# Vaccine effectiveness against influenza A(H1N1)pdm09 and A(H3N2): I-MOVE primary care multicentre study, Europe, 2021–22

Esther Kissling, Epiconcept, on behalf of the I-MOVE primary care network

# Introduction

- In **2021-22 influenza A**, mainly **A(H3N2),** circulating in Europe
- Northern Hemisphere (egg-based) vaccine recommendation:
  - A/Victoria/2570/2019 (H1N1)pdm09-like virus (clade **6B.1A.5a.2**)
  - A/Cambodia/e0826360/2020 (H3N2)-like virus (clade **3C.2a1b.2a.1**)
- I-MOVE primary care network
  - Estimating **influenza VE since 2008**
  - **Multicentre case control** study
  - 2021-22: **10 study sites in 9 countries**
- COVID-19 pandemic
  - Changes in healthcare-seeking guidance
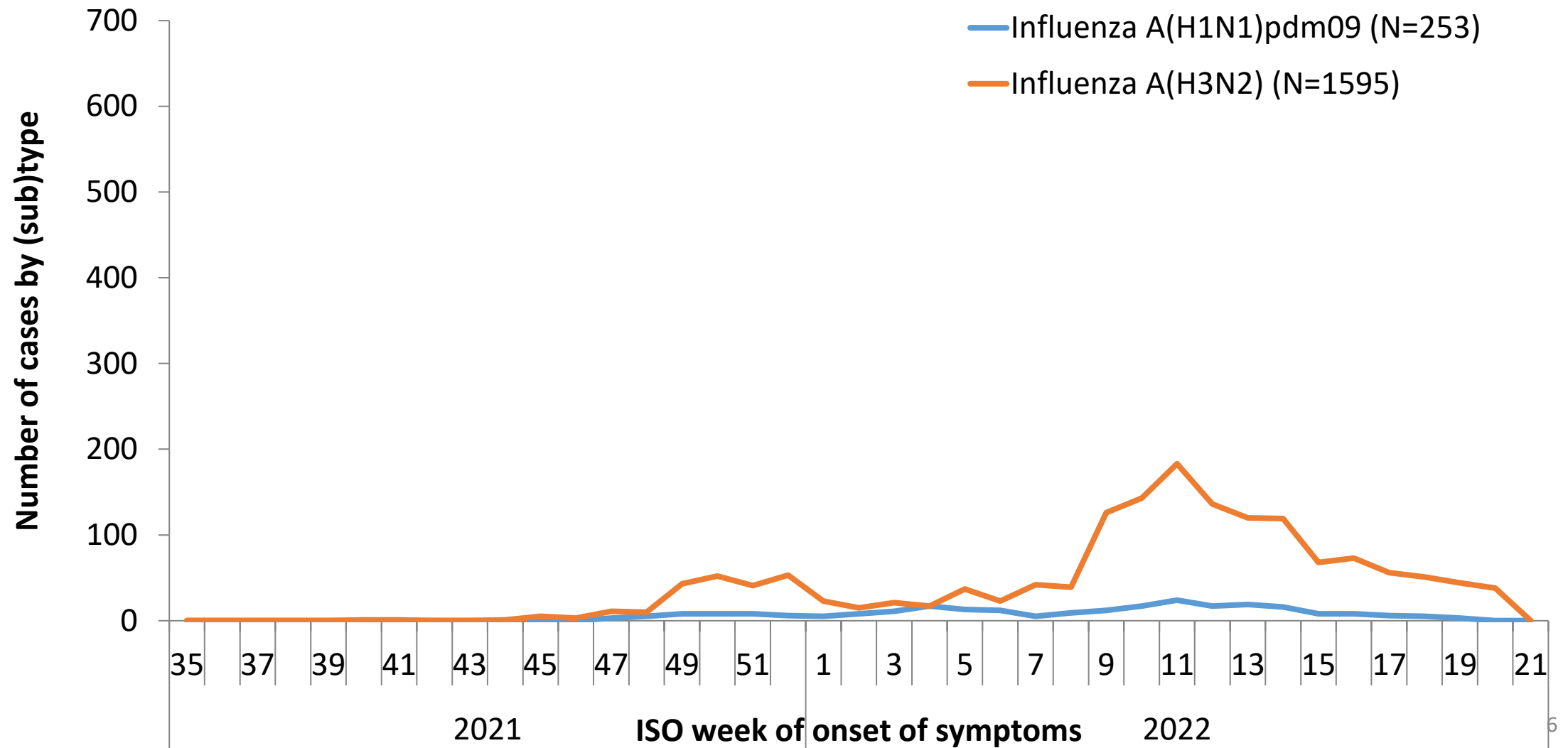  - High incidence of SARS-CoV-2 in 2021-22



2
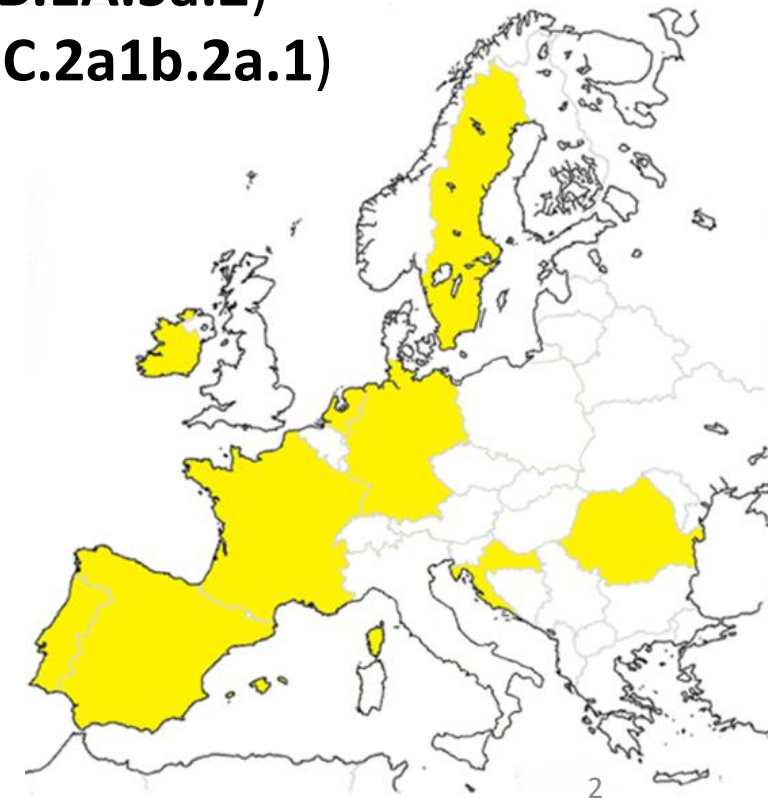
# Methods

- Study population: Patients consulting primary care physicians
- **Systematic selection** of ILI/ARI patients to swab
- EU ILI or ARI; swabbed <8 days after symptom onset
- Test-negative design: (sub)type-specific analysis
  Case: **A(H1N1)pdm09, A(H3N2)**;
  Control: influenza negative
- Vaccinated: Onset ≥14 days after vaccination,
  **< 14 days excluded**
- Onset date unavailable in one site → imputation
  (using median days between onset and swab of pooled data)

# Methods

- Logistic regression VE=(1-OR)*100; Complete case analysis; Individual data pooled with study site as fixed effect
  - Adjusted for age, sex, symptom onset date, presence of chronic condition
- Analysis by age, target group for vaccination, time since vaccination
- **Sensitivity analysis**: exclusion of SARS-CoV-2 positive controls (potential correlation of influenza and COVID-19 vaccination)*
- 9/10 study sites systematically select samples for **genetic sequencing**

* Doll et al, Clin Infect Dis. 2022

# Results

**Number of ILI patients by case status and week of symptom onset, I-MOVE primary care multicentre study, 2021–22**

Influenza A(H1N1)pdm09 (N=253)
Influenza A(H3N2) (N=1595)

