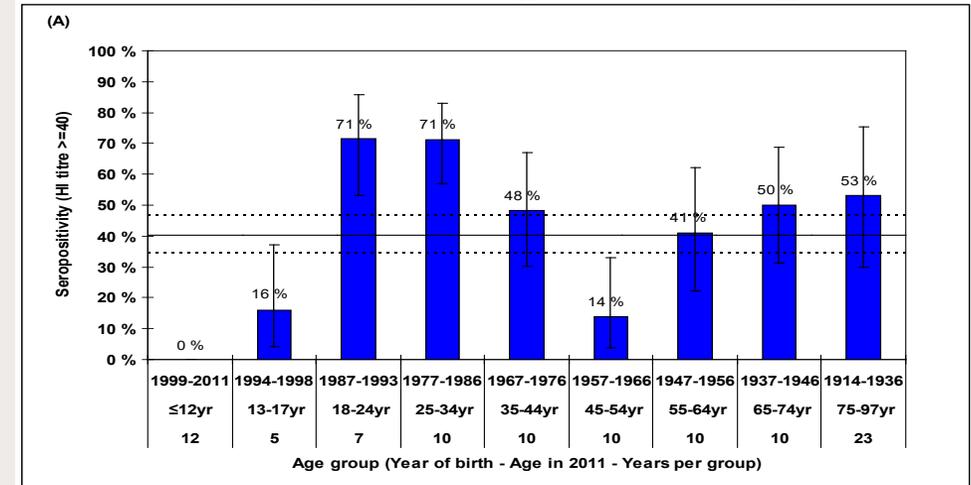


# Cross-reactive antibody to swine-origin A(H3N2)v in 2011; and antibody to H3N2 in the 1990s

- This swine virus variant is absent from Europe
- But we had the ancestral seasonal virus in the 1990s
- We measured substantial immunity against it in sera from 2011
- This mirrors immunity measured in the 1990s; in the same birth year groups; against the ancestral human virus HA from 1995
- This immunity may limit potential and impact of epidemic/pandemic spread

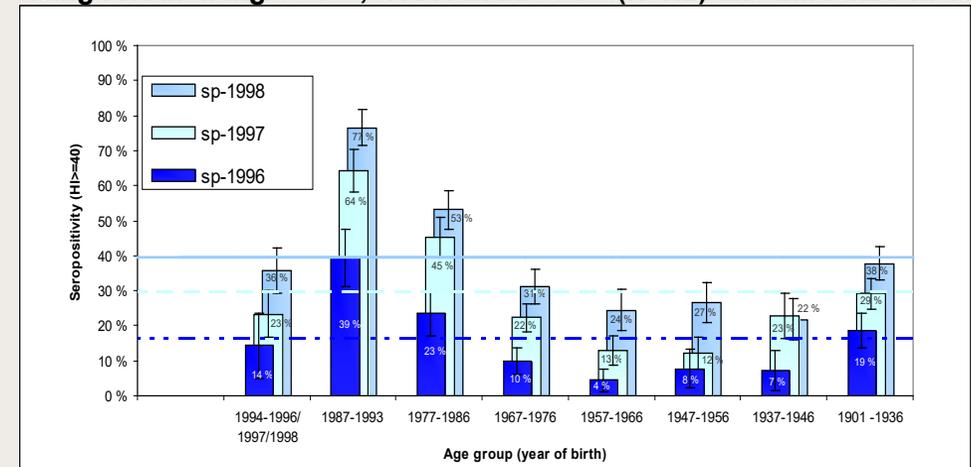
Waalén et al. 2012  
Eurosurveillance 17(19).

**Fig. 1. Prevalence of cross-reactive antibody (A) and GMT (B) to influenza A/Indiana/08/11(H3N2)v virus, Norway, sera collected August 2011**



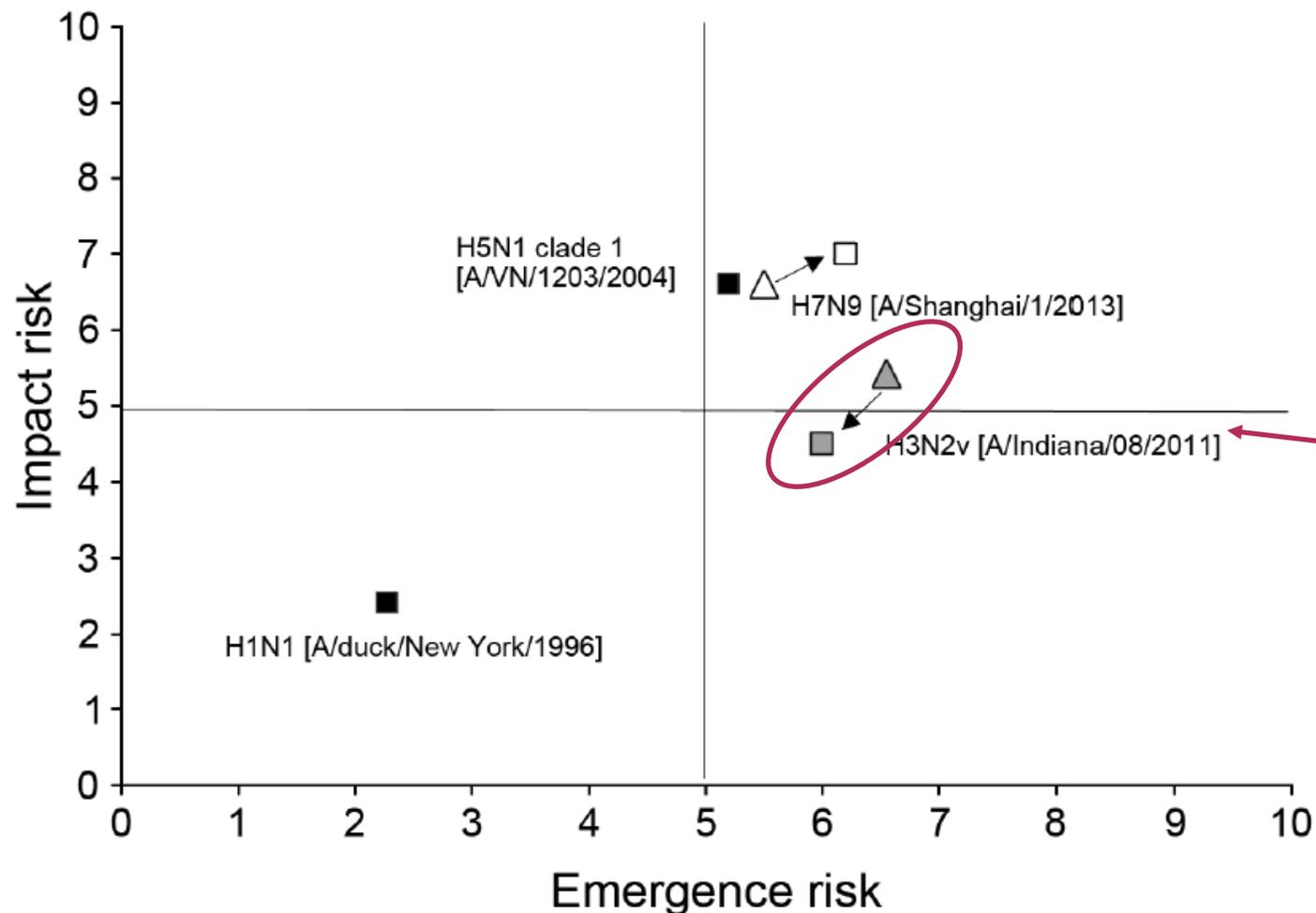
Panel A: Percent positivity for 'All ages' is shown as horizontal solid line with 95% CI (dotted line).  
Panel B: Geometric mean titres by age group. Annotations as for panel A

