

SARS-Cov-2 re-infection cases



Criteria, caveats assessing re-infection

Diagnostic setting

- molecular (PCR) testing mostly
- re-infection > virus absent in between [two] consecutive infections
 - prolonged viral persistence, up to 100 (?) days (detection ?)
 - 'false' positive PCR diagnostics in first episode
 - additional diagnostic samples available ? (serology ?)
- viral load (shedding) primary infection versus re-infection ?
- Infectious virus detected after re-infection (transmission)
- Sequencing: divergent strains in primary and re-infection (always ?)
- Immunological/serological characteristics
 - 1. learning from primary and secondary characteristics
 - 2. logical framework of useful data (statistics)
 - 3. valid diagnostic criteria (algorithm)

Population setting: serological markers & boosting

SARS-Cov-2 re-infection cases (selected n=19)

Volg #	unilab#	Rob: 2nd episode(en PCR+); 0=nee; 1= ja, 2=ja, afwijkende ab	Wantai	VNT50	IgG (GMC) S1	IgG (GMC) RBD	Ai% S1	Ai% RBD	sex	age	days between onset 1 and onset 2	days between onset 2 and serum collectio n
4	4752000007	0	23,52	80	52,76	53,87	55	58	M	10	82	12
6	4752000009	0	23,53	320	92,93	80,90	50	67	M	55	88	3
1	4722001582	1	21,59	160	45,15	51,68	58	68	M	65	94	2
3	4752000006	1	25,24	15	9,67	8,36	51	63	M	18	64	7
5	4752000008	1	22,74	30	26,15	19,01	39	48	M	47	85	6
8	4752000011	1	21,38	<10	5,30	5,12	51	59	M	52	115	7
10	4752000014	1	27,04	40	38,43	34,38	65	72	F	22	74	29
11	4752000015	1	22,01	80	42,18	61,40	36	48	M	59	79	6
12	4752000016	1	23,44	60	79,46	271,42	47	21	F	57	74	3
13	4752000018	1	23,95	560	315,52	751,05	57	39	F	64	84	13
14	4752000019	1	19,6	40	14,53	20,06	69	57	F	31	118	12
15	4752000020	1	21,19	40	13,07	16,42	70	73	M	85	122	14
16	4752000021	1	23,74	560	198,19	194,86	63	79	F	78	73	6
17	4752000022	1	23,38	20	17,26	18,05	43	80	F	22	62	5
18	4752000023	1	16,86	20	12,17	11,55	41	59	F	50	57	12
19	4752000024	1	11,11	<10	3,74	6,59	36	32	F	31	119	6
20	4752000025	1	24	<10	5,63	5,48	62	64	F	21	125	1
28	4752000033	1	26,42	40	50,45	40,35	65	69	M	62	133	19
29	4752000034	1	20,41	15	5,09	8,60	60	45	M	31	133	7
2	4752000005	2	23,64	560	480,55	1952,06	29	26	F	54	63	4
7	4752000010	0, 1/2 ? no ab	0,66	<10	1,14	2,00			F	46	105	3
9a	4752000013	0, no ab	0,02						M	64	79	3
9	4752000012	0, still episode 1	18,46	60	5,97	8,56	46	45	M	51	100	-47

SARS-Cov-2 MIA (MBA)

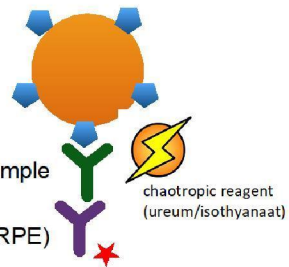


microsphere bead 1

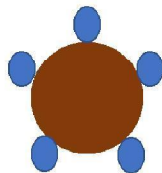
S1 [HPLC, gen-2]
Sino Biological

IgG (IgM, IgG) in sample

detection (anti-IgG RPE)



