RECOVER Closing Conference

Transmission in households

Patricia Bruijning-Verhagen MD, PhD

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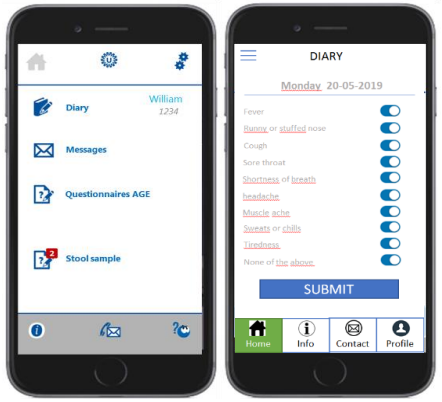
Objectives

Estimate key transmission characteristics of SARS-CoV-2 and factors influencing transmission

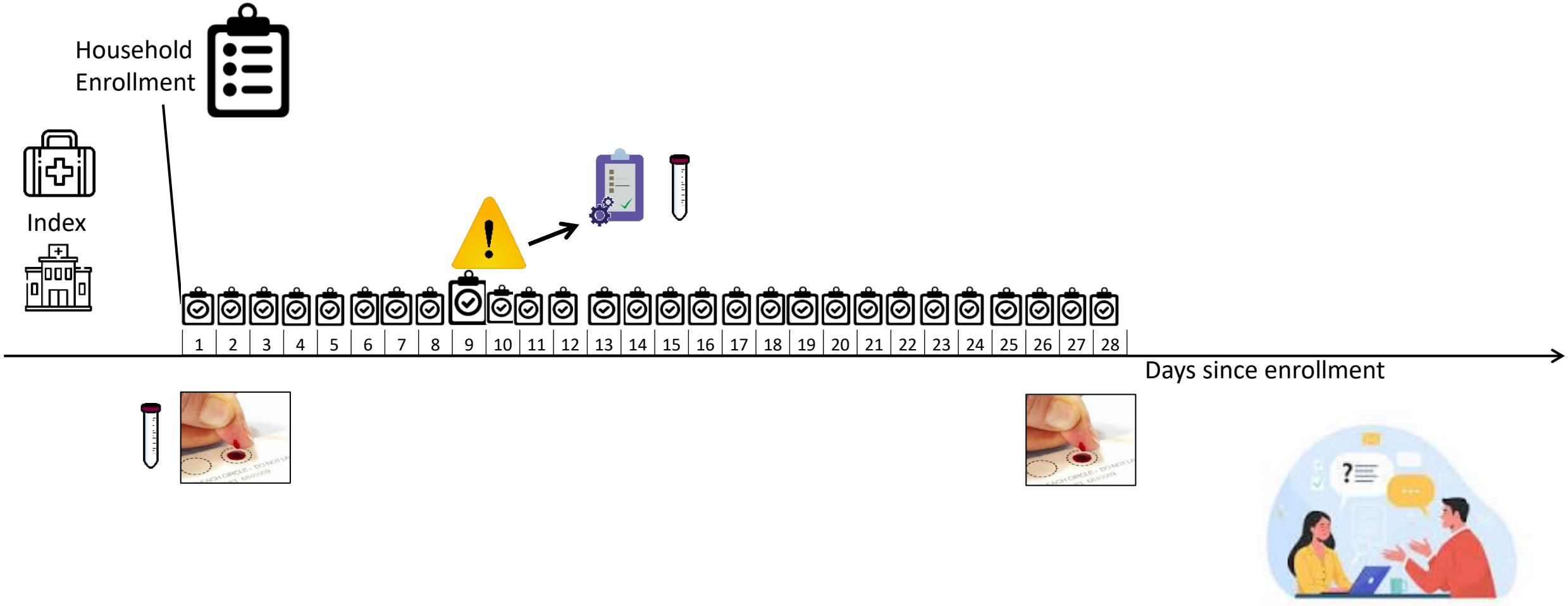
Specifically;

- Estimate transmission rates
- susceptibility and infectiousness by age
- Household and behavioral characteristics that influence transmission
- As input for mathematical modeling on testing and quarantining strategies
- Describe emotional wellbeing and support requirements for affected households