**Fig. 2. HI (A) and GMT (B) results of sera collected in 1996, 1997 and 1998 using A/Nanchang/933/95, a A/Wuhan/359/95(H3N2)-like influenza virus**



Horizontal lines, Panel A, Seropositivity for 'All ages' (95%CI) were: 16% ( 2.1%), 30% ( 2.0%) and 40% ( 2.1%) for 1996, 1997 and 1998, respectively, and Panel B, HI GMT (95%CI) for 'All ages' were: 9.6 (9.1-10.1), 12.9 (12.3-13.6) and 18.3 (17.4-19.2) for 1996, 1997 and 1998, respectively.

# Our data used to down-adjust the US CDC global risk assessment (IRAT) for influenza A/H3N2v from US



**Figure 2.** Influenza Risk Assessment Tool scores for 4 influenza viruses on the basis of potential risk to achieve “sustained human-to-human transmission” (emergence) and potential risk “for significant impact on public health” (impact). Black squares in top right quadrant and lower left quadrant represent risk scores for H5N1 clade 1 and H1N1, respectively. White triangle represents risk score for H7N9 in mid-April 2013; white square represents risk score for the same virus in mid-May 2013. Gray triangle represents risk score for H3N2v as of December 2011; gray square represents risk score for same virus in December 2012. Emergence risk is the risk summary score for the question, “What is the risk that a virus not currently circulating in the human population has the potential for sustained human-to-human transmission?” Impact risk is the risk summary score for the question, “If the virus were to achieve sustained human-to-human transmission, what is the risk that a virus not currently circulating in the human population has the potential for significant impact on public health?”

# Objective: Support WHO Vaccine strain selection

- Serosurvey data always included in our seasonal report to the biannual Influenza Vaccine Composition Meeting
- Some times we can point out strains and age segments with weaker or stronger immunity
- .. And some times point out where human antibodies discriminate differently from the ferret antisera used for characterisation



Influenza Epidemiological Information prepared for the  
WHO Informal Meeting on Strain Composition for  
Inactivated Influenza Vaccines for use in the Season 2013-14  
Geneva, February 2013

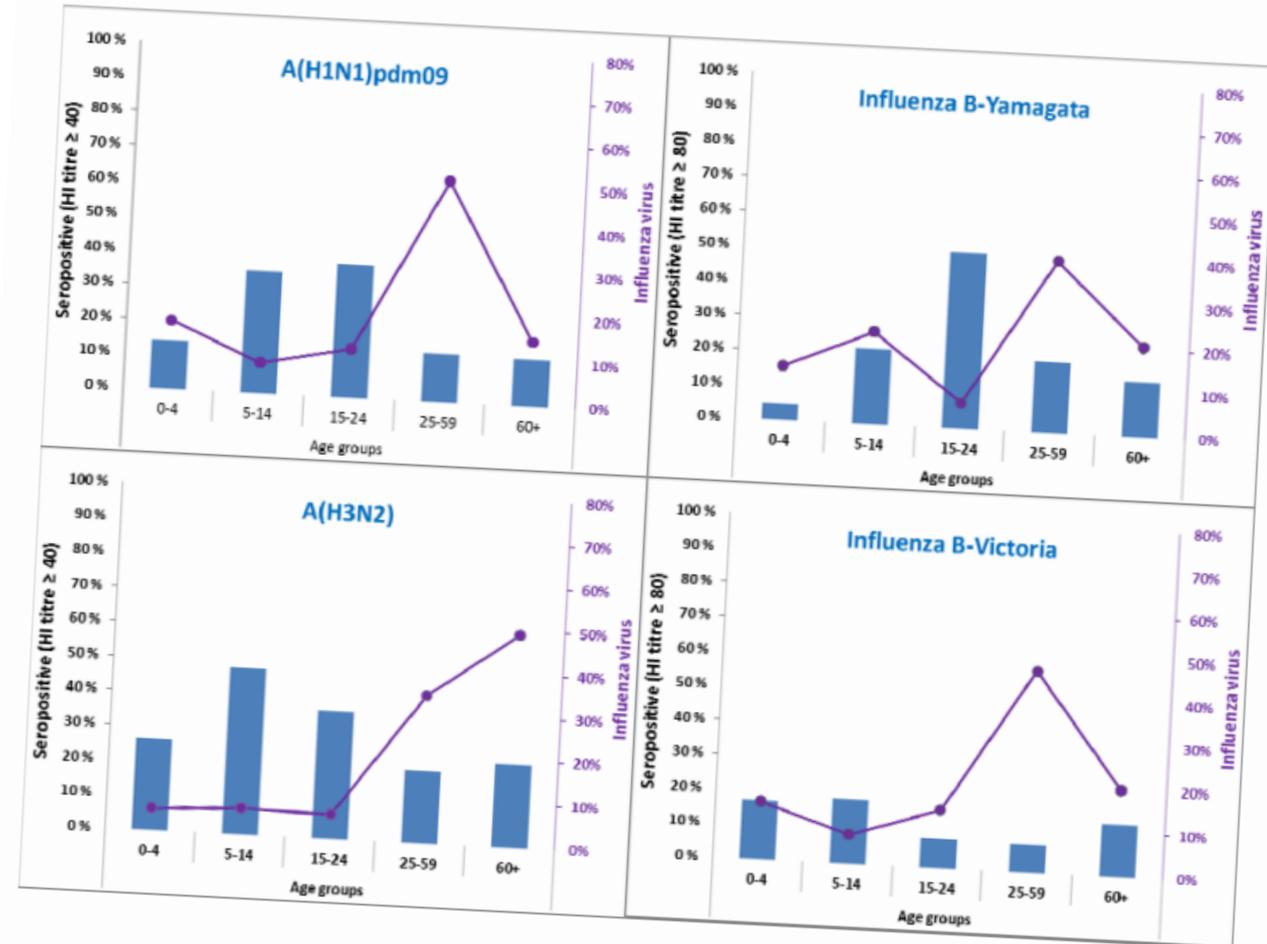


Figure 1. Prevalence of protective antibody to various influenza viruses in August 2012 (bars) and the age distribution of detected influenza viruses in the 2012/2013 influenza season (up to week 5, 2012).