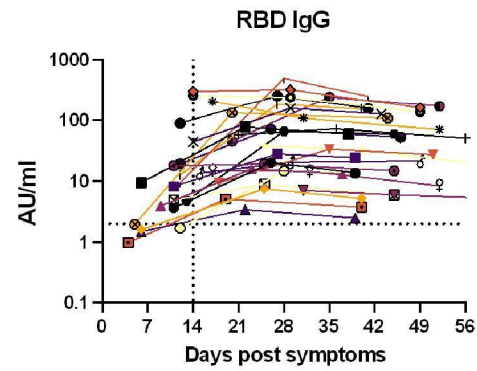
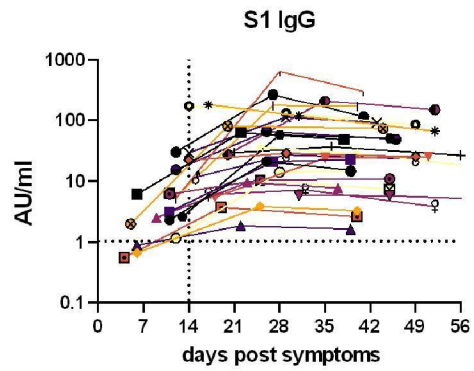
bead 2
N (Sino)



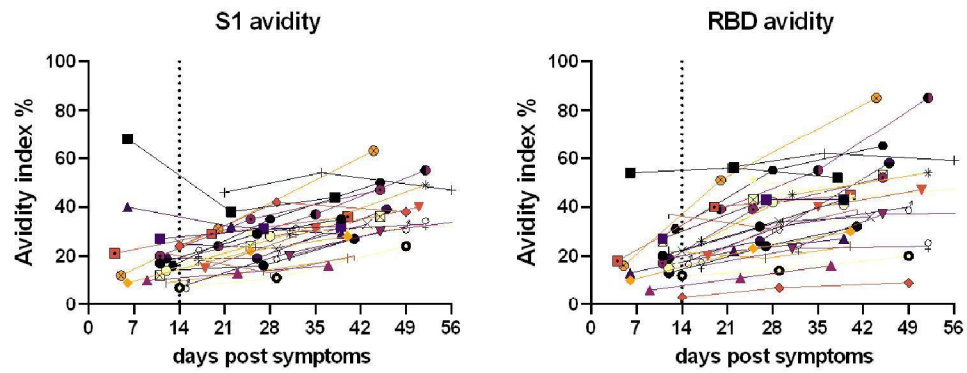
bead 3
RBD (Sino)

Bead 4, 5, 6, ...
OC43, etc.

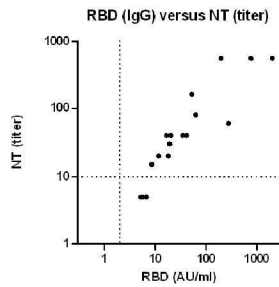
IgG/MIA quantitative response after primary infection



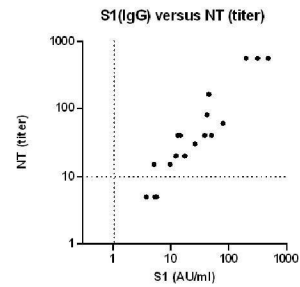
IgG/MIA avidity index (% binding) after primary infection



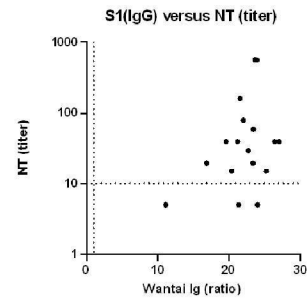
Correlation IgG/MIA with VNT - re-infection cases only