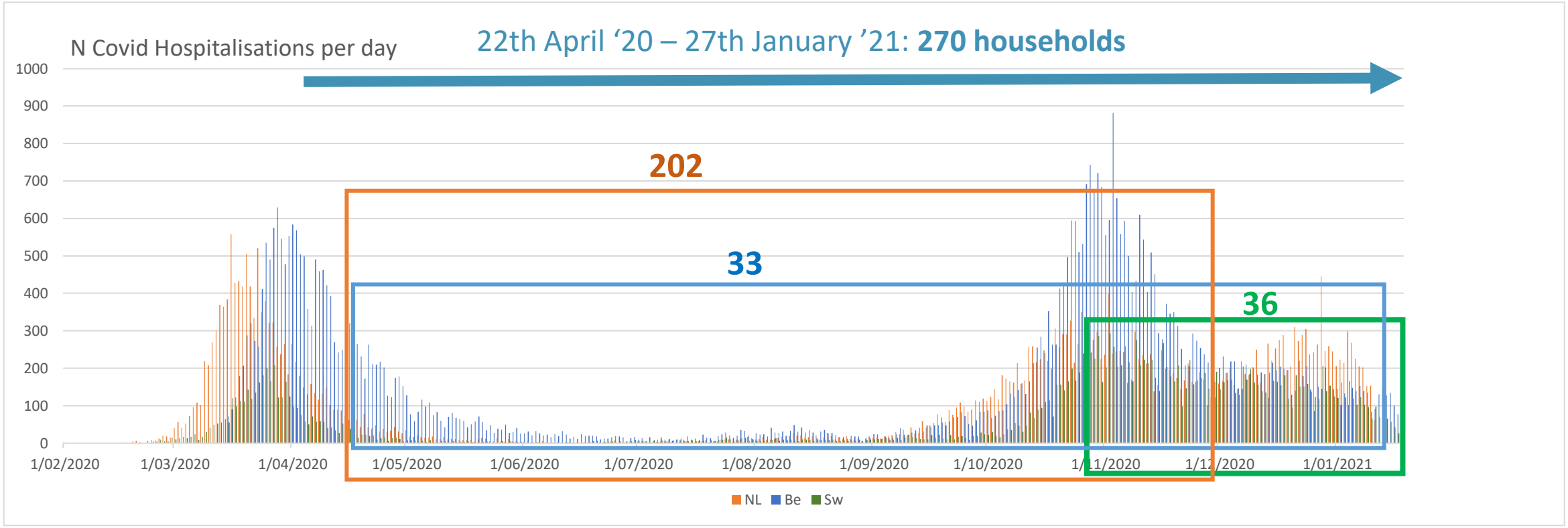
RECOVER household study: Conducting ‘covid-proof’- research



Study design; Index case ascertainment



Results and outcome



Sample completeness

	Enrollment		Upon symptoms	End of study
	DBS	**NTS***	**NTS**	**DBS**
Total samples requested	920	884	165	920
Missing result due to incomplete sampling n(%)	35 (3.8%)	48 (4.8%)	21 (12.7%)	58 (6.3%)
Missing result due to insufficient sampling n(%)	167 (18.2%)	-	-	85 (9.2%)

* No PCR samples collected for index cases in Switzerland.
^ No stool samples collected in Switzerland.

Results and outcome

- High household secondary attack rate: 45.7% (39.7-51.7)
- Most secondary cases positive at enrollment
- No effects of infection control interventions in the household