# Objective: Support WHO Vaccine strain selection



- Serosurvey data always included in our seasonal report to the biannual Influenza

## Vaccine Composition Meeting

- Example:  
«The wall of immunity», first post-pandemic winter 2010-2011

**Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2011-12 Geneva, February 2011**

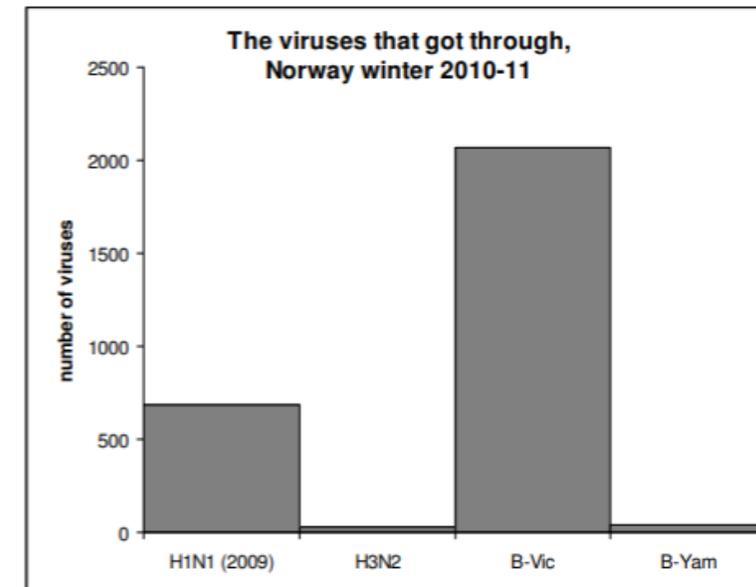
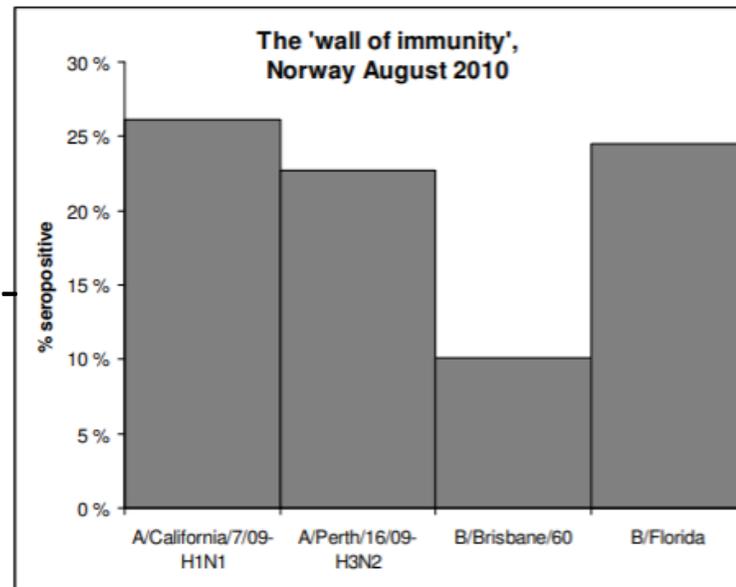


Figure 1. The all-ages prevalence in Norway of antibodies to the different influenza viruses, August 2010 (panel A; per cent of sera with HI titre  $\geq 40$  for influenza A and  $\geq 80$  for influenza B); and the number of viruses detected in the national surveillance network (panel B – for influenza A, the proportions of H1N1 and H3N2 in subtyped viruses has been projected onto the not-subtyped A viruses; and for influenza B, the proportion of Victoria vs. Yamagata lineages has been projected on the non-characterised B viruses).

### Contents

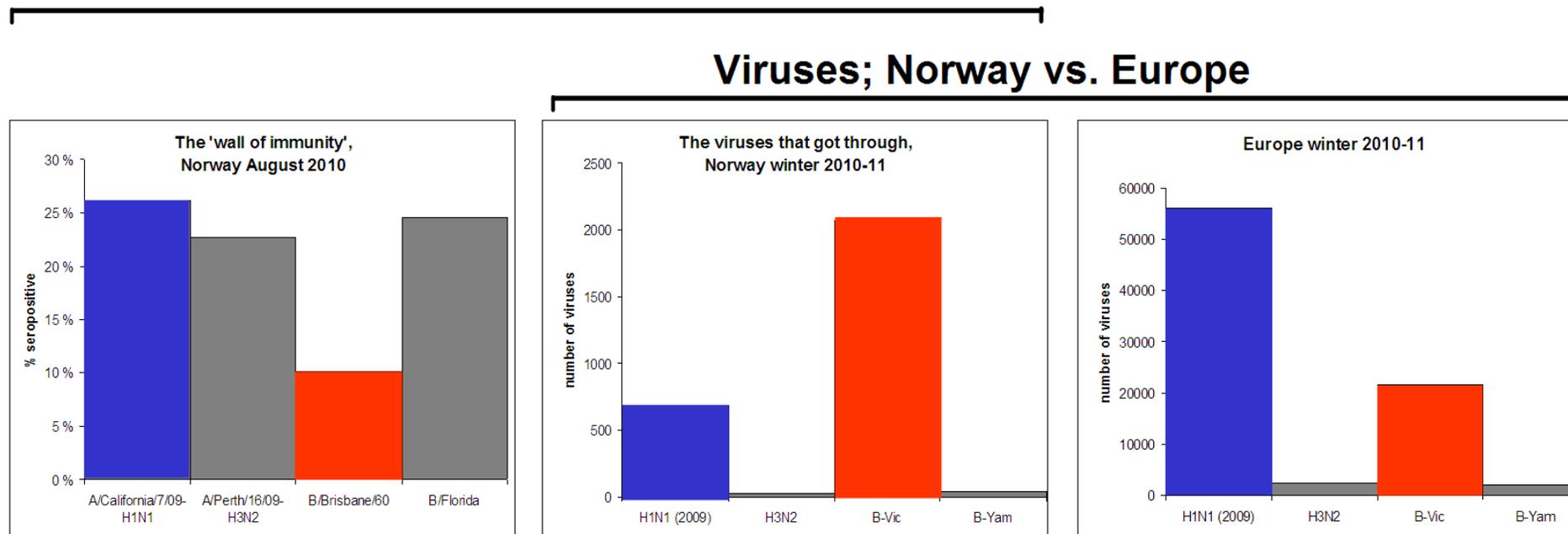
1: Epidemiological Data obtained from sera collected in August 2010.....	2
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# Immune status and predictive value