Pearson r	
r	0.7458
95% confidence interval	0.4280 to 0.8995
R squared	0.5563

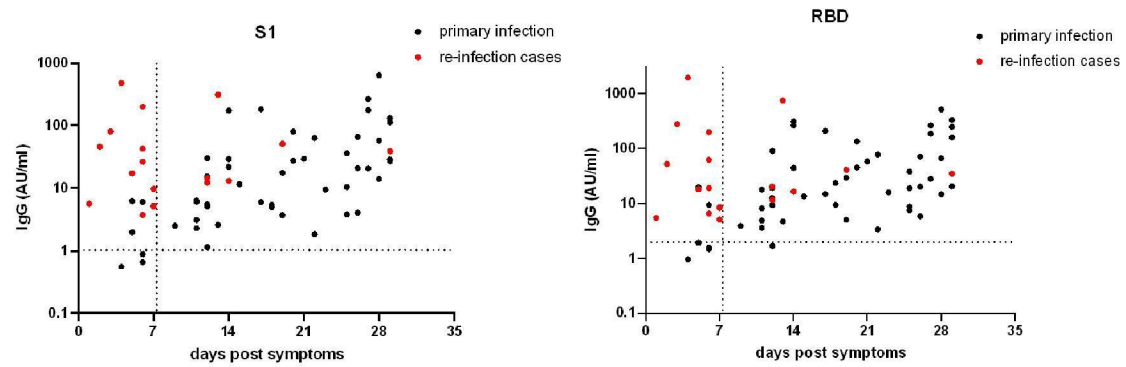


Pearson r	
r	0.9154
95% confidence interval	0.7833 to 0.9684
R squared	0.8379



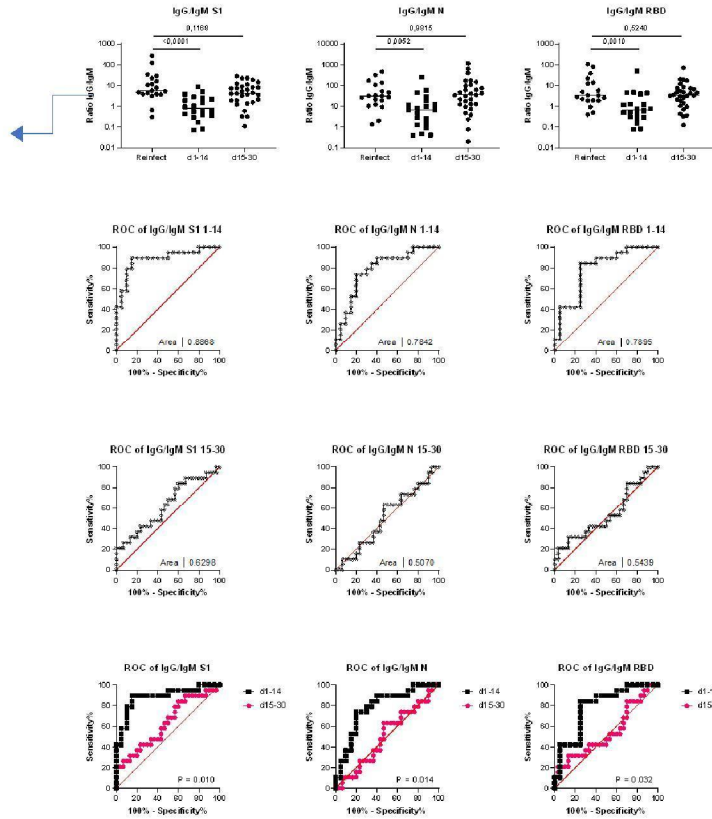
Pearson r	
r	0.2342
95% confidence interval	-0.2813 to 0.6320
R squared	0.05484

Immunological characteristics > IgG quantitative response
primary cases / re-infection cases
time/disease relationship