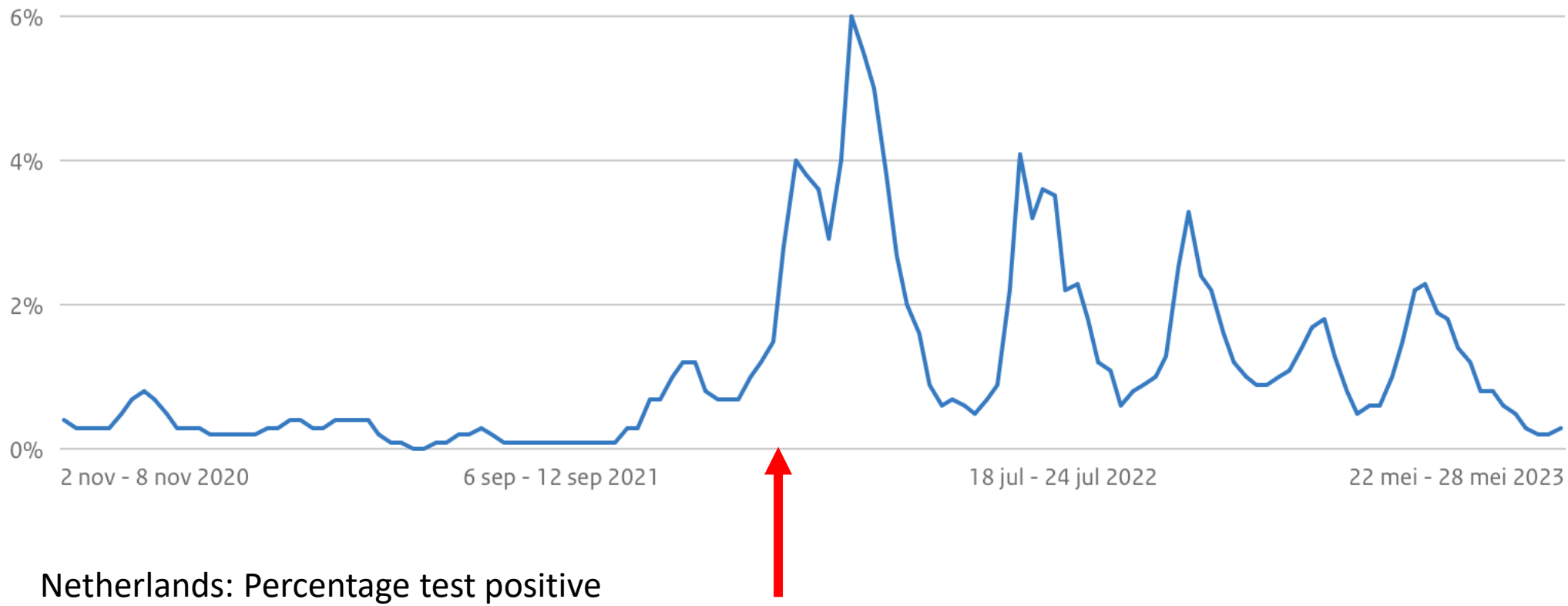
>> role for rapid testing

Verberk et al. Transmission of SARS-CoV-2 within households: a remote prospective cohort study in European countries. European Journal of Epidemiology 2022

Determinants of secondary attack rate

Characteritics	Per person SAR (95% CI)	P-value univariable OR	Multivariable OR (95% CI)	P-value multivariable OR
Age index case, years		0.016		0.04
>18	48.5 (41.9–55.1)		Ref	
12-18	34.6 (17.9–55.6)		0.71(0.38–1.14)	
<12	25.0 (9.6–49.4)		0.52(0.20–0.97)	
Symptom status index case		0.006		0.03
Acute respiratroy illness	37.3 (31.9-43.0)		Ref.	
Mild symptoms	21.3 (13.8-31.5)		0.35 (0.16-0.77)	
Asymptomatic	8.0 (1.2-38.9)		0.42 (0.05-3.29)	