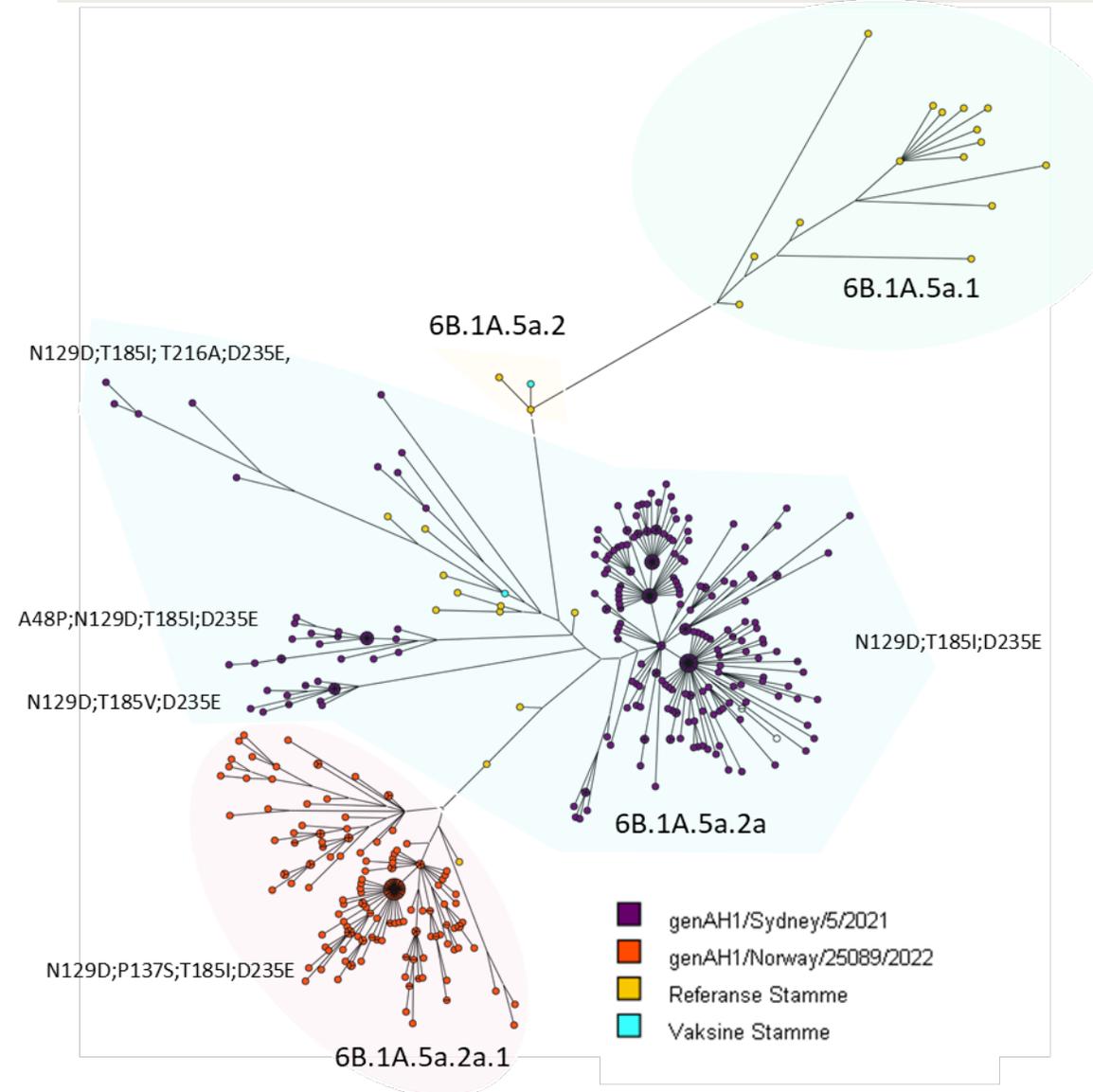
## 2010: Return to seasonal influenza after the 2009 pandemic

### Norway; immunity vs. viruses

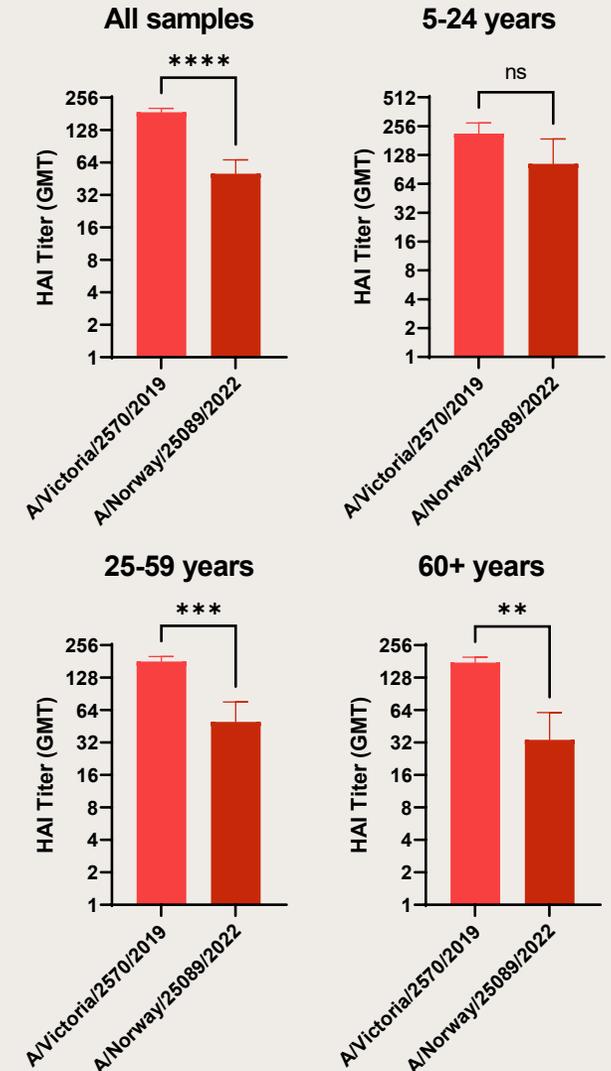


- Serosurveys can have predictive value
- Elsewhere in Europe: a big second A(H1N1)pdm09 pandemic wave;
  - Unknown: what was the immunity elsewhere in Europe?
  - Pandemic vaccine coverage was particularly high in some Nordic countries

