

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)

SARS-Cov-2 re-infection cases (selected n=19)												days between onset 2 and serum collectio n
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	-4

SARS-Cov-2 MIA (MBA)

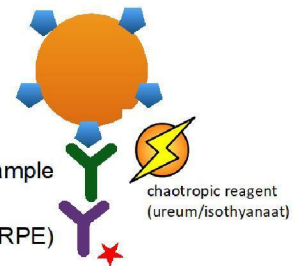


microsphere bead 1

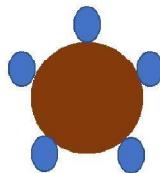
S1 [HPLC, gen-2]
Sino Biological

IgG(IgM, IgG) in sample

detection (anti-IgG RPE)



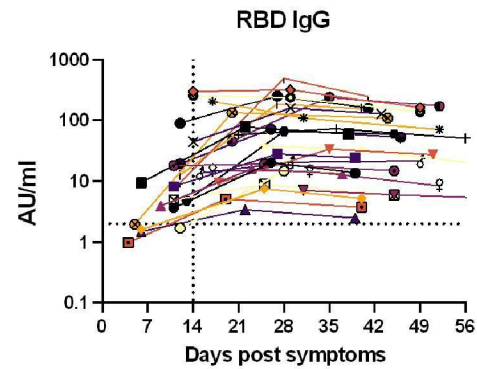
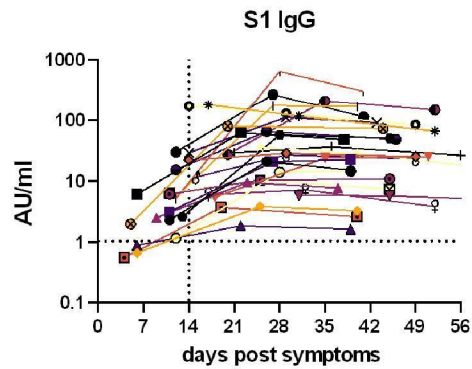
bead 2
N (Sino)



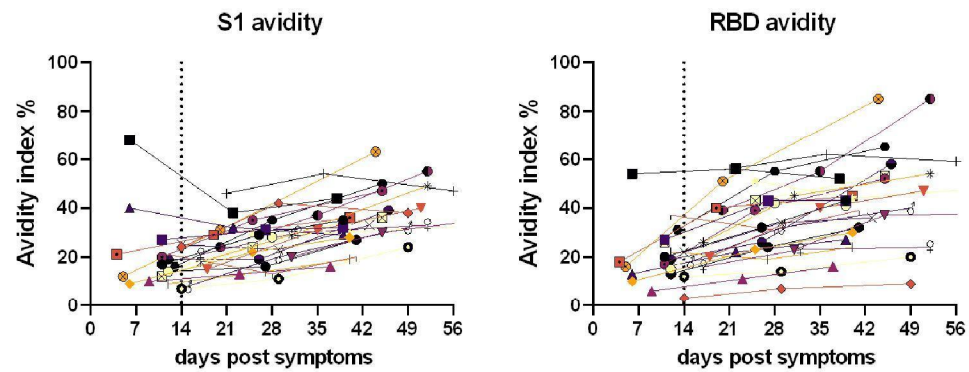
bead 3
RBD (Sino)

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

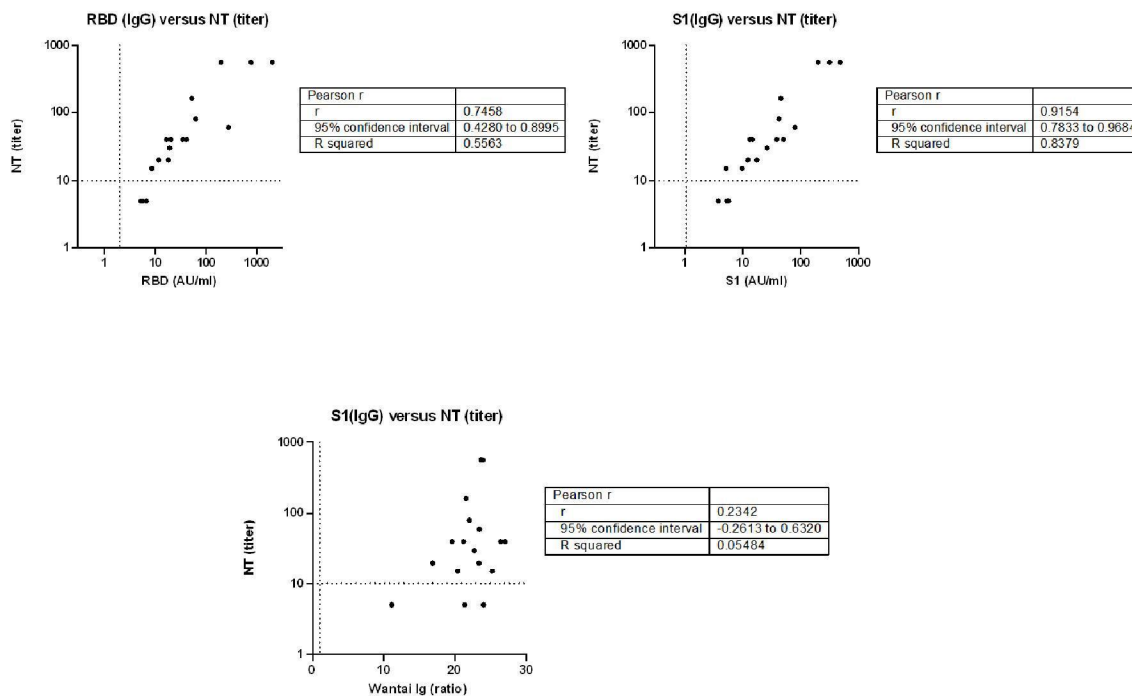
IgG/MIA quantitative response after primary infection