Omicron arrives…

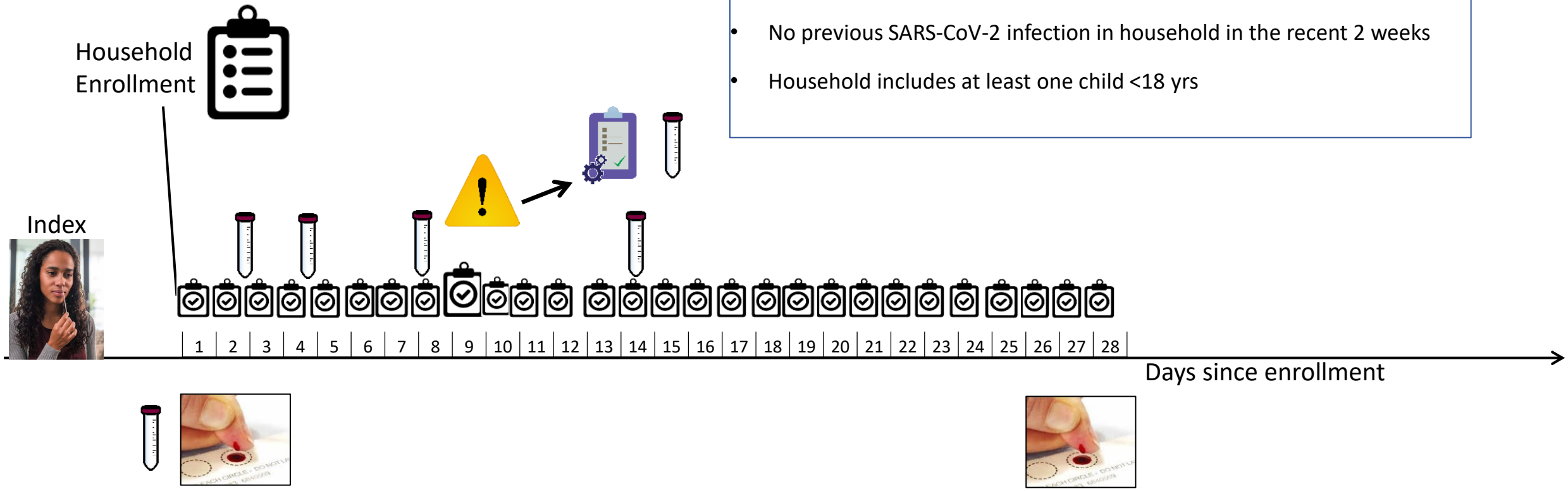


Netherlands: Percentage test positive

RECOVER-VERDI

Household eligibility:

- SARS-CoV-2 positive index case < 48 hrs (PCR or antigen)
- At least one household member **without** a positive test at enrollment
- No previous SARS-CoV-2 infection in household in the recent 2 weeks
- Household includes at least one child <18 yrs



Methods

79 household enrolled with SARS-CoV2 positive index case

Period: January 2022-March 2022 (Omicron BA1/BA2)

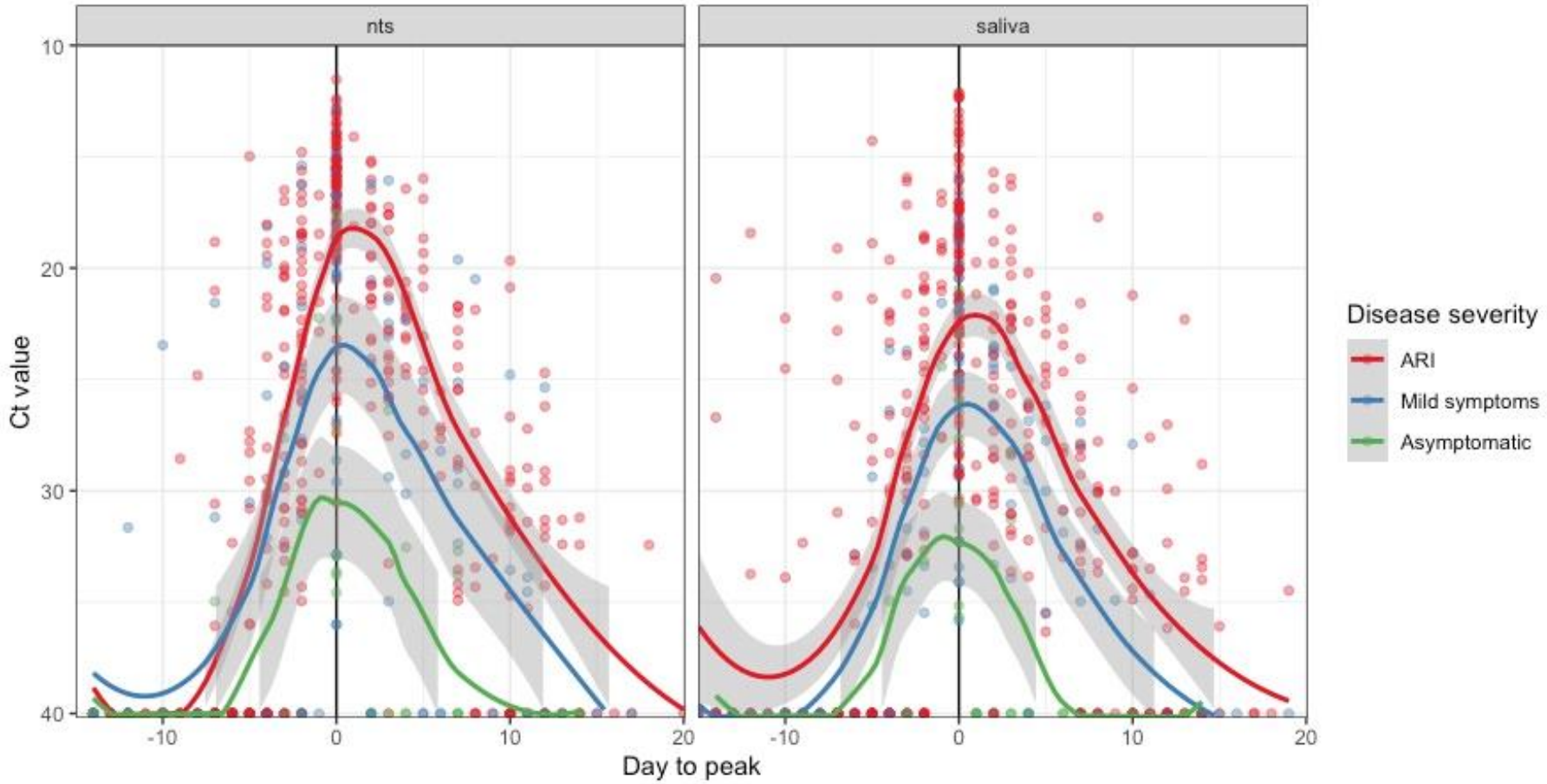
Biological samples	Day 0	Day 2	Day 4	Day 7	Day 14	New onset respiratory illness	End follow-up ± Day 35
Nose-throat swab	x	x	x	x	x	x	
Saliva	x	x	x	x	x	x	
Dry blood spot	x						x