# Supporting VCM: 2022: Less immunity against new H1 clade 5a.2a.1



- «last-minute» HAI on selected sera; with medium/high titre against 5a.2 mother clade virus
- Done just before February 2023 WHO Vaccine Composition Meeting
- We found lower immunity against the 5a.2a.1 clade virus in those 25 yr and older
- Ferret sera didn't distinguish!**
- A 5a.2a.1 virus was recommended for the current 2023/2024 NH season vaccine

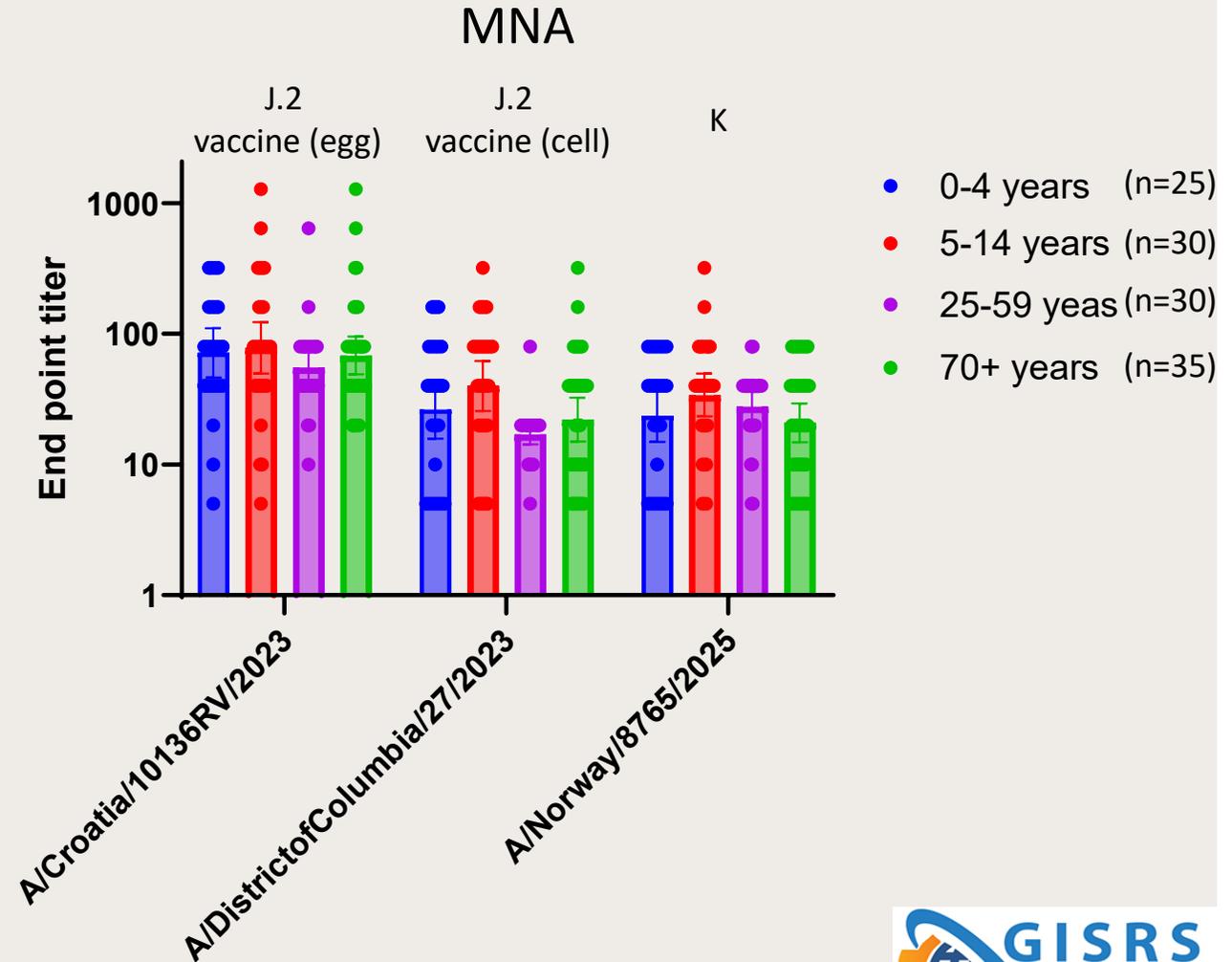


# 2025: Immunity against H3N2 K subclade in residual sera



HI failed for some of the H3N2 antigens, we resorted to microneutralisation assay (MNA)

- Residual sera from August 2025
- Sera tested by MNA against egg- and cell-based vaccine virus (J.2 subclade), and A/Norway/8765/2025 (K subclade).
- Majority had titres  $\geq 40$  against K subclade.
  - 56% 0-4 years titre  $\geq 40$ .
  - 67% 5-14 years titre  $\geq 40$ .
  - 63% 25-59 years titre  $\geq 40$
  - 43% 70+ years titre  $\geq 40$ .
- We thus see considerable cross neutralisation