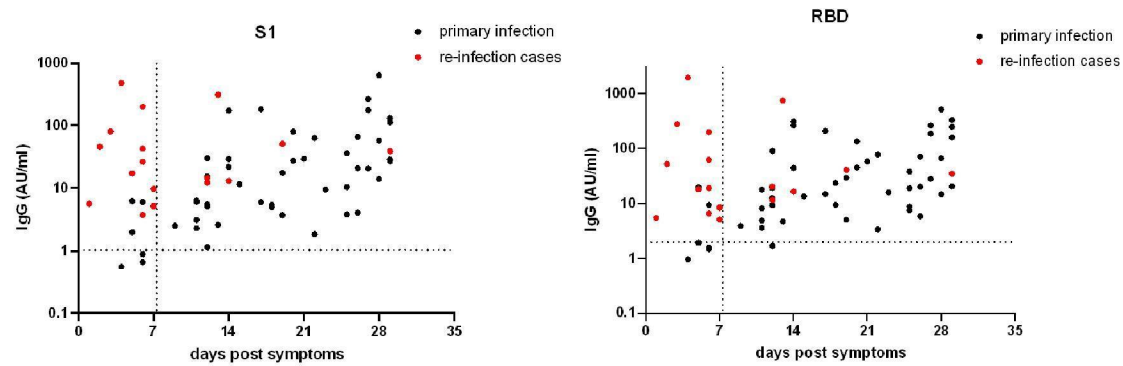
IgG/MIA avidity index (% binding) after primary infection