Number of cases by (sub)type

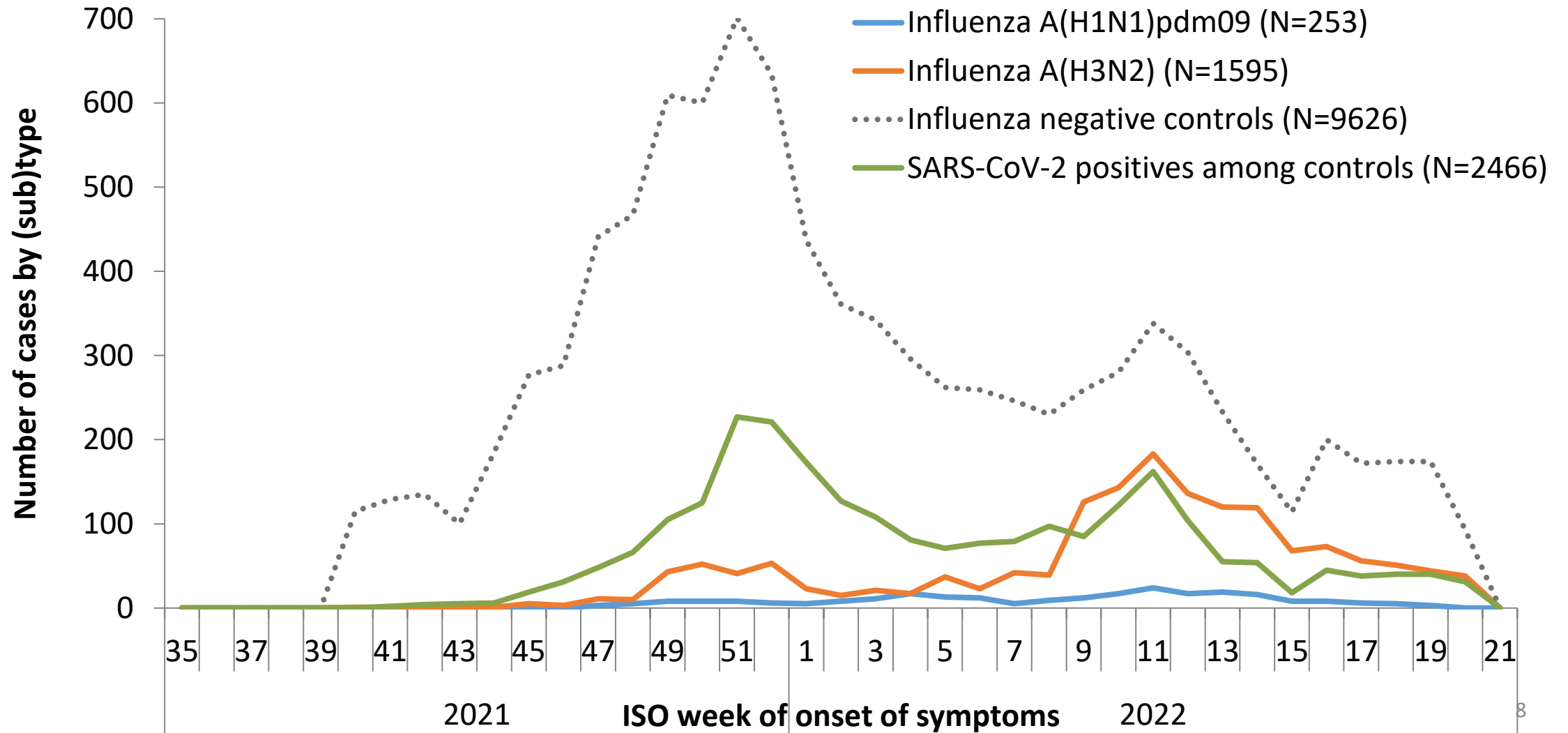ISO week of onset of symptoms

2021    2022

# Number of ILI patients by case status and week of symptom onset, I-MOVE primary care multicentre study, 2021–22

# Number of ILI patients by case status and week of symptom onset, I-MOVE primary care multicentre study, 2021–22



Legend:
- Influenza A(H1N1)pdm09 (N=253)
- Influenza A(H3N2) (N=1595)
- Influenza negative controls (N=9626)
- SARS-CoV-2 positives among controls (N=2466)

Y-axis: Number of cases by (sub)type (0–700)

X-axis: ISO week of onset of symptoms — 2021 (35, 37, 39, 41, 43, 45, 47, 49, 51) / 2022 (1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21)

# Number of ILI patients by case status and week of symptom onset, I-MOVE primary care multicentre study, 2021–22



Legend:
- Influenza A(H1N1)pdm09 (N=253)
- Influenza A(H3N2) (N=1595)
- Influenza negative controls (N=9626)
- Vaccinated patients (N=1974)
- SARS-CoV-2 positives among controls (N=2466)

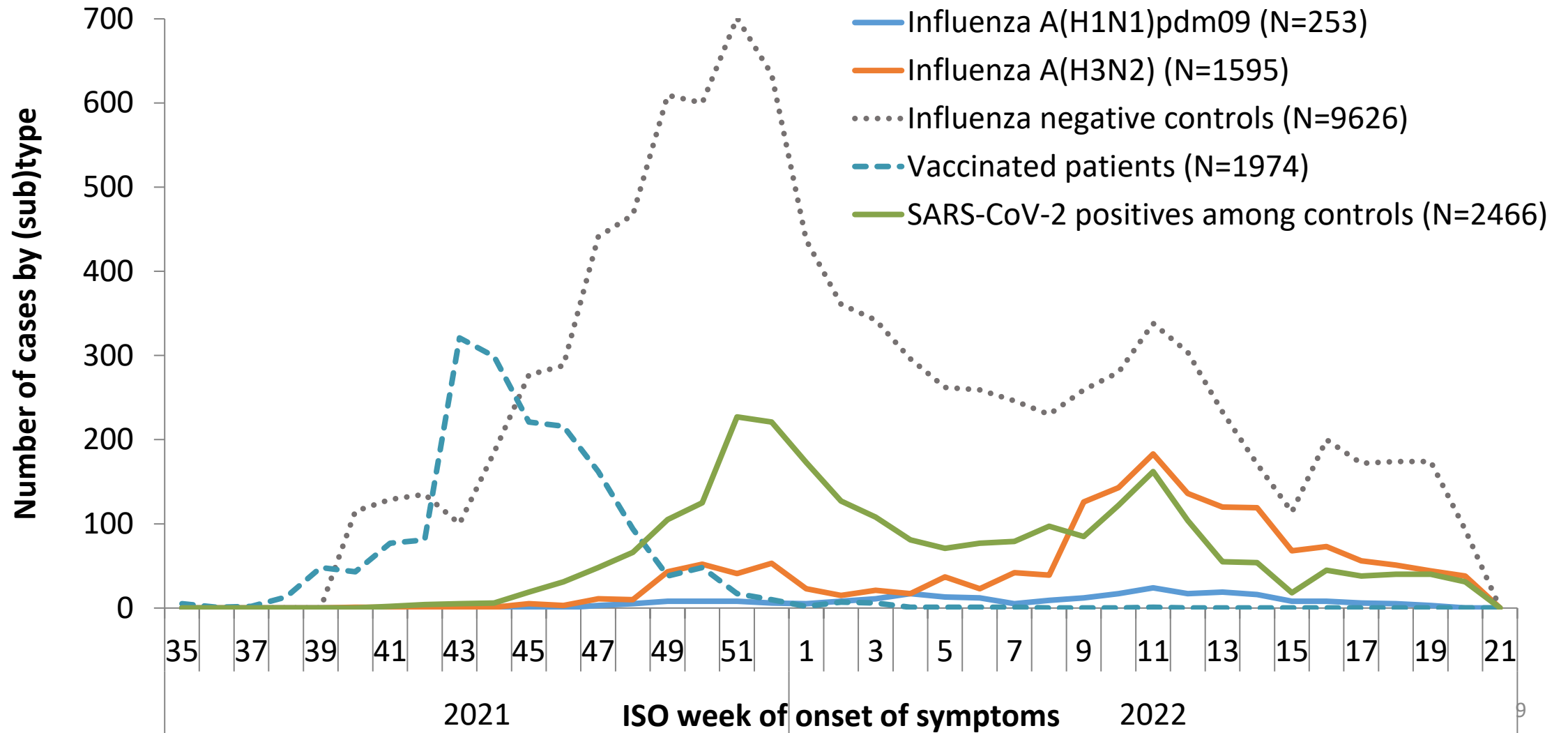Y-axis: Number of cases by (sub)type

X-axis: ISO week of onset of symptoms (2021, 2022)

# Number of ILI patients by case status and week of symptom onset, I-MOVE primary care multicentre study, 2021–22



Legend:
- Influenza A(H1N1)pdm09 (N=253)
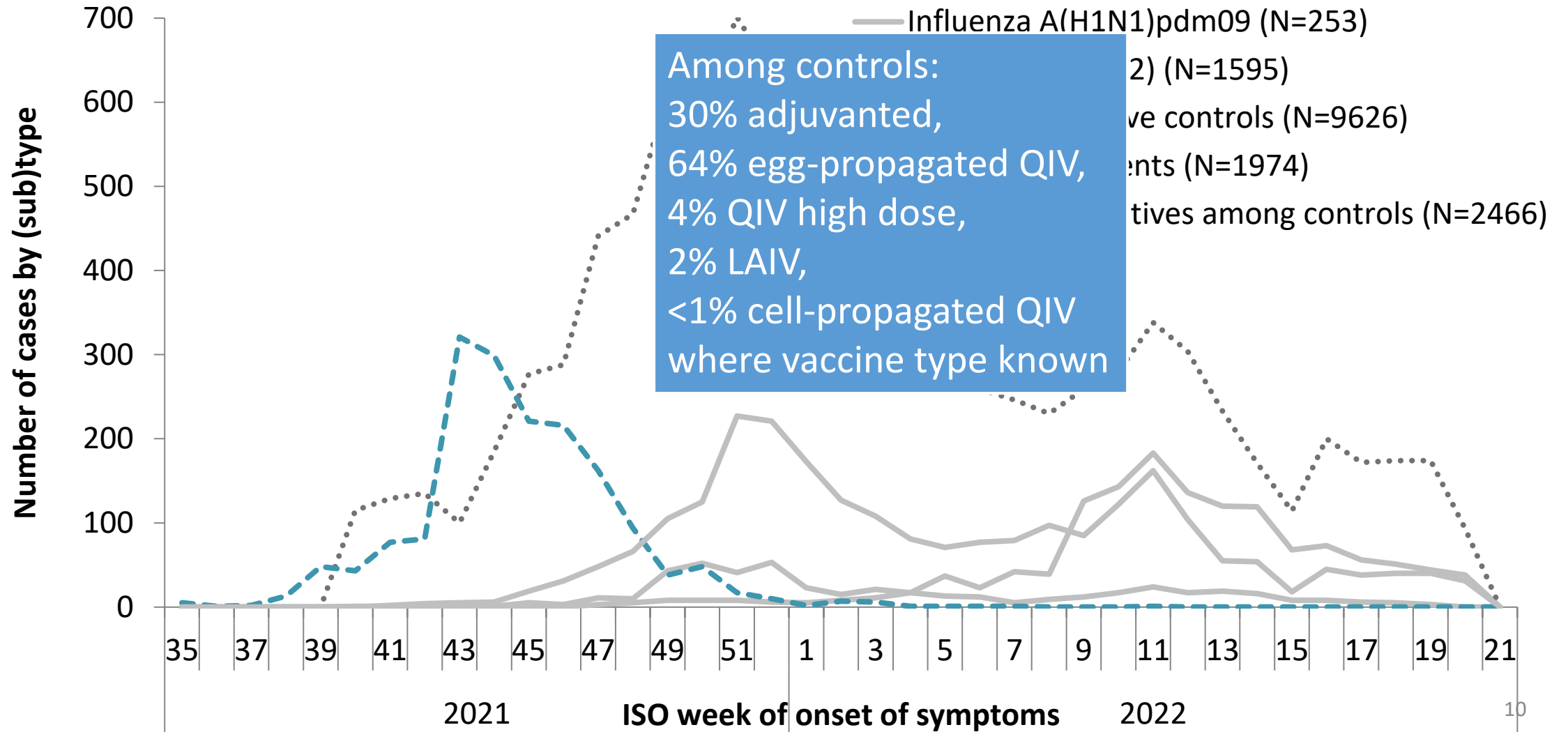- ...2) (N=1595)
- ...ve controls (N=9626)
- ...ents (N=1974)
- ...tives among controls (N=2466)