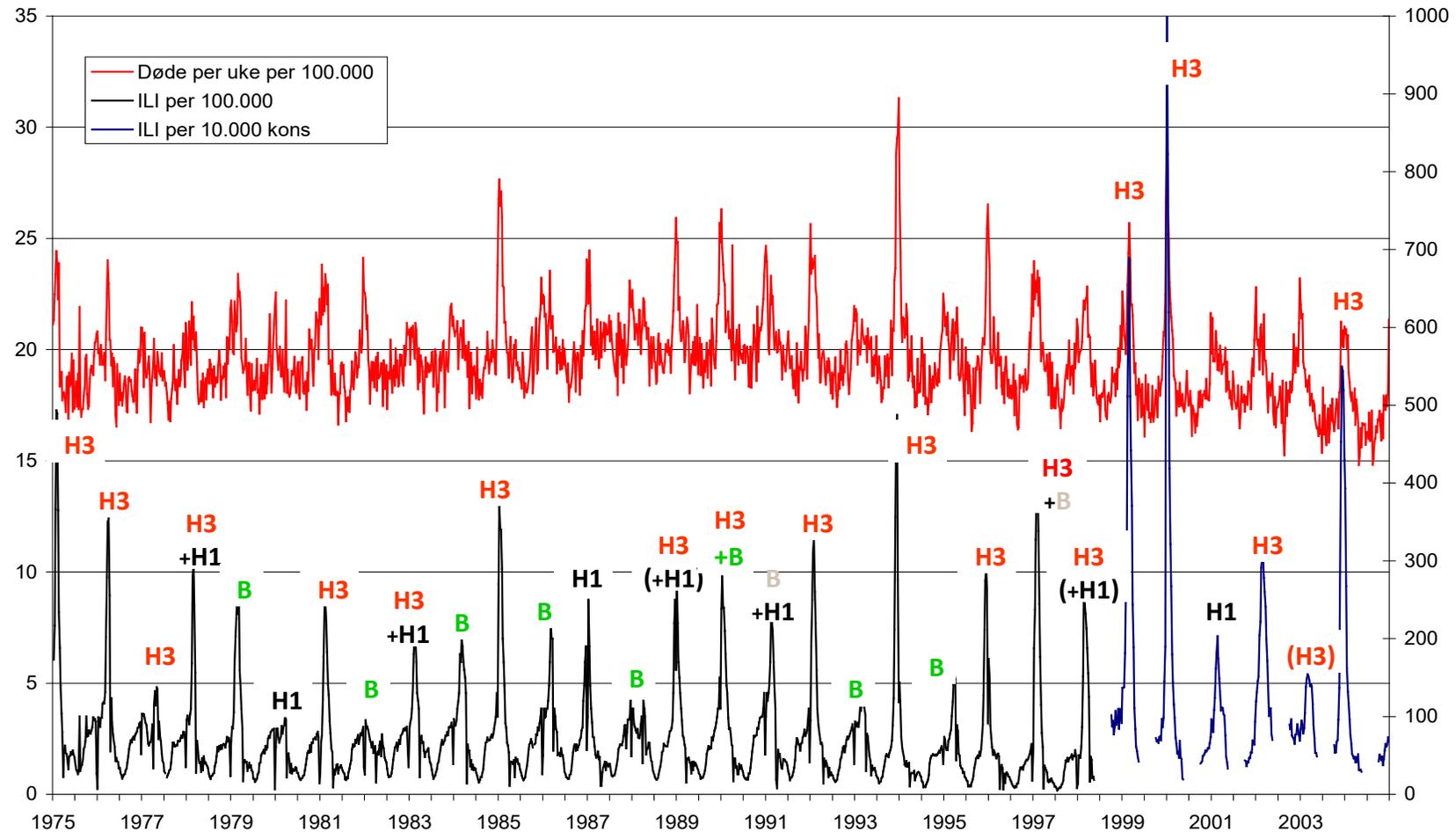


# Serosurvey complements in-season surveillance

## Influenza outbreaks and immunity over decades

### Influenza surveillance in Norway:

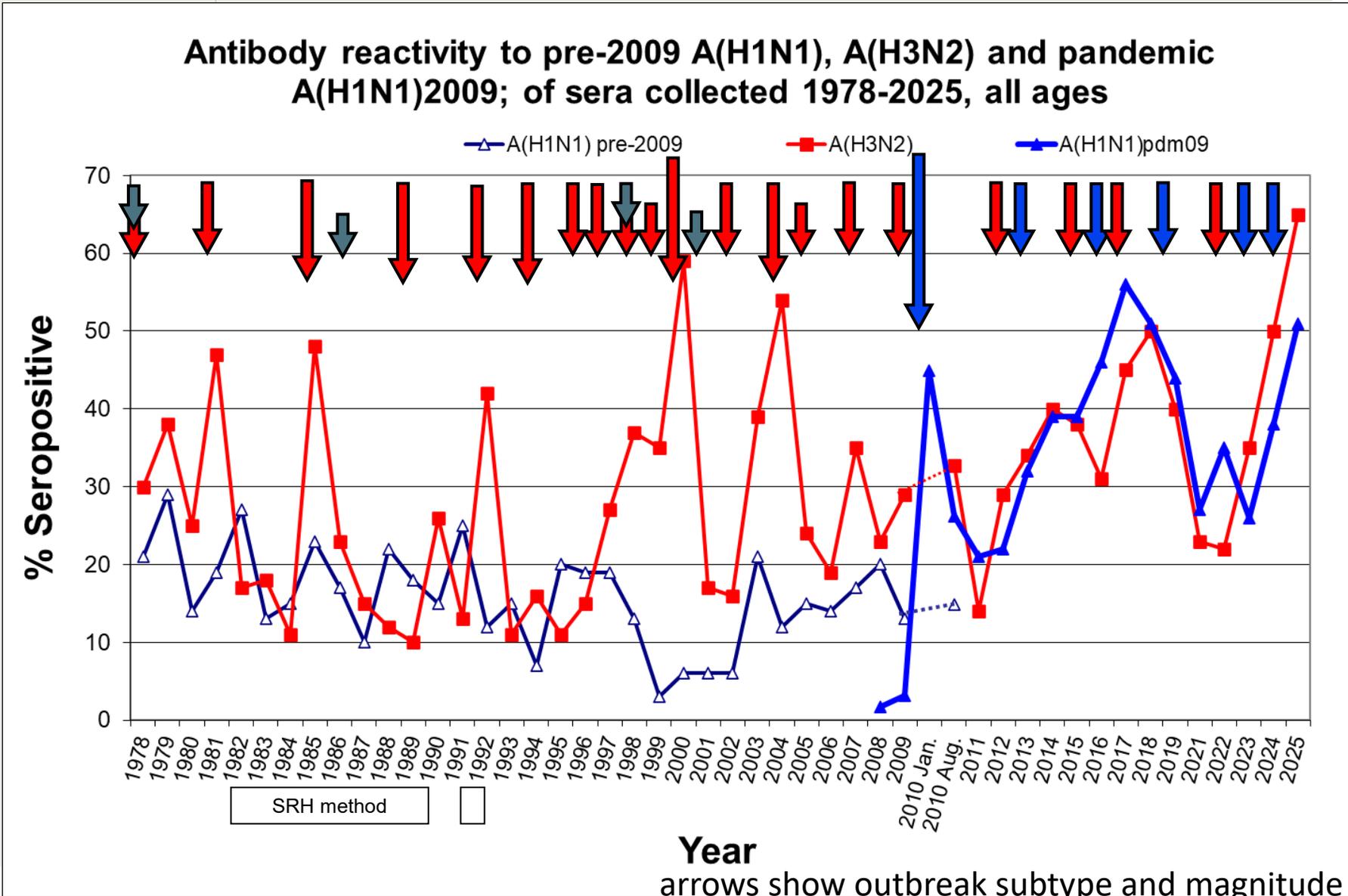
- Virological data since 1950s
- Clinical (ILI) surveillance since 1975
- The most intense and severe epidemics tend to be driven by A(H3N2)
- Types and subtypes tend to alternate between seasons



# Influenza A immunity over >4 decades



- The major flu A epidemics until 2009 were all A(H3N2), reflected by large seroprevalence fluctuations
- The 1977 reemerging A(H1N1) had lower impact; and lower HAI seroprevalence
- The A(H1N1)pdm09 pandemic lineage displaced the pre-2009 H1N1 lineage and has caused major outbreaks with 3-year intervals since 2009; with seroprevalence patterns on par with A(H3N2)