Secondary attack rates in household members

	All N=195 (%)	Infected N= 132 (%)	Uninfected N= 63(%)	SAR 48%	OR (95% CI)	P-value
Female	95 (48.7%)	65 (49.2%)	30 (47.6%)		0.94 (0.52, 1.68)	0.8
Median Age (IQR)	39 (11-45)	36 (10-43)	43 (16-47)		0.98 (0.96, 0.99)	**<0.001**
Immune status at baseline						
Primary vaccinated	55 (28.2%)	35 (26.5%)	20 (31.7%)		Reference	
Not vaccinated	51 (26.2%)	43 (32.6%)	8 (12.7%)		2.84 (1.34, 6.03)	**0.006**
Incomplete vacc	6 (3.1%)	2 (1.5%)	4 (6.3%)		0.71 (0.27, 1.86)	0.5
Primary + Booster	83 (42.6%)	52 (39.4%)	31 (49.2%)		0.96 (0.58, 1.59)	0.9
Prior infection	28 (14.4%)	14 (10.6%)	14 (22.2%)		0.50 (0.26, 0.96)	**0.037**
Age Index						
Child	112 (58.3%)	84 (64.6%)	28 (45.2%)		Reference	
Adolescent	53 (27.6%)	28 (21.5%)	25 (40.3%)		0.33 (0.13, 0.89)	**0.028**
Adult	27 (14.1%)	18 (13.8%)	9 (14.5%)		1.03 (0.31, 3.44)	>0.9
Unknown	3	2	1			

SAR: secondary attack rate

Viral load kinetics by disease severity



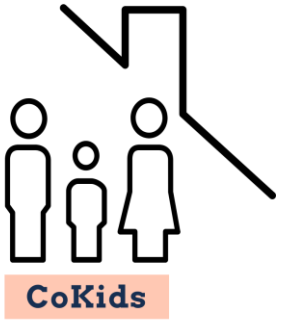
More severe symptom status associated with higher viral load peak