Among controls:
30% adjuvanted,
64% egg-propagated QIV,
4% QIV high dose,
2% LAIV,
<1% cell-propagated QIV
where vaccine type known

Y-axis: Number of cases by (sub)type

X-axis: ISO week of onset of symptoms

2021    2022

# Influenza A(H1N1)pdm09

# Pooled VE against A(H1N1)pdm09, all ages, by age group, I-MOVE primary care multicentre study, 2021–22 (FR, NL, DE)



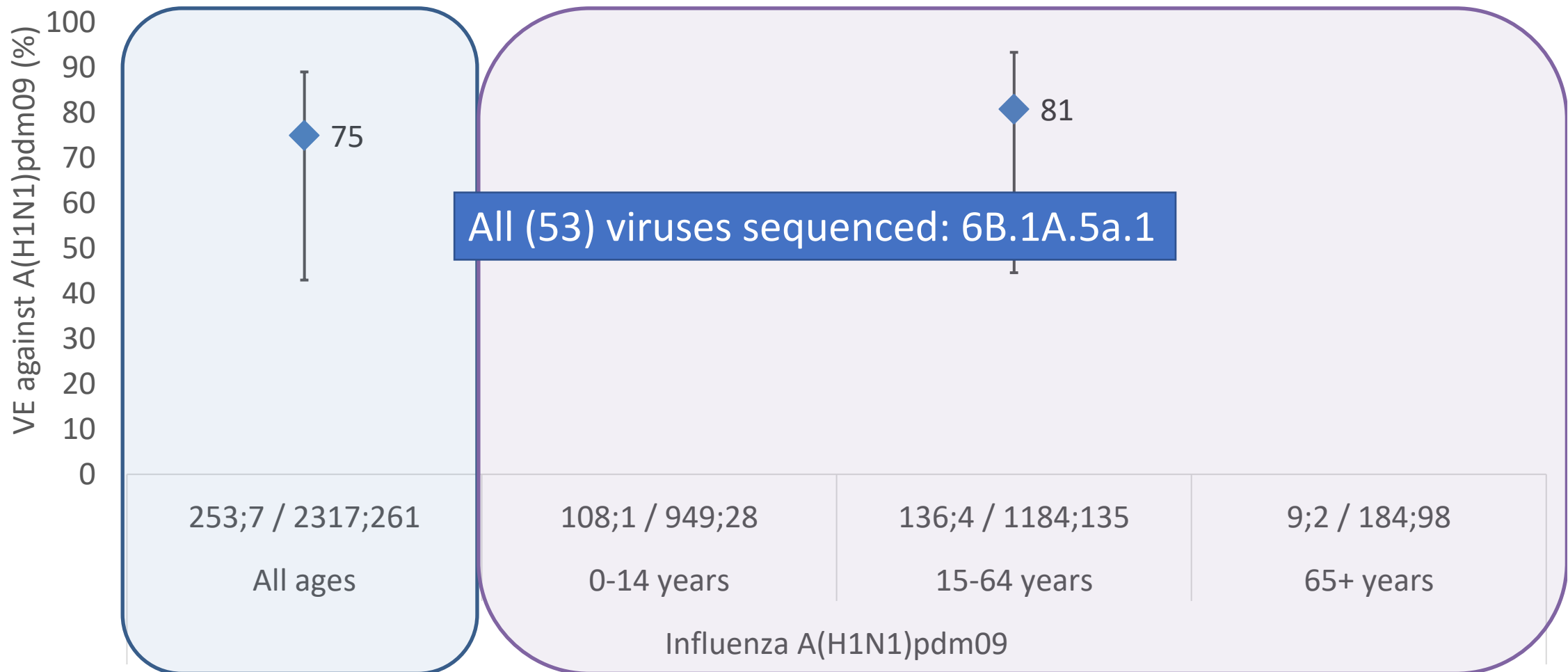| | Influenza A(H1N1)pdm09 | | |
|---|---|---|---|
| 253;7 / 2317;261 | 108;1 / 949;28 | 136;4 / 1184;135 | 9;2 / 184;98 |
| All ages | 0-14 years | 15-64 years | 65+ years |

Cases; vaccinated / Controls; vaccinated

# Pooled VE against A(H1N1)pdm09, all ages, by age group, I-MOVE primary care multicentre study, 2021–22 (FR, NL, DE)



All (53) viruses sequenced: 6B.1A.5a.1

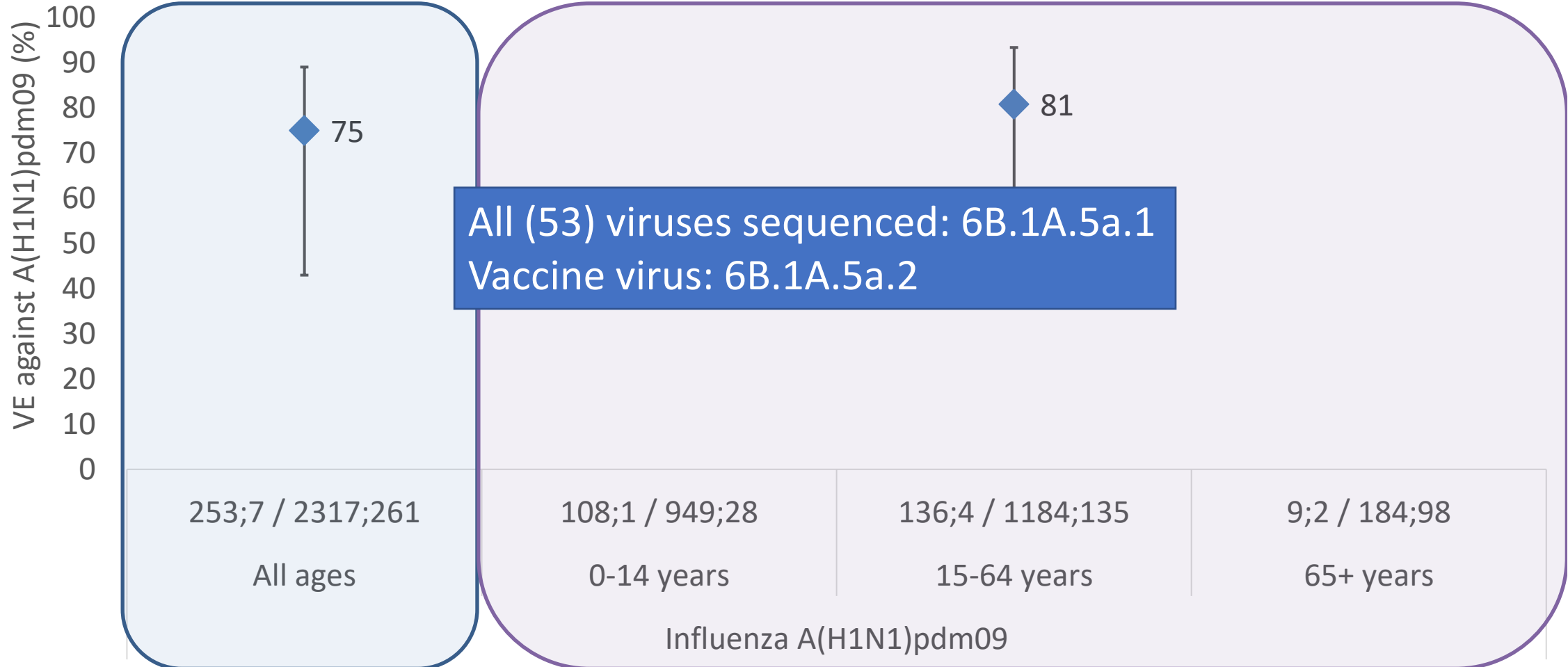| | | | |
|---|---|---|---|
| 253;7 / 2317;261 | 108;1 / 949;28 | 136;4 / 1184;135 | 9;2 / 184;98 |
| All ages | 0-14 years | 15-64 years | 65+ years |
| | Influenza A(H1N1)pdm09 | | |