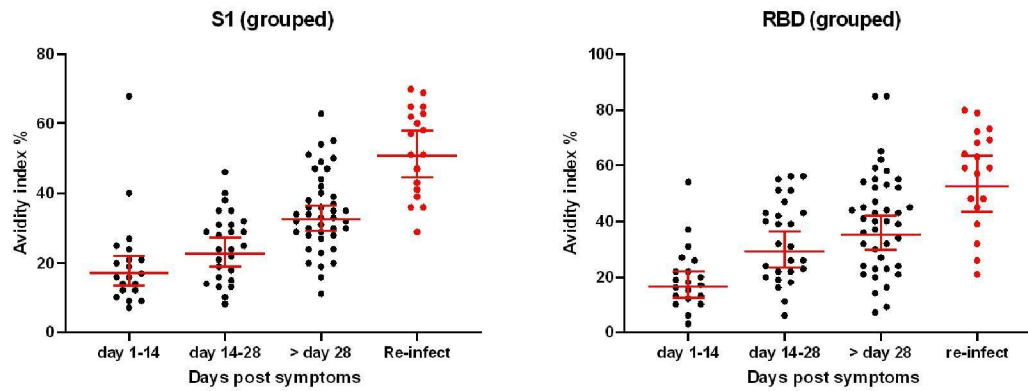


IgG/IgM relationship

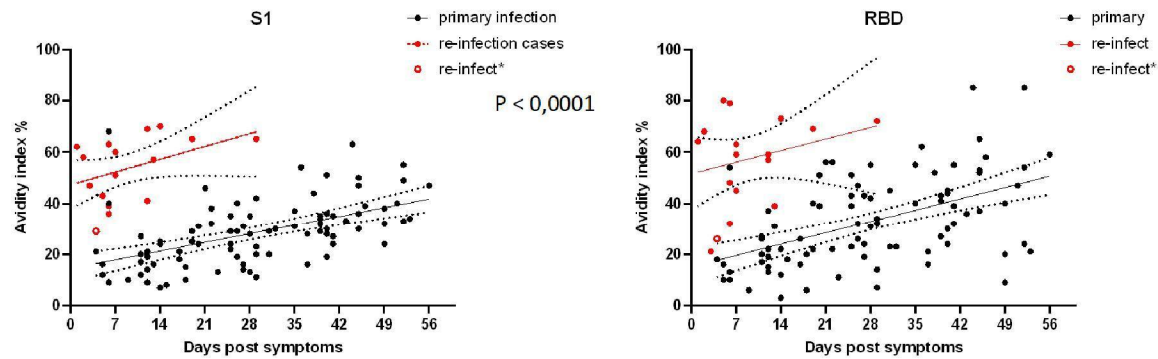
	sens	spec
> 3.683	78.95	85.00
> 3.767	78.95	90.00
> 3.856	73.68	90.00
> 4.107	68.42	90.00
> 4.547	63.16	90.00
> 4.921	57.89	90.00
> 5.190	57.89	95.00
> 5.458	52.63	95.00
> 6.727	47.37	95.00
> 8.241	42.11	95.00
> 9.586	42.11	100.00



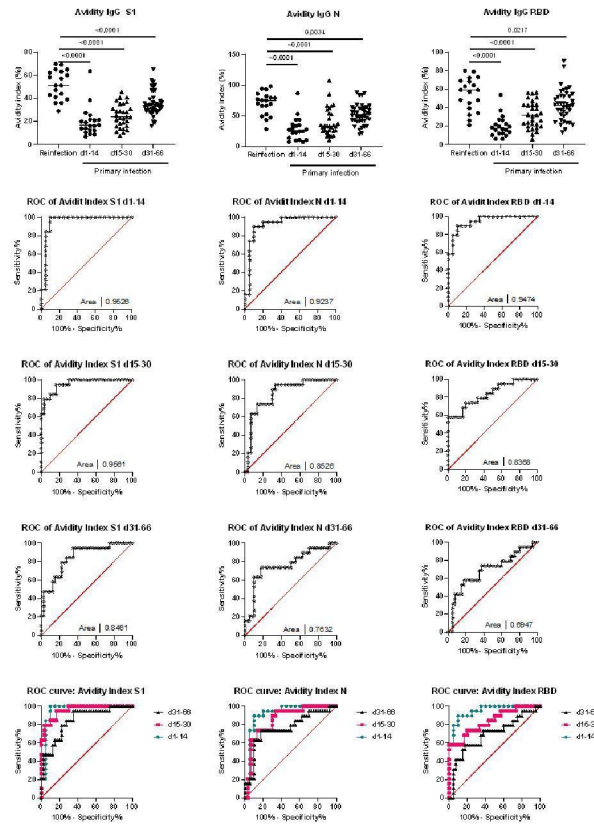
IgG avidity (grouped primary cases, re-infection cases)