Impact of variant and immune status on SARS-CoV2 symptomatology

April 2020-Jan 2021

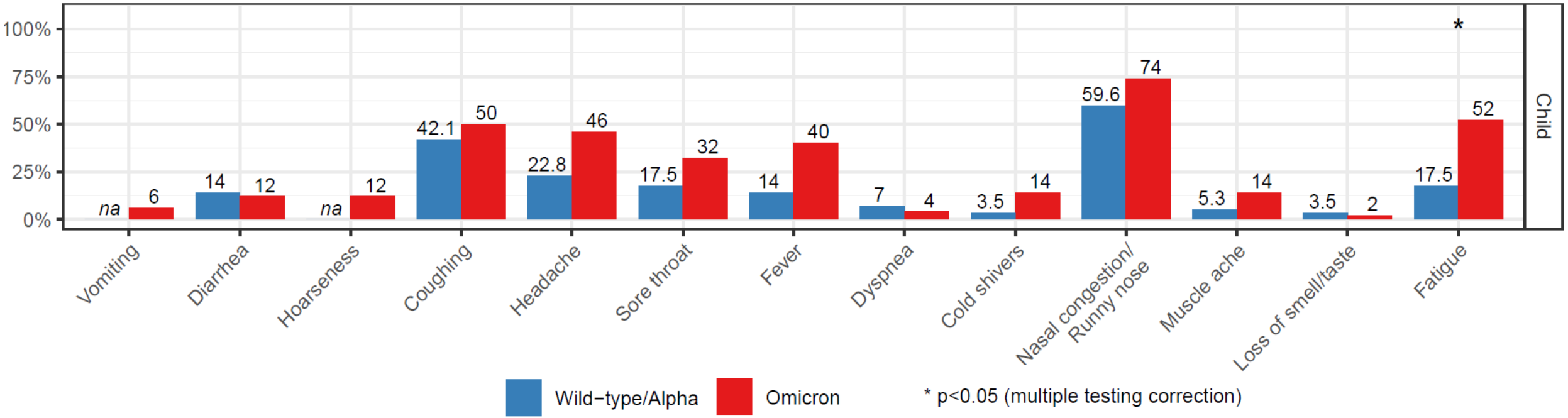
August 2020-Jun 2021

January 2022-March 2022



Westerhof et al. Int J Infect Dis 2023

Omicron vs wild-type/alpha symptoms in children



Higher symptom burden with Omicron variant versus wild-type/Alpha variant in children

Westerhof et al. Int J Infect Dis 2023

Effect of baseline coronavirus antibodies

Objective:

to understand the effect of coronavirus antibody status (SARS-CoV2 and seasonal) on disease and transmission risk following exposure to SARS-CoV2

We focus on 3 related research questions

- **baseline coronavirus antibody profile and the probability of acquiring SARS-CoV2 infection**
- **baseline coronavirus antibody profile and SARS-CoV2 symptom burden**
- **baseline coronavirus antibody profile and SARS-CoV2 viral load kinetics**

Antibody measurement

- **Measured antibodies**
  - SARS
  - MERS
  - SARS-CoV-2
  - NL63
  - 229E

  } Alpha coronaviruses

  - HKU1
  - OC43

  } Beta coronaviruses

  - Influenza A H1N1

- **Dry blood spots**
- **multiplex protein microarray**
- **Final dilution 1:40**
- **Right censored antibody levels ~ 67000**