Cases; vaccinated / Controls; vaccinated

# Pooled VE against A(H1N1)pdm09, all ages, by age group, I-MOVE primary care multicentre study, 2021–22 (FR, NL, DE)



**All (53) viruses sequenced: 6B.1A.5a.1**
**Vaccine virus: 6B.1A.5a.2**

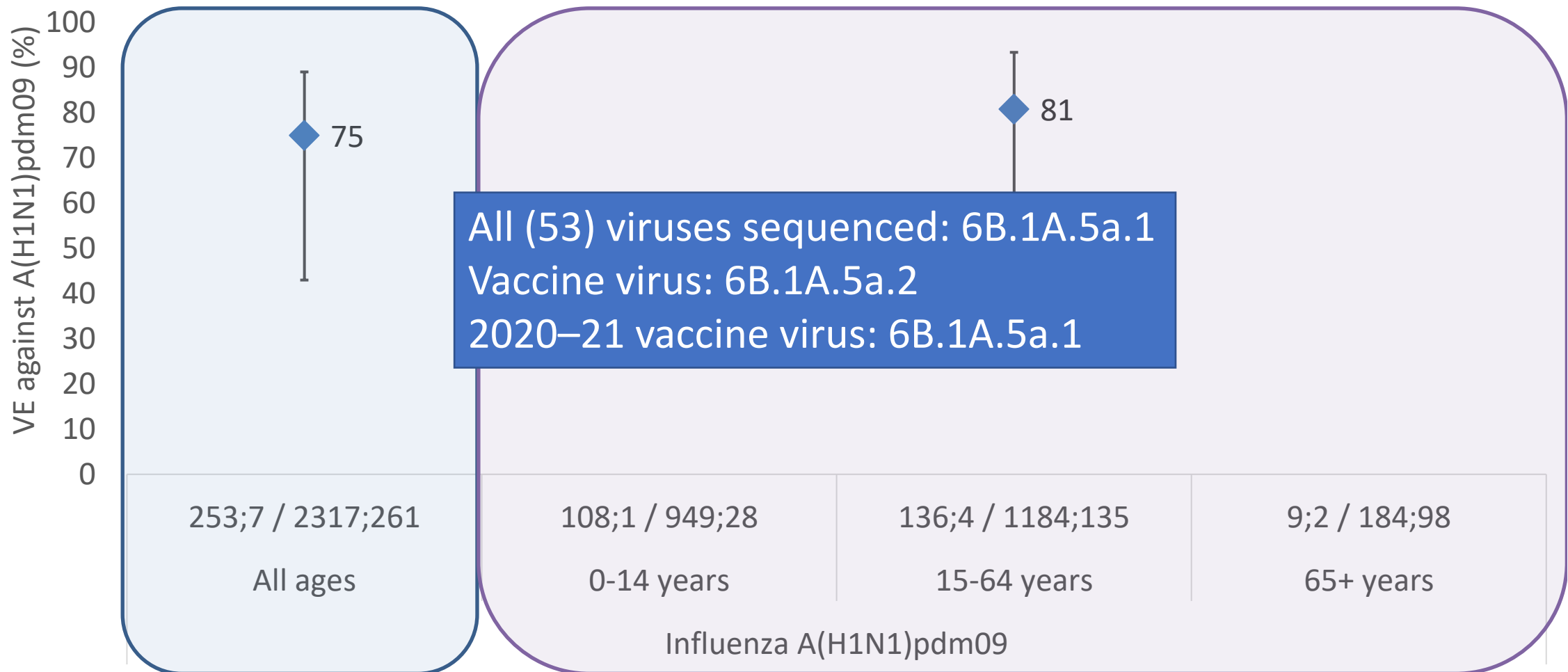| | | | |
|---|---|---|---|
| 253;7 / 2317;261 | 108;1 / 949;28 | 136;4 / 1184;135 | 9;2 / 184;98 |
| All ages | 0-14 years | 15-64 years | 65+ years |
| | Influenza A(H1N1)pdm09 | | |

VE against A(H1N1)pdm09 (%)

Cases; vaccinated / Controls; vaccinated

# Pooled VE against A(H1N1)pdm09, all ages, by age group, I-MOVE primary care multicentre study, 2021–22 (FR, NL, DE)



All (53) viruses sequenced: 6B.1A.5a.1
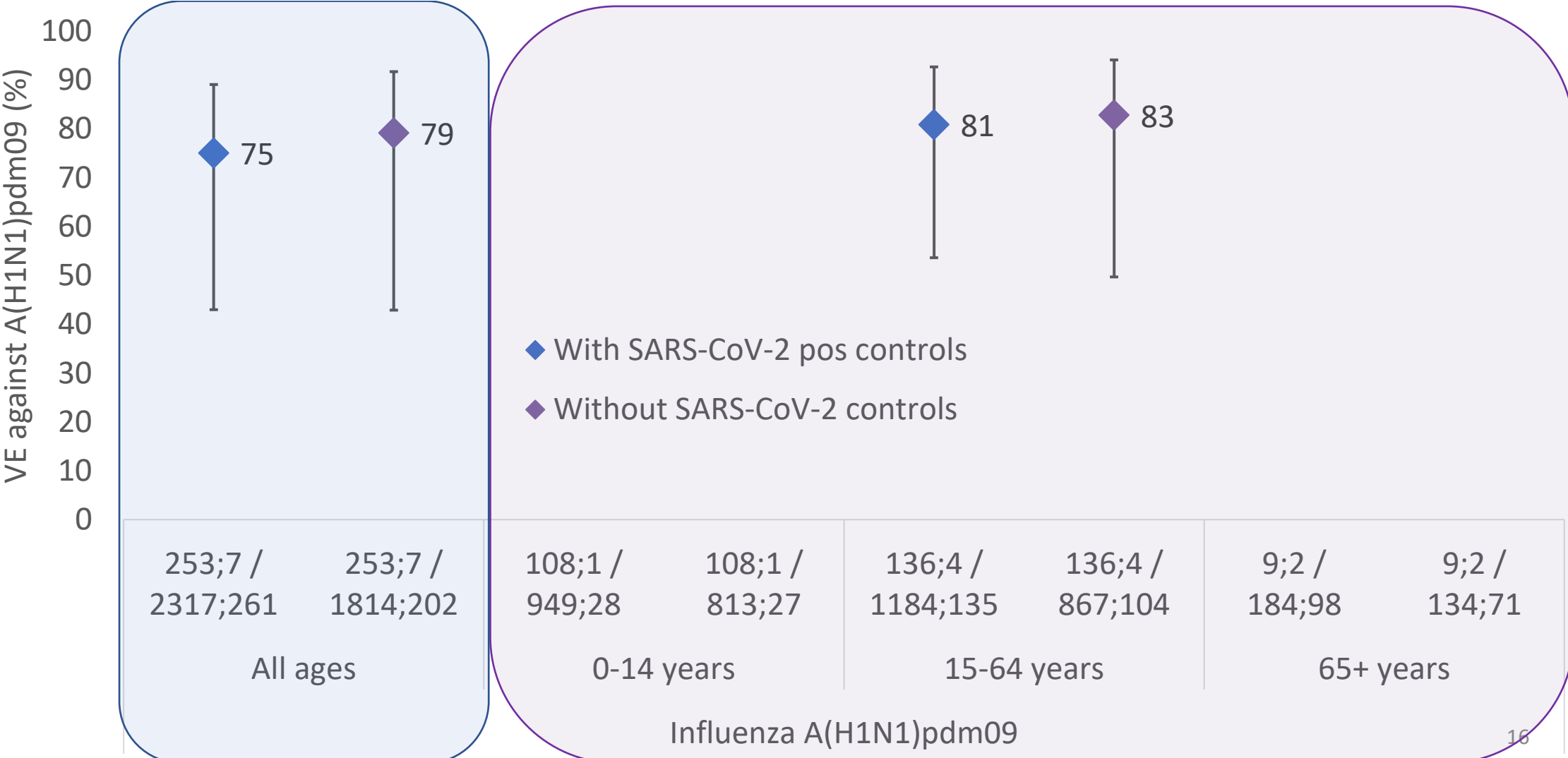Vaccine virus: 6B.1A.5a.2
2020–21 vaccine virus: 6B.1A.5a.1