IgG avidity index – primary infection versus re-infection
Time/Disease relationship

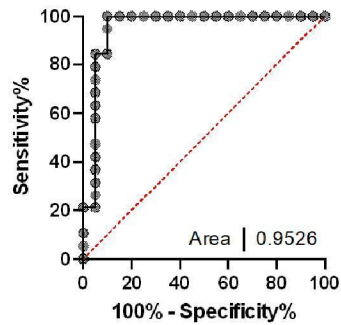


ROC
 Optimal avidity 'cut-off'
 to define re-infection



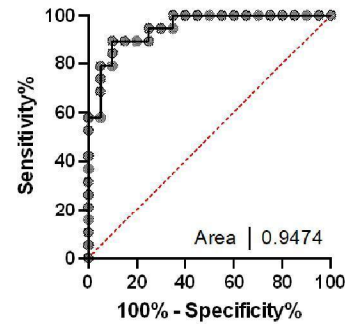
Optimal avidity 'cut-off' to define re-infection

ROC of Avidity Index S1 d1-14



	Sensitivity%	95% CI	Specificity%	95% CI
> 26.38	100,0	83,18% to 100,0%	85,00	63,96% to 94,76%
> 28.17	100,0	83,18% to 100,0%	90,00	69,90% to 98,22%
> 32.50	94,74	75,36% to 99,73%	90,00	69,90% to 98,22%
> 37.17	84,21	62,43% to 94,48%	90,00	69,90% to 98,22%
> 38.67	84,21	62,43% to 94,48%	95,00	76,39% to 99,74%

ROC of Avidity Index RBD d1-14



	Sensitivity%	95% CI	Specificity%	95% CI
> 28.75	89,47	68,61% to 98,13%	85,00	63,96% to 94,76%
> 31.30	89,47	68,61% to 98,13%	90,00	69,90% to 98,22%
> 33.00	84,21	62,43% to 94,48%	90,00	69,90% to 98,22%
> 35.51	78,95	56,67% to 91,49%	90,00	69,90% to 98,22%
> 38.01	78,95	56,67% to 91,49%	95,00	76,39% to 99,74%
> 42.00	73,68	51,21% to 88,19%	95,00	76,39% to 99,74%
> 46.50	68,42	46,01% to 84,64%	95,00	76,39% to 99,74%
> 50.90	57,89	36,28% to 76,86%	95,00	76,39% to 99,74%
> 55.40	57,89	36,28% to 76,86%	100,0	83,89% to 100,0%

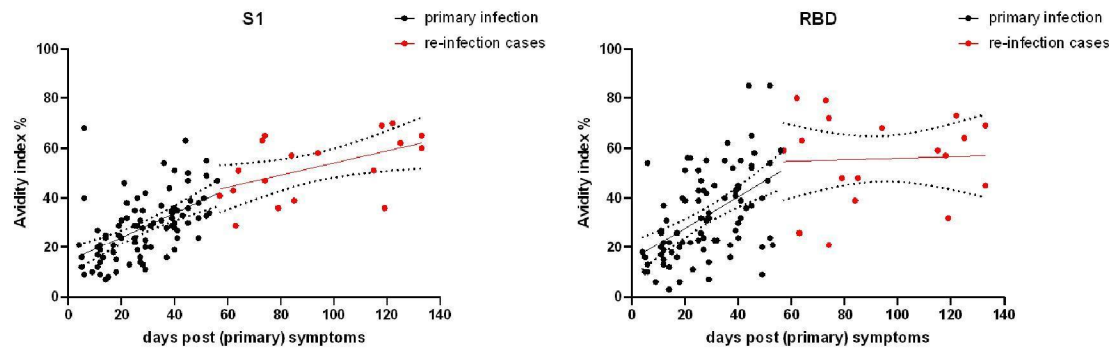
Discussion points

- IgG avidity supports discrimination between recent and past Cov-2 infection
- Correlation between IgG (MIA) and NT
(additional primary FFX/NT data required to support correlation)
- One exceptional case at day 4 with very high IgG (IgM) and low avidity