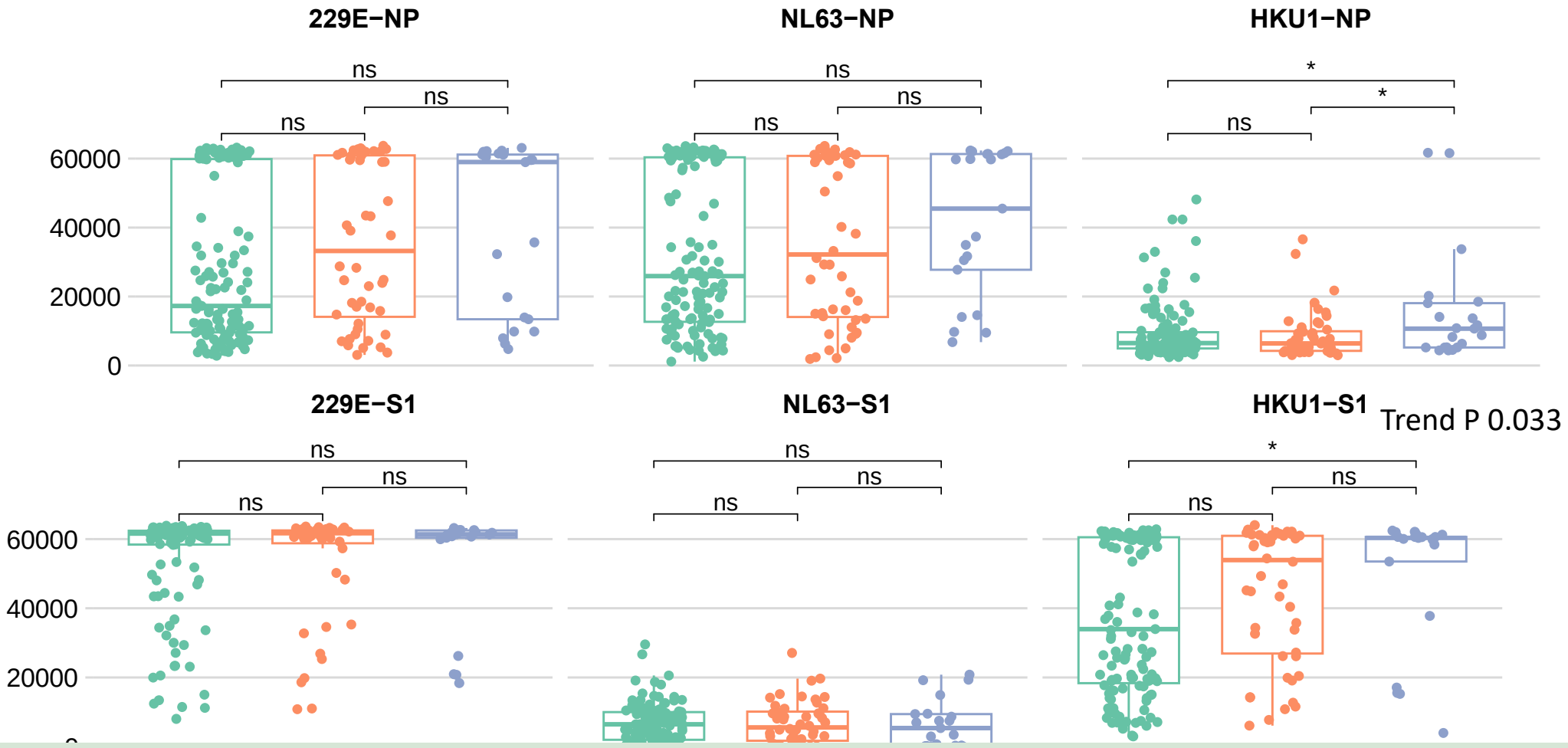
Coronavirus baseline antibody status high or low per target

SARS-CoV-2 high vs low antibody levels for:	aOR (95% CI) for infection [1]	P-value
ecto	0.44 (0.22, 0.84)	**0.014**
S1	0.42 (0.21, 0.81)	**0.011**
NP	0.64 (0.32, 1.23)	0.2
Cumulative 3 targets	0.61 (0.44, 0.84)	**0.003**
Seasonal coronaviruses high vs low antibody levels for:	**aOR (95% CI) [2]**	**P-value**
NL63 three targets	1.09 (0.69, 1.74)	0.7
229E two targets	0.82 (0.52, 1.29)	0.4
HKU1 two targets	0.81 (0.51, 1.30)	0.4
OC43 one target	1.46 (0.38, 2.96)	0.3
Influenza A H1N1 high antibody level	0.93 (0.45, 1.92)	0.8

[1] *Adjusted for age and age index.*
[2] *Adjusted for age, age index and SARS-CoV-2 cum 'high' antibody levels.*

High SARS-CoV2 antibody levels associated with lower risk of infection
No independent effect of seasonal coronavirus antibody levels on infection risk

Seasonal coronavirus baseline antibodies and symptoms status



No significant associations, but general trend towards lower symptom burden when various seasonal coronavirus antibody levels are high