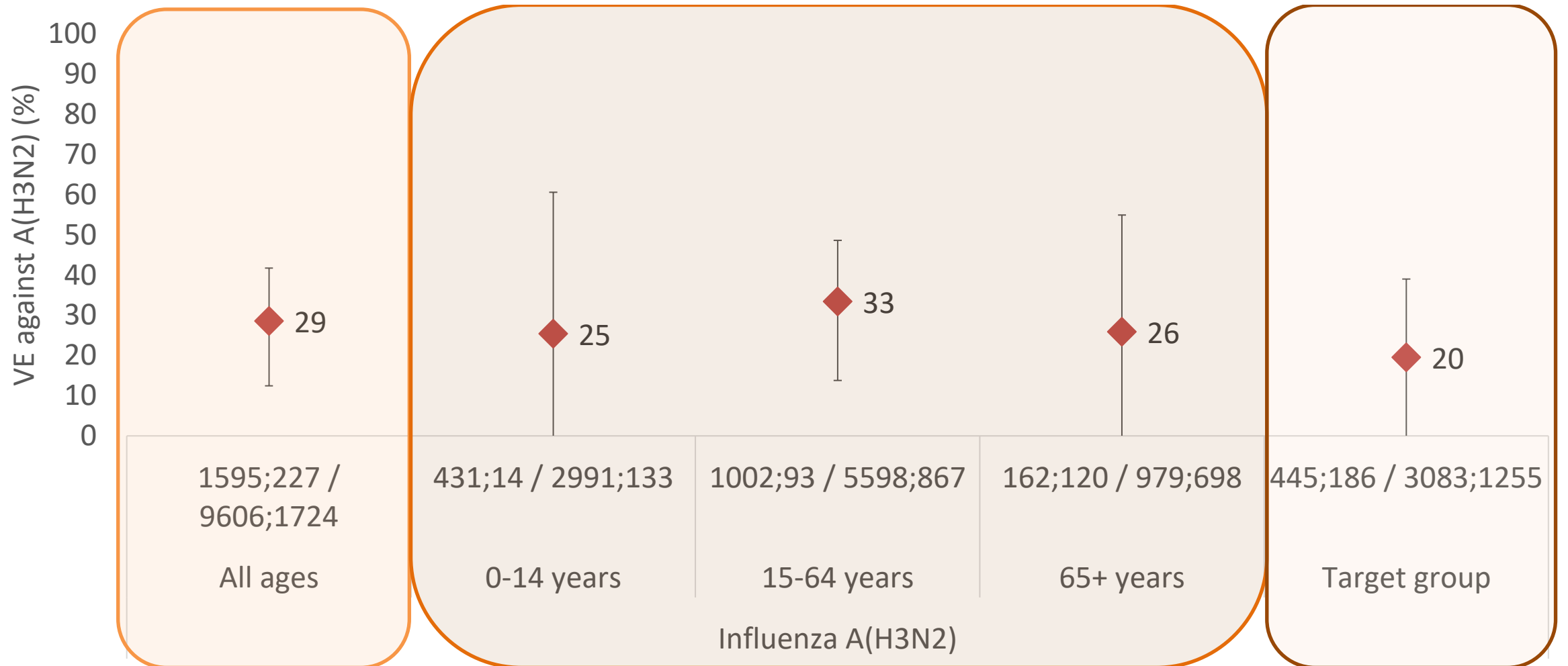Cases; vaccinated / Controls; vaccinated

# Sensitivity analysis: Pooled VE against A(H1N1)pdm09, all ages, by age group, in-/excluding SARS-CoV-2 positive controls, I-MOVE primary care multicentre study, 2021–22



VE against A(H1N1)pdm09 (%)

◆ With SARS-CoV-2 pos controls
◆ Without SARS-CoV-2 controls

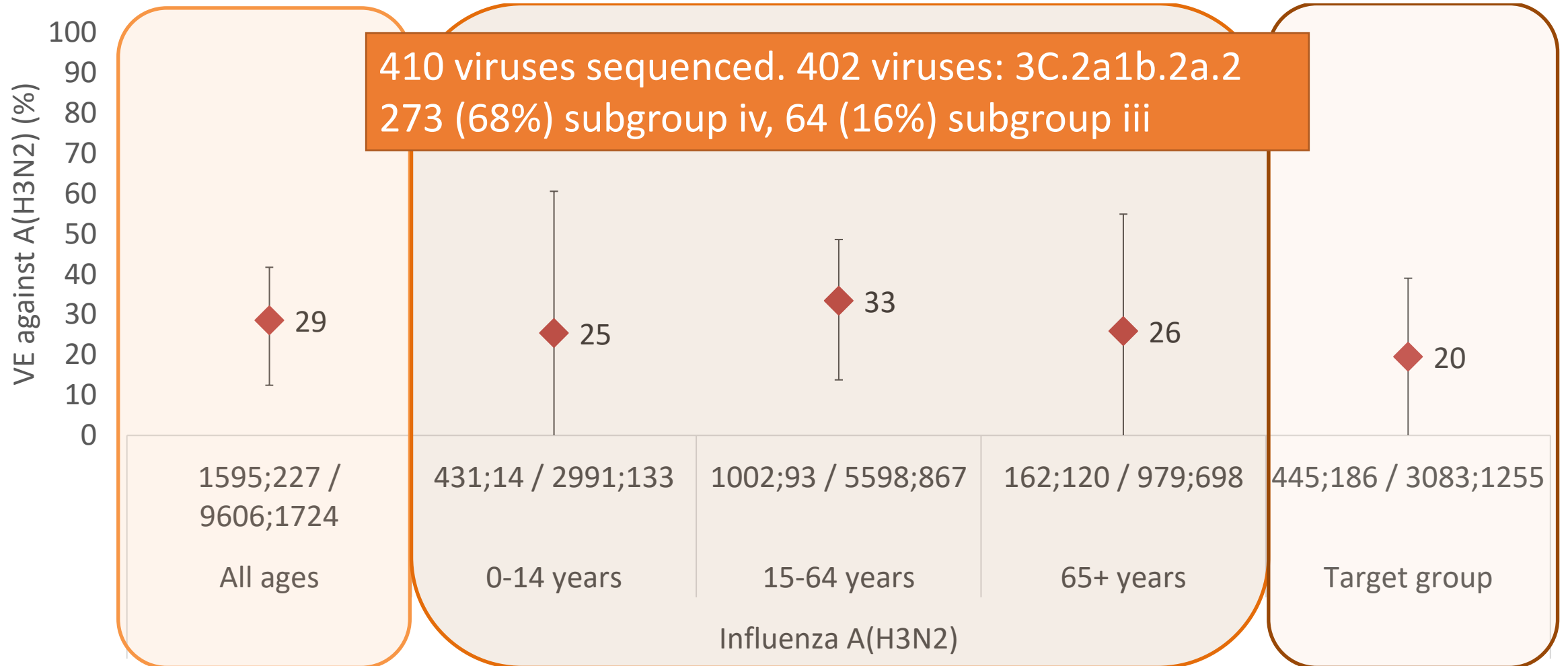| | | | | | |
|---|---|---|---|---|---|
| 253;7 / 2317;261 | 253;7 / 1814;202 | 108;1 / 949;28 | 108;1 / 813;27 | 136;4 / 1184;135 | 136;4 / 867;104 | 9;2 / 184;98 | 9;2 / 134;71 |
| All ages | | 0-14 years | | 15-64 years | | 65+ years | |

Influenza A(H1N1)pdm09

75    79    81    83

# Influenza A(H3N2)

# Pooled VE against A(H3N2), all ages, by age and vaccine target group, I-MOVE primary care multicentre study, 2021–22



VE against A(H3N2) (%)

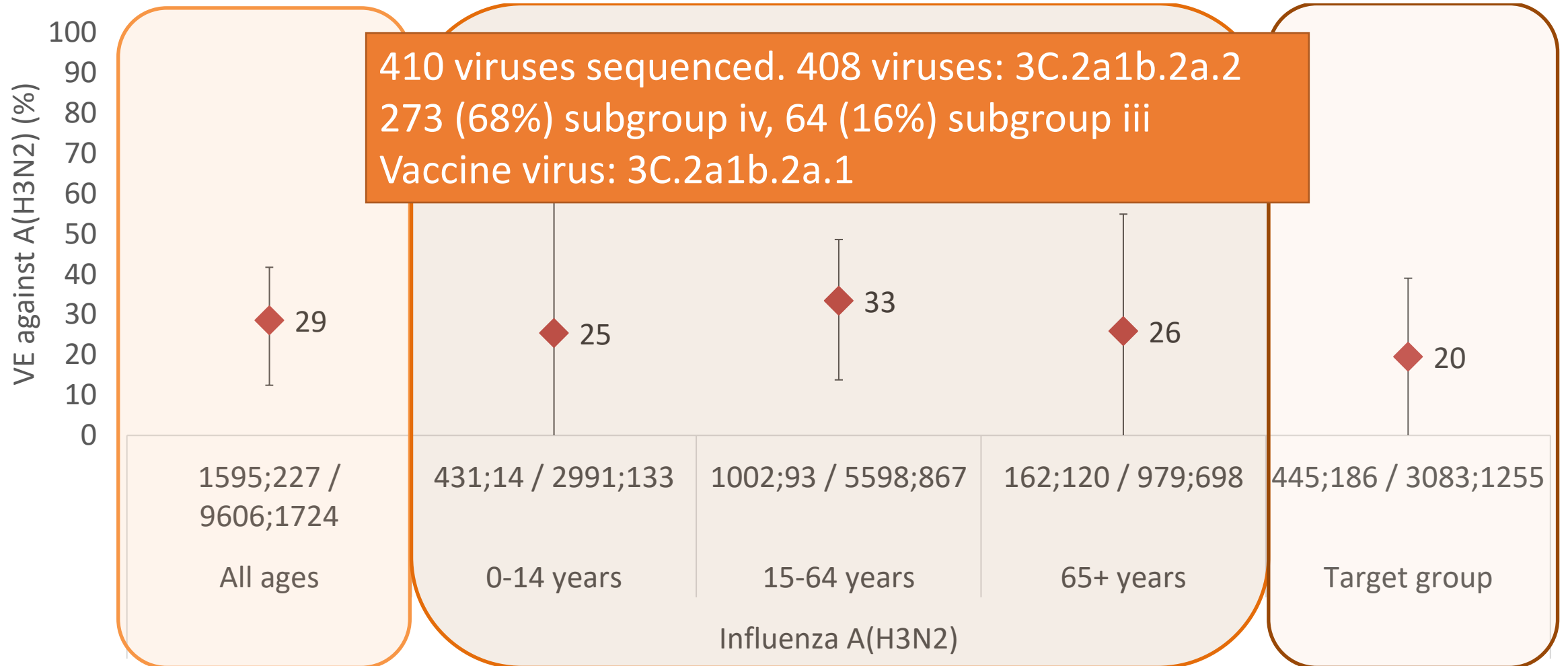| | 29 | 25 | 33 | 26 | 20 |
|---|---|---|---|---|---|
| | 1595;227 / 9606;1724 | 431;14 / 2991;133 | 1002;93 / 5598;867 | 162;120 / 979;698 | 445;186 / 3083;1255 |
| | All ages | 0-14 years | 15-64 years | 65+ years | Target group |