# Different eras of influenza B

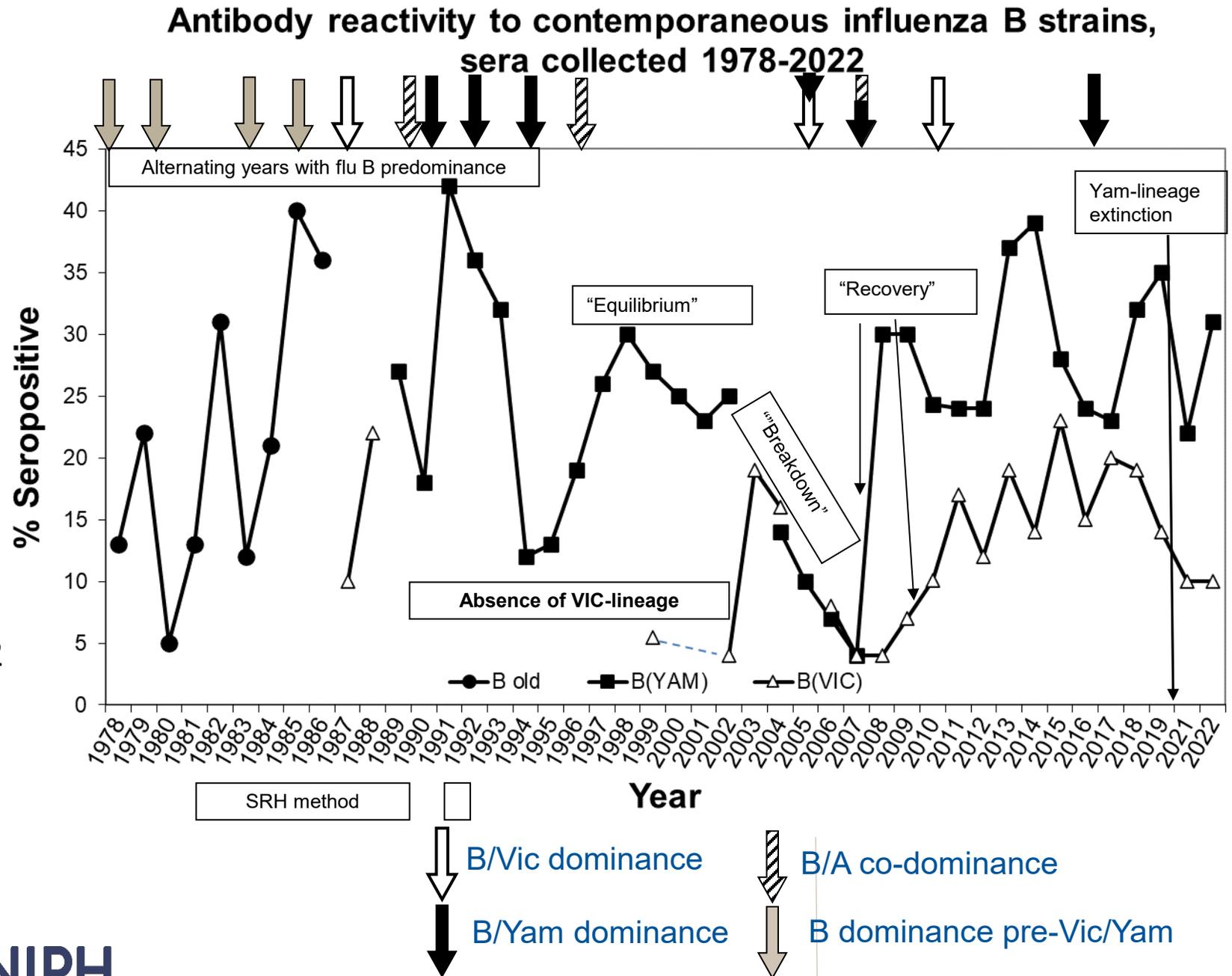
The influenza B epidemic and immunity patterns have changed over the four decades

During the period covered,

- the B/Victoria-lineage emerged (ca 1987); then disappeared from global circulation (ca 1991); and re-emerged (2002)
- the B/Yamagata-lineage emerged (1988) and recently disappeared (during COVID-19)
- Patterns of influenza B epidemics and immunity have changed

# Influenza B immunity over four decades

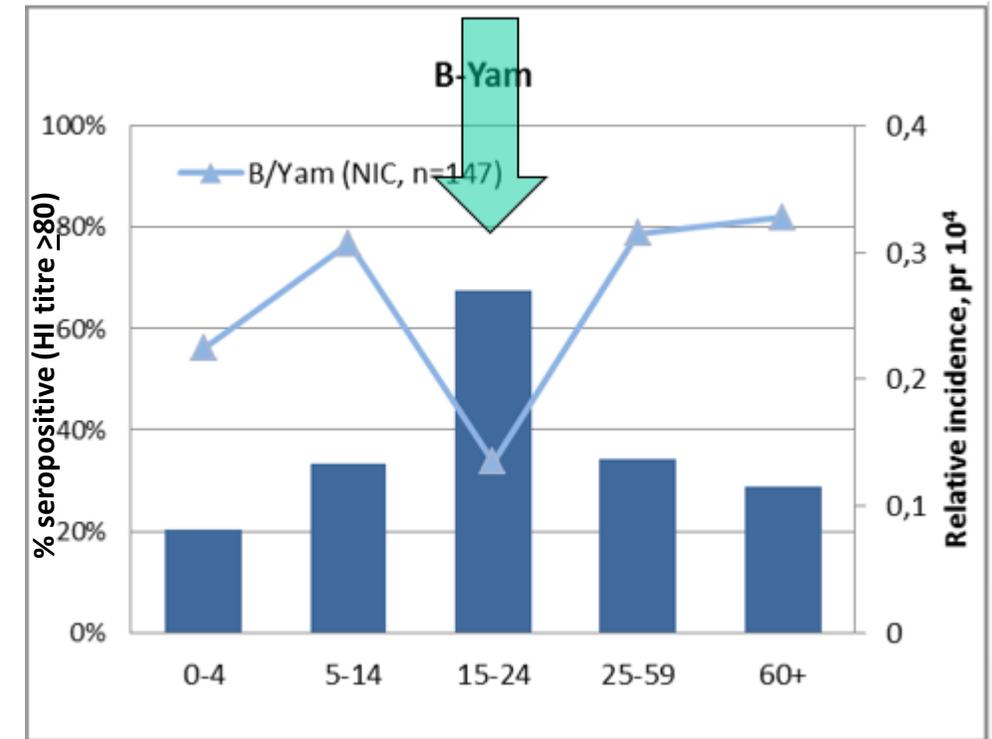
- Annual Serosurvey provides insight on changing patterns of influenza B epidemiology over several decades
- Emergence of distinct Victoria/2/1987 & Yamagata/16/1988 lineages
- Absence of B/Vic-lineage 1990-2002
- Until 1995, type B alternated with type A as the dominant virus
- After 2002 until 2020, the two lineages cocirculated. . .