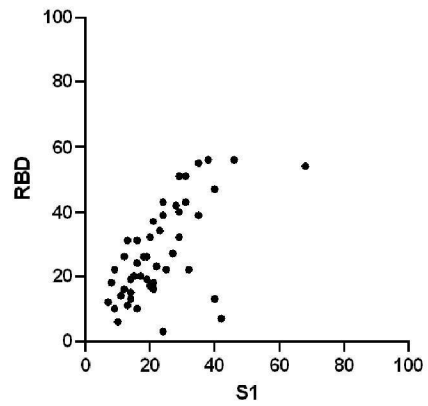
- Framework pub
 - (clinical) case description
 - discard cases with insufficient confirmatory data
 - diagnostic confirmation of cases (PCR, Wantai Ig serology)
 - molecular criteria for re-infection (variants, timing, etc.)
 - Imm. Characteristics (time/disease criteria)
 - VNT, IgG (MIA) titers , avidity (IgG/IgM ratio)
 - Statistical criteria
 - Diagnostic Algorithm, ..

appendix

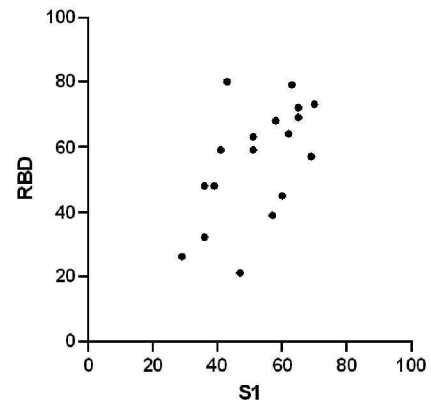
IgG avidity index primary and re-infect cases
time/disease relationship according to "first episode"



AI primary day 1-30 (S1 versus RBD)



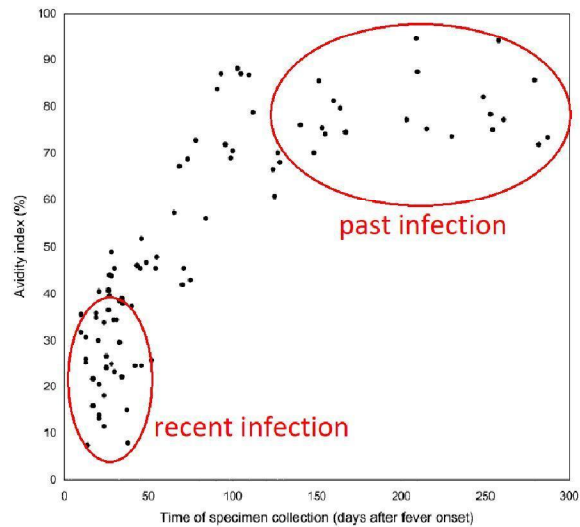
AI re-infect (S1 versus RBD)



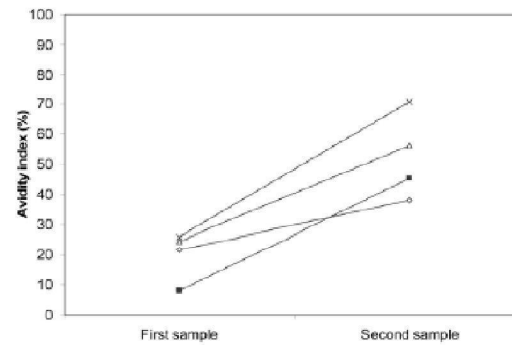
Antibody Avidity Maturation during Severe Acute Respiratory Syndrome–Associated Coronavirus Infection

The Journal of Infectious Diseases 2005;192:166–9

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A. Paired samples collected ≤ 50 days apart



C. Paired samples collected 101-150 days apart