Influenza A(H3N2)

Cases; vaccinated / Controls; vaccinated

# Pooled VE against A(H3N2), all ages, by age and vaccine target group, I-MOVE primary care multicentre study, 2021–22



410 viruses sequenced. 402 viruses: 3C.2a1b.2a.2
273 (68%) subgroup iv, 64 (16%) subgroup iii

VE against A(H3N2) (%)

| | All ages | 0-14 years | 15-64 years | 65+ years | Target group |
|---|---|---|---|---|---|
| VE | 29 | 25 | 33 | 26 | 20 |
| Cases;vaccinated / Controls;vaccinated | 1595;227 / 9606;1724 | 431;14 / 2991;133 | 1002;93 / 5598;867 | 162;120 / 979;698 | 445;186 / 3083;1255 |

Influenza A(H3N2)

Cases; vaccinated / Controls; vaccinated

# Pooled VE against A(H3N2), all ages, by age and vaccine target group, I-MOVE primary care multicentre study, 2021–22



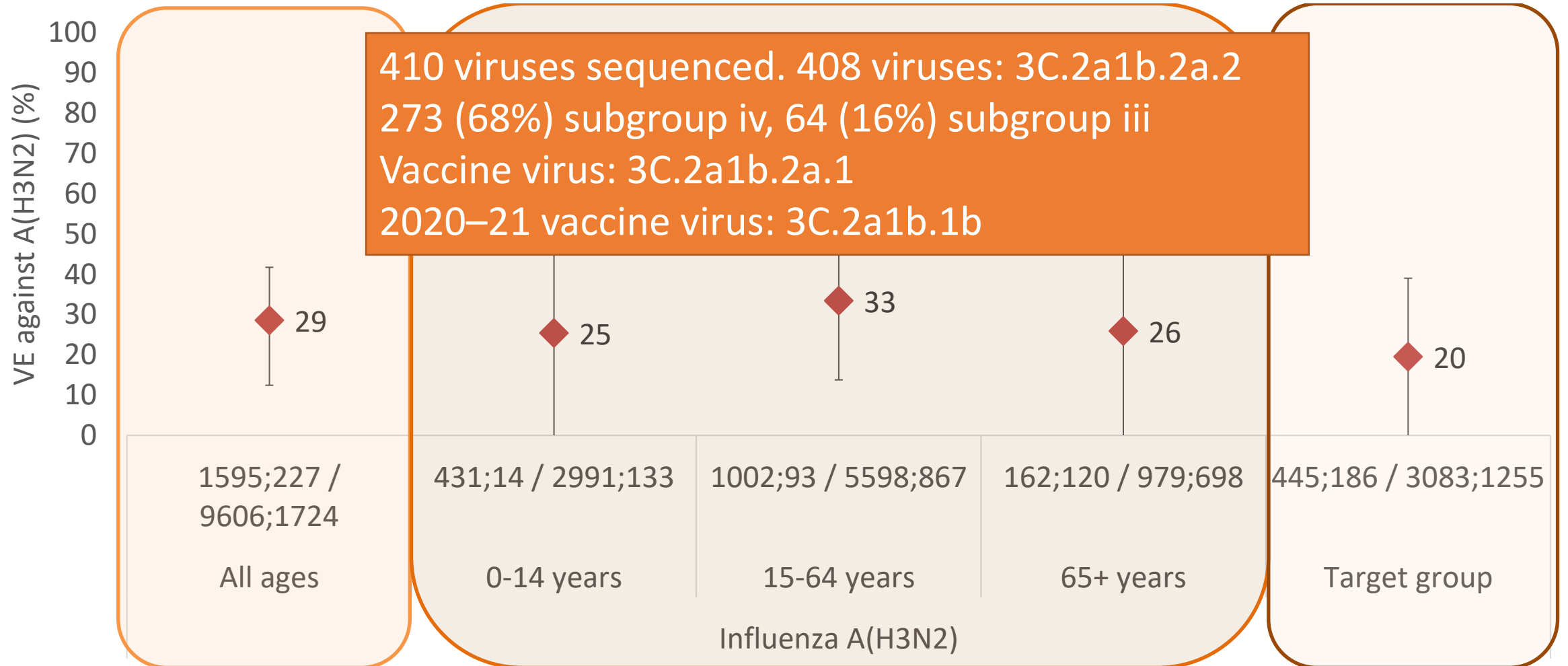410 viruses sequenced. 408 viruses: 3C.2a1b.2a.2
273 (68%) subgroup iv, 64 (16%) subgroup iii
Vaccine virus: 3C.2a1b.2a.1

VE against A(H3N2) (%)

| | All ages | 0-14 years | 15-64 years | 65+ years | Target group |
|---|---|---|---|---|---|
| VE | 29 | 25 | 33 | 26 | 20 |
| Cases;vaccinated / Controls;vaccinated | 1595;227 / 9606;1724 | 431;14 / 2991;133 | 1002;93 / 5598;867 | 162;120 / 979;698 | 445;186 / 3083;1255 |

Influenza A(H3N2)

Cases; vaccinated / Controls; vaccinated

# Pooled VE against A(H3N2), all ages, by age and vaccine target group, I-MOVE primary care multicentre study, 2021–22



VE against A(H3N2) (%)

410 viruses sequenced. 408 viruses: 3C.2a1b.2a.2
273 (68%) subgroup iv, 64 (16%) subgroup iii
Vaccine virus: 3C.2a1b.2a.1
2020–21 vaccine virus: 3C.2a1b.1b

| All ages | 0-14 years | 15-64 years | 65+ years | Target group |
|---|---|---|---|---|
| 29 | 25 | 33 | 26 | 20 |
| 1595;227 / 9606;1724 | 431;14 / 2991;133 | 1002;93 / 5598;867 | 162;120 / 979;698 | 445;186 / 3083;1255 |

Influenza A(H3N2)

Cases; vaccinated / Controls; vaccinated

21

# Pooled VE against A(H3N2), all ages, by time since vaccination, I-MOVE primary care multicentre study, 2021–22



Cases/ controls
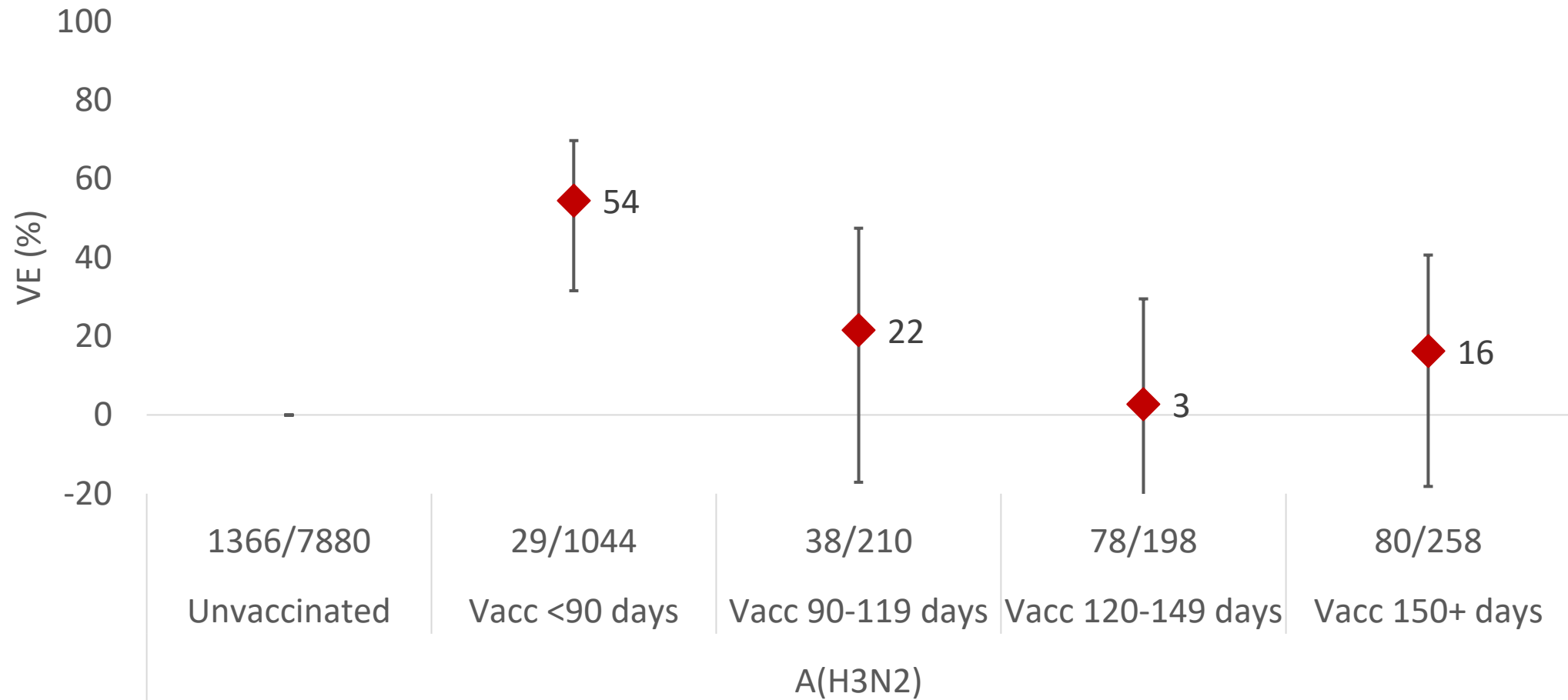
# Sensitivity analysis: Pooled VE against A(H3N2), all ages, by age and vaccine target group, in-/excluding SARS-CoV-2 positive controls, I-MOVE primary care multicentre study, 2021–22