# Assessing age-specific susceptibility



- Pre-season seroprevalences often correspond to in-season incidence pattern (but not always)
- Several large flu B epidemics with B/Yamagata-lineage viruses in the 1990s:  
a lasting imprint on those undergoing their first flu B infections during that decade?



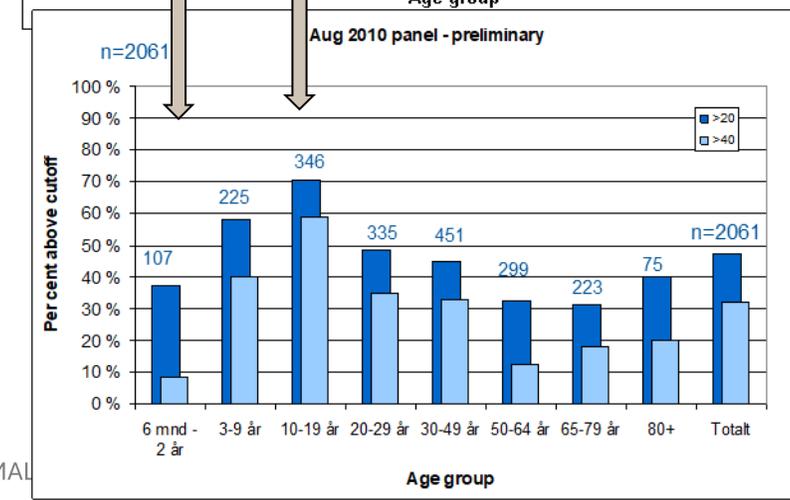
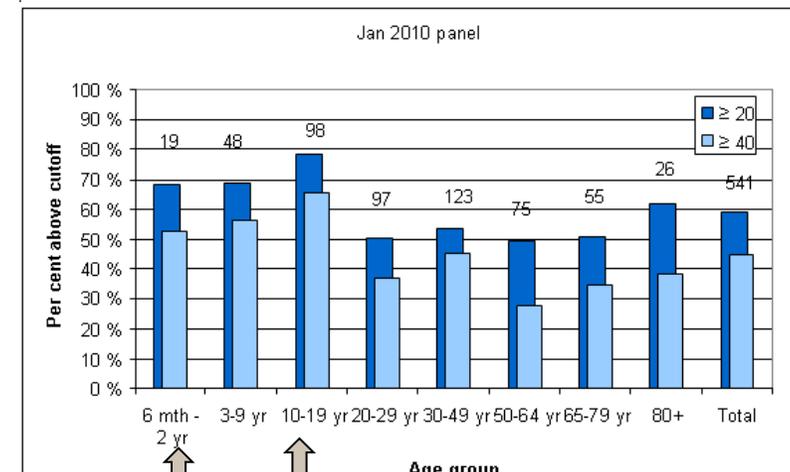
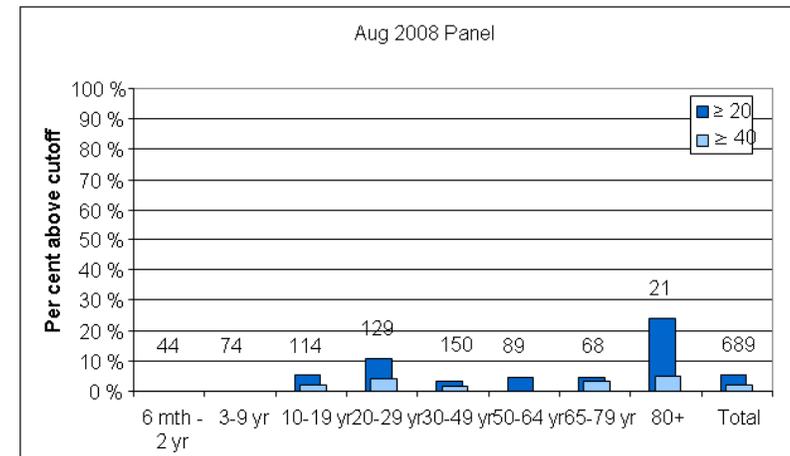
Prevalence of protective antibody to B/Massachusetts/2/2012 (Yam) in August 2013 (bars) and per-age incidences of detected influenza B/Yamagata lineage in the 2013-2014 influenza season

# Immunity through the 2009 pandemic:

## HI Antibody against H1pdm09 in Norway;

### Aug 2008 / January 2010 / August 2010

- Main pandemic wave plus mass vaccination in autumn 2009
- Substantial increase in all age groups
- Highest in age below 20
  - Highest recorded incidence
  - High vaccine uptake
- Overall high seroprotection rate
- Match to estimates of infected and recorded vaccination uptake (approx. 20% infected; 45% vaccinated)
- Some decline from January to August 2010
  - Large drop in age group <3yr (and in 50-64 yr group)
  - But still considerable population immunity
- As shown, Norway had no second pandemic wave in 2010-2011





# Immunity against other viruses

- The sera have been used to chart population immunity to poliovirus and measles virus.
- With the emergence of the COVID-19 pandemic, the sera have also been used to follow the development of humoral immunity against SARS-CoV-2 as the pandemic has unfolded and the virus evolved.

# Looking forward

## Some objectives

- 1. Survive:** Preserve and maintain the collection and the core approach that represents comparability throughout decades
- 2. Exploit:** Capitalise on the historic data and materials for long-perspective analyses
- 3. Evolve:** Develop in ways that maximises usefulness for knowledge and public health
  1. Targeted and 'panoramic' studies
  2. Collaborations and more sophisticated data analysis
  3. Laboratory methods and aspects of immunity
- 4. Expand?**
  1. Reach out to and advocate for comparable serosurveys from other countries/regions
  2. More pathogens



# Acknowledgements



- Laboratories contributing residual sera across Norway
- Currently: Akershus University Hospital, Drammen hospital, Førde Hospital, Haukeland University Hospital/Bergen, Finnmark Hospital/Hammerfest, Innlandet Hospital/Lillehammer, Levanger Hospital, Molde Hospital, Nordland Hospital/Bodø, Ullevål/Oslo University Hospital, St. Olav Hospital/Trondheim, Unilabs Laboratory Medicine AS/Skien, Stavanger University Hospital, Sørlandet Hospital/Kristiansand, University Hospital of Northern Norway/Tromsø, Vestfold Hospital/Tønsberg and Østfold Hospital/Kalnes.
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Prior NIC Directors Lars Haaheim, Liv Flugsrud
- WHO Collaborating Centre; Worldwide Influenza Centre at the Francis Crick Institute, UK
- AURORAE consortium and ECDC for making this webinar happen



**What do you consider to be the most important added value of influenza serosurveillance?**