Viral load kinetics by baseline SARS-CoV2 antibody status

SARS-CoV-2 high vs low antibody levels for:	Difference in peak -Ct value	**p-value**	Difference in time to peak –CT-value[1]	**p-value**	Difference in days with Ct value <40	**p-value**	Difference in days with Ct value <30	**p-value**
ecto (vs low)	0.43 (-1.8, 2.6)	0.7	0.11 (-3.2, 3.4)	>0.9	-1.1 (-3.3, 1.0)	0.3	-1.2 (-2.9, 0.54)	0.2
NP (vs low)	1.7 (-0.34, 3.7)	0.1	-1.9 (-5.0, 1.2)	0.2	0.44 (-1.6, 2.5)	0.7	-0.14 (-1.8, 1.5)	0.9
S1 (vs low)	-1.1 (-3.3, 1.2)	0.3	-0.69 (-4.0, 2.6)	0.7	-0.2 (-2.4, 2.0)	0.9	-0.76 (-2.5, 1.0)	0.4
Cumulative 3 targets	0.31 (-0.75, 1.4)	0.6	-0.64 (-2.2, 0.96)	0.4	-0.19 (-1.2, 0.86)	0.7	-0.48 (-1.3, 0.35)	0.3

Adjusted for age and age of index.

No significant differences in viral load kinetics between subjects with high or low SARS-CoV2 antibody status

Results for saliva samples similar (data not shown)

Viral load kinetics by seasonal coronavirus antibody levels

Seasonal coronavirus high vs low antibody levels	Difference in peak -Ct value	**p-value**	Difference in time to peak –CT-value[1]	**p-value**	Difference in days with Ct value <40	**p-value**	Difference in days with Ct value <30	**p-value**
NL63	-.1.1 (-2.5, 0.26)	0.12	0.5 (-1.5, 2.6)	0.6	0.5 (-1.3, 1.5)	0.9	0.21 (-0.88, 1.3)	0.7
229E	0.14 (-1.3, 1.5)	0.8	-0.01 (-2.1, 2.1)	>0.9	-0.67 (-2.1, 0.71)	0.3	-0.61 (-1.7, 0.48)	0.3
HKU1	0.75 (-0.69, 2.2)	0.3	-2.3 (-4.5, 0.18)	**0.036**	-0.03 (-1.5, 1.4)	>0.9	-0.11 (-1.3, 1.1)	0.9
OC43	-1.3 (-3.4, 0.84)	0.2	1.1 (-2.2, 4.3)	0.5	-0.56 (-2.7, 1.5)	0.6	-0.49 (-2.2, 1.2)	0.6
Influenza A H1N1	-0.68 (-2.8, 1.4)	0.5	-0.54 (-3.7, 2.6)	0.7	-1.4 (-3.5, 0.70)	0.2	-0.94 (-2.6, 0.7)	0.3

Adjusted for age and age of index, and cummiulative number of SARS-CoV-2 'high' antibody levels..

No differences in viral load kinetics between subjects with high or low seasonal coronavirus antibody status

Summary

Upon emergence of the heterotypic Omicron variant;

- High SARS-CoV-2 antibody levels at baseline, but not seasonal coronavirus antibody levels decreased the risk of Omicron BA1/BA2 infection in exposed household members.

When infected with Omicron BA1/BA2;

- SARS-CoV2 antibody levels do not influence symptom status
- SARS-CoV2 antibody levels do not influence viral load kinetics
- High titers of antibodies against seasonal coronaviruses show an inverse trend with symptom severity.
- Seasonal coronavirus antibody levels do not influence viral load kinetics

Conclusions

- Recover household studies have generated detailed insights into transmission characteristics, SARS-CoV2 disease burden and immunity, and their evolution over time.
- In particular the study of households with children at different phases of the pandemic generated a unique cohort.
- Recover household studies also served as basis for social sciences studies and modelling work.
- The development of a fully remote household study infrastructure was unique at the time, with many potential future applications

Lessons learned and recommendations

- Shortage of sampling materials > local production
- Strong collaboration with testing facilities for rapid enrollment
- IT infrastructure not ready for digital IC > regulatory and ethical approval of IC modules
- Fully remote cohort studies doable, but efforts required to keep subjects engaged;
  - personal phone calls,
  - frequent messaging and notifications,
  - real-time study dashboard,
  - remote monitoring of study procedures



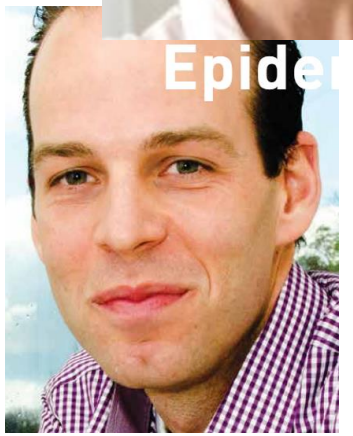








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