Cases; vaccinated / Controls; vaccinated

23
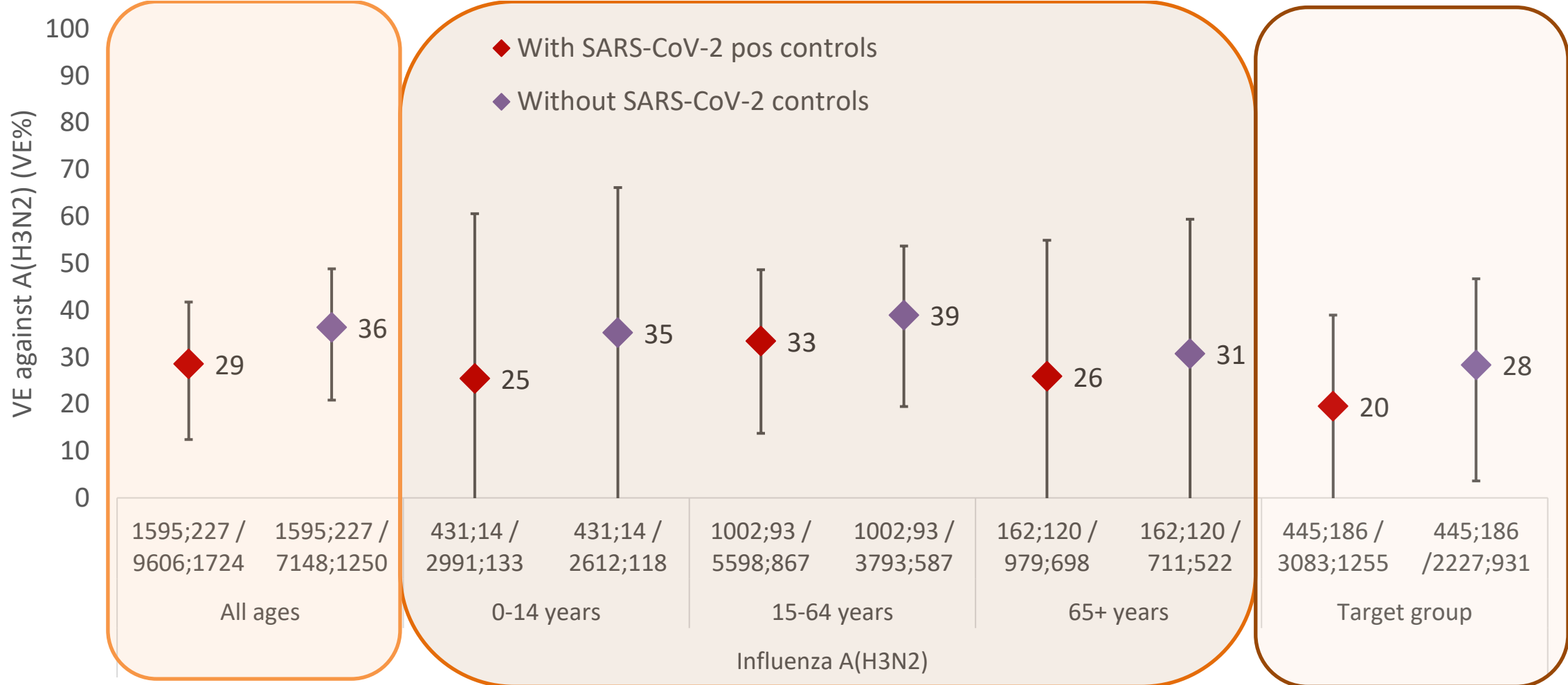
# Discussion: VE against influenza A(H1N1)pdm09

- 2021–22 season: Mainly influenza A(H3N2), some A(H1N1)pdm09
- VE against **A(H1N1)pdm09: 75%**
  - Low numbers
  - **Highest I-MOVE A(H1N1)pdm09 VE since 2009** (often 50–59%)
  - Circulating variant 6B.1A.5a.1, vaccine variant 6B.1A.5a.2
    - Antisera against vaccine virus recognised 5a.1 viruses poorly*
    - Lasting effect of 2020–21 vaccination on A(H1N1)pdm09?
    - Similar VE as UKHSA against emergency department visits **
    - Bias due to differential exposures to virus among vaccinated and unvaccinated (due to COVID-19 restrictions)? Is it possible to have a bias only for one subtype?

* WHO report on recommendations for vaccines for 2022-23 NH influenza season; ** https://www.gov.uk/government/statistics/annual-flu-reports/surveillance-of-influenza-and-other-seasonal-respiratory-viruses-in-winter-2021-to-2022#vaccination

# Discussion: VE against influenza A(H3N2)

- **VE against A(H3N2): 29%;** similar by age group (25–33%)

- **Comparable to I-MOVE A(H3N2) VE in other seasons**

- Indication that the **VE is lower in the vaccination target group**
  - Greater likelihood of **differential exposure** among vaccinated/unvaccinated among risk groups?

- Mainly **3C.2a1b.2a.2** circulating
  - Antisera against 2a.1 vaccine virus recognised 2a.2 viruses poorly*
    - Compatible with low VE

- **Some indication that A(H3N2) VE declined over time:** long season

* WHO report on recommendations for vaccines for 2022-23 NH influenza season

# Conclusions

- Long season; large study: reasonable precision
- Encouraging VE against A(H1N1)pdm09, although little circulation
- A(H3N2) VE lower at ~30%, as expected
- 25% of controls SARS-CoV-2 positive
  - VE higher (2–9% absolute) after exclusion of SARS-CoV-2 controls
- Important to question VE results in light of changes in healthcare systems and behaviour related to pandemic
- Excellent achievement to have I-MOVE VE estimates, given high workload at GP, regional PH and national PH level

# Big thank you in particular to study sites

❖ **Patients, influenza sentinel networks**

❖ **Study sites I-MOVE multicentre case control 2021–22**

  ❖ **Croatia, IPH:** V Visekruna, S Kurečić Filipović, B Kaić, I Pem Novosel, G Petrovic, M Ilić, I Mlinarić

  ❖ **France, Sentinelles:** A Vilcu, M. Mahmadi-Moindze, T Blanchon, A Falchi; **Institut Pasteur**: V Enouf, S van der Werf

  ❖ **Germany, RKI:** S Buda, U Preuss, L Goerlitz, K Tolksdorf, R Duerrwald, M Wedde

  ❖ **Ireland, HSE-HPSC:** L Domegan, J O'Donnell, A McKenna; **UCD-NVRL**: C Bennett, J Connell

  ❖ **The Netherlands, RIVM:** M de Lange, A Meijer, F Dijkstra, R van Gageldonk**; Nivel:** M Hooiveld

  ❖ **Portugal, Inst Nac Saude Dr Ricardo Jorge:** I Kislaya, A Machado, R Guiomar, A Rodrigues, V Gomez, B Nunes

  ❖ **Romania, Cantacuzino Institut:** M Lazar, A Ivanciuc, ME Mihai

  ❖ **Spain, CNE & ISCIII:** A Larrauri, C Mazagatos; **CNM & ISCIII**: F Pozo, I Casas

  ❖ **Spain, ISPL, Navarra**: J Castilla, I Casado Buesa, I Martínez-Baz, C Burgui

  ❖ **Sweden:** A Wiman, A Carnahan, N Latorre-Margalef, L Dillner

❖ **ECDC:** A Omokanye, S Bacci, M Kaczmarek, L Pastore Celentano

❖ **Epiconcept:** M Maurel, M Valenciano, A Moren, A Rose, V Nancey, C Laniece Delauney, A Nardone

❖ **Other partner institutes**

I-MOVE is part of the ECDC VEBIS project from July 2022.

# Big thank you in particular to study sites

- ❖ **Patients, influenza sentinel networks**
- ❖ **Study sites I-MOVE multicentre case control 2021–22**
  - ❖ **Croatia, IPH:** V Visekruna, S Kurečić Filipović, B Kaić, I Pem Novosel, G Petrovic, M Ilić, I Mlinarić
  - ❖ **France, Sentinelles:** A Vilcu, M. Mahmadi-Moindze, T Blanchon, A Falchi; **Institut Pasteur**: V Enouf, S van der Werf
  - ❖ **Germany, RKI:** S Buda, U Preuss, L Goerlitz, K Tolksdorf, R Duerrwald, M Wedde
  - ❖ **Ireland, HSE-HPSC:** L Domegan, J O'Donnell, A McKenna; **UCD-NVRL**: C Bennett, J Connell
  - ❖ **The Netherlands, RIVM:** M de Lange, A Meijer, F Dijkstra, R van Gageldonk**; Nivel:** M Hooiveld
  - ❖ **Portugal, Inst Nac Saude Dr Ricardo Jorge:** I Kislaya, A Machado, R Guiomar, A Rodrigues, V Gomez, B Nunes
  - ❖ **Romania, Cantacuzino Institut:** M Lazar, A Ivanciuc, ME Mihai
  - ❖ **Spain, CNE & ISCIII:** A Larrauri, C Mazagatos; **CNM & ISCIII**: F Pozo, I Casas
  - ❖ **Spain, ISPL, Navarra**: J Castilla, I Casado Buesa, I Martínez-Baz, C Burgui
  - ❖ **Sweden:** A Wiman, A Carnahan, N Latorre-Margalef, L Dillner
- ❖ **ECDC:** A Omokanye, S Bacci, M Kaczmarek, L Pastore Celentano
- ❖ **Epiconcept:** M Maurel, M Valenciano, A Moren, A Rose, V Nancey, C Laniece Delauney, A Nardone
- ❖ **Other partner institutes**

# Genetic drift AH3
## Jun 2022

| | 3C.2a1b.1a Denmark-like | | 3C.2a1b.1b HongKong-like | | 3C.2a1b.2a.1 Cambodia-like | 3C.2a1b.2a.2 Bangladesh-like none | 3C.2a1b.2a.2 Bangladesh-like E50K, F79V, I140K | | 3C.2a1b.2a.2 Bangladesh-like (i) and (ii) | | 3C.2a1b.2a.2 Bangladesh-like (iii) | | 3C.2a1b.2a.2 Bangladesh-like (iv) | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| France | 5 | 9,6 | 1 | 1,9 | - | - | - | | - | | 5 | 9,6 | 41 | 78,8 | 52 |
| Germany | - | | - | | - | - | 5 | 8,5 | 1 | 1,7 | 3 | 5,1 | 50 | 84,7 | 59 |
| Ireland | 1 | 1,5 | - | | - | - | - | | - | | 6 | 9,1 | 59 | 89,4 | 66 |
| Navarre | - | | - | | - | - | - | | - | | 32 | 43,2 | 42 | 56,8 | 74 |
| Netherlands | - | | - | | - | 1 | 0,7 | 59 | 43,4 | 1 | 0,7 | 9 | 6,6 | 66 | 48,5 | 136 |
| Portugal | 1 | 7,7 | - | | - | - | - | | - | | 7 | 53,8 | 5 | 38,5 | 13 |
| Romania | - | | - | | - | - | - | | - | | 9 | 56,3 | 7 | 43,8 | 16 |
| Spain | - | | - | | - | - | - | | - | | 8 | 25,0 | 24 | 75,0 | 32 |
| Sweden | - | | - | | - | - | - | | - | | - | | 18 | 100,0 | 18 |
| **Total** | 7 | 1,5 | 1 | 0,2 | - | - | 65 | 13,9 | 2 | 0,4 | 79 | 17,0 | 312 | 67,0 | 466 |

Instituto de Salud Carlos III

I-MOVE

# Genetic drift AH3
## Jun 2022
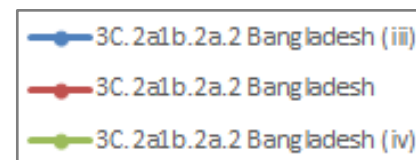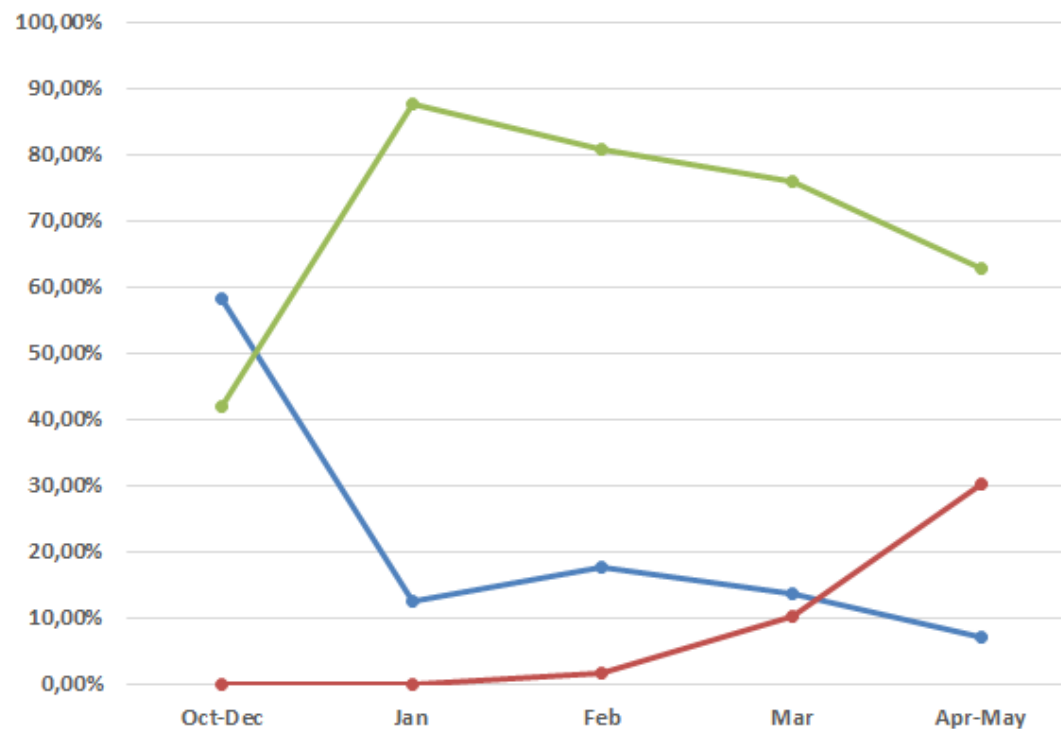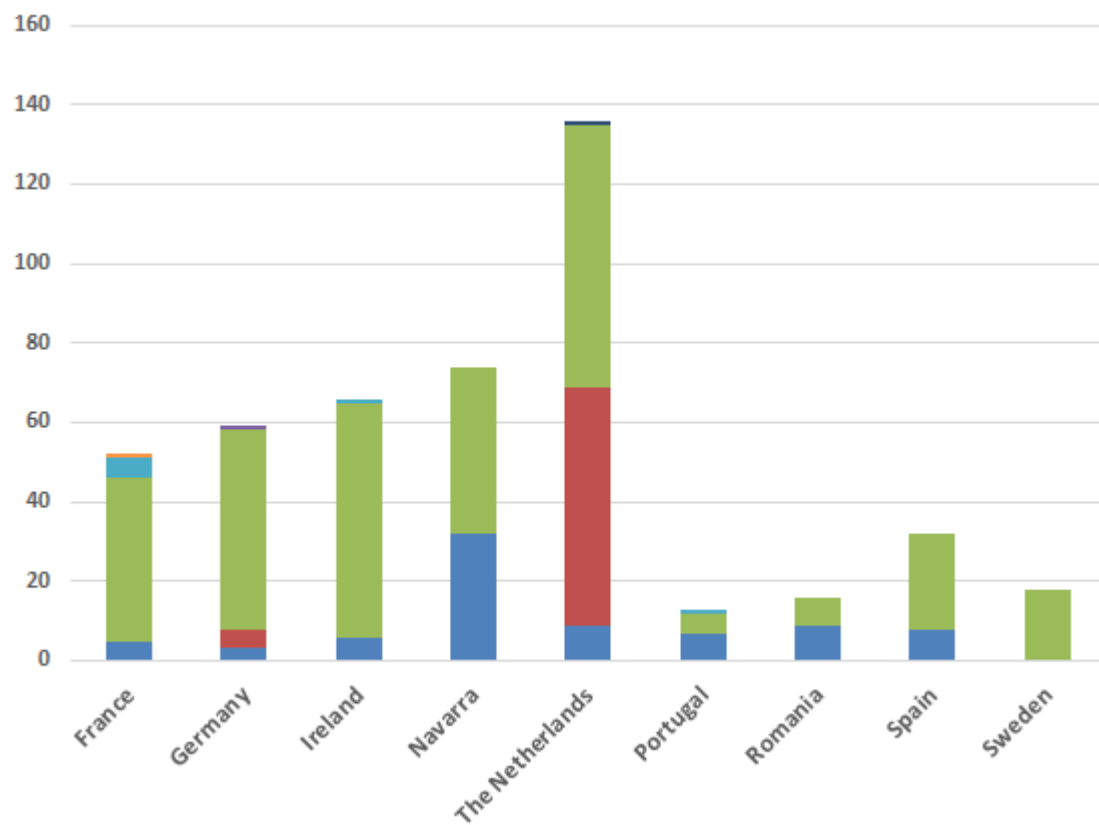
# Genetic drift AH1
## Jun 2022

| | 6B.1A.5a.2 Victoria-like | 6B.1A.5a.2 Victoria-like K54Q+ … | | 6B.1A.5a.1 Guangdong-like | | 6B.1A.5a.1 Guangdong-like P137S+G155E | Total |
|---|---|---|---|---|---|---|---|
| France | - | - | | 27 | 100,0 | - | 27 |
| Germany | - | - | | 3 | 100,0 | - | 3 |
| Ireland | - | 1 | 100,0 | - | | - | 1 |
| Navarre | - | - | | - | | - | - |
| Netherlands | - | - | | 29 | 100,0 | - | 29 |
| Portugal | - | - | | - | | - | - |
| Romania | - | - | | - | | - | - |
| Spain | - | - | | - | | - | - |
| Sweden | - | - | | - | | - | - |
| **Total** | - | 1 | 1,7 | 59 | 98,3 | - | 60 |

Instituto de Salud Carlos III

I-MOVE