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



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

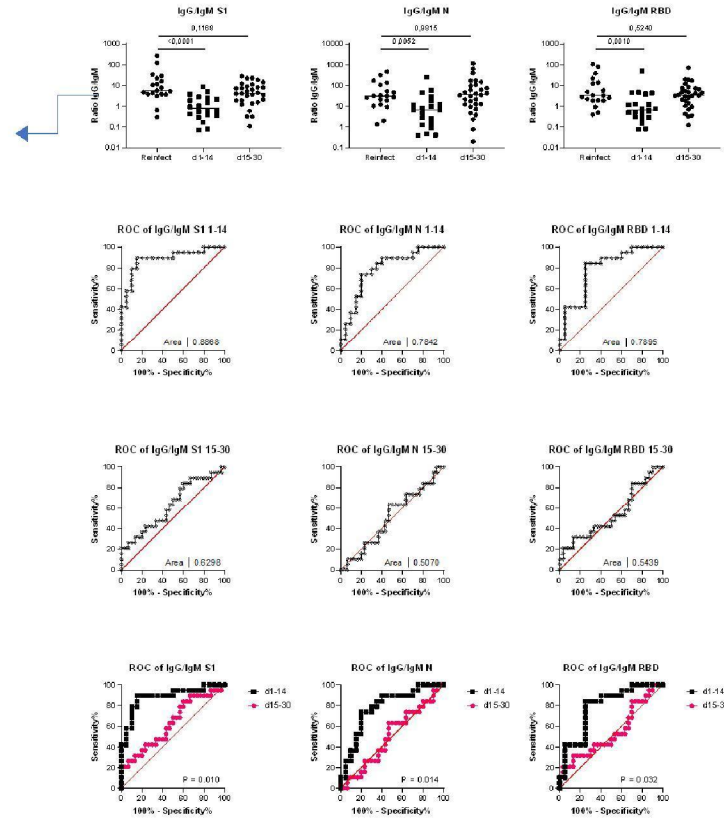


IgG/IgM relationship

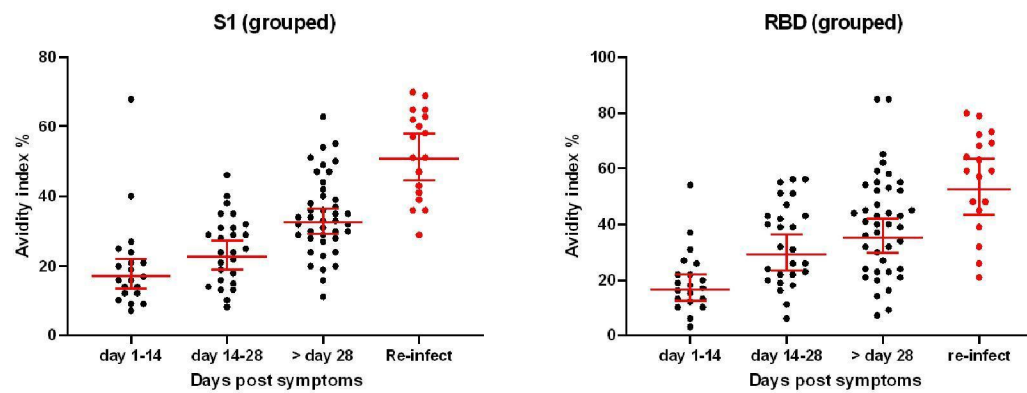
> 3.683
> 3.757
> 3.856
> 4.107
> 4.547
> 4.921
> 5.190
> 5.458
> 6.727
> 8.241
> 9.586

sens spec

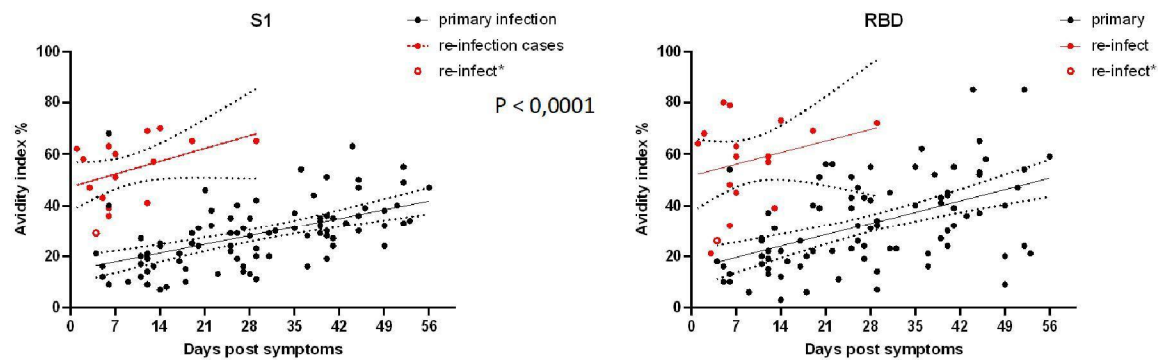
78.95	85.00
78.95	90.00
73.68	90.00
68.42	90.00
63.16	90.00
57.89	90.00
57.89	95.00
52.63	95.00
47.37	95.00
42.11	95.00
42.11	100.0



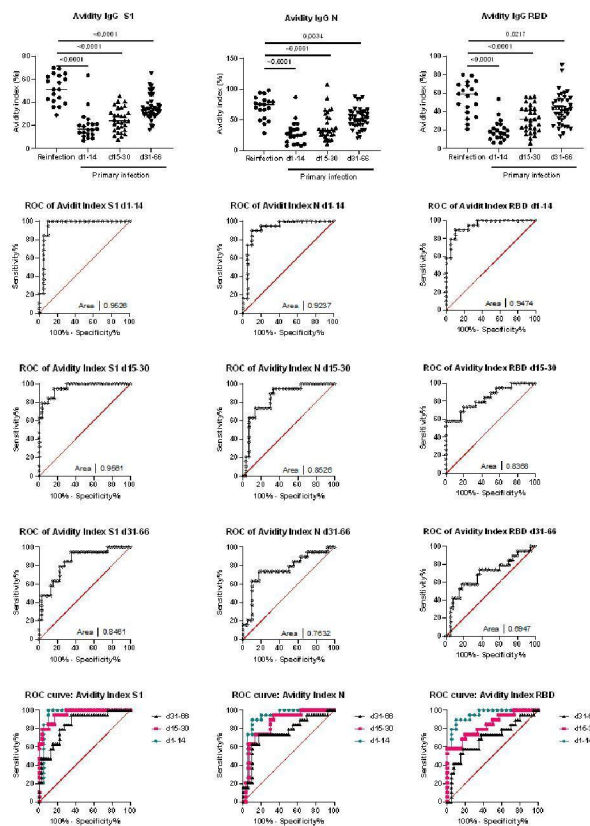
IgG avidity (grouped primary cases, re-infection cases)



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

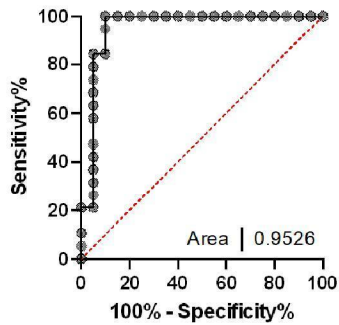


ROC
Optimal avidity 'cut-off'
to define re-infection



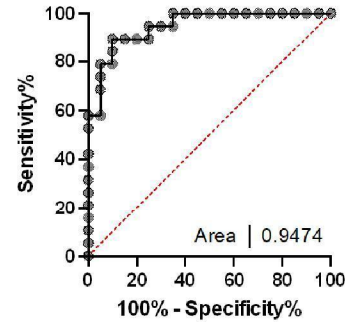
Optimal avidity 'cut-off' to define re-infection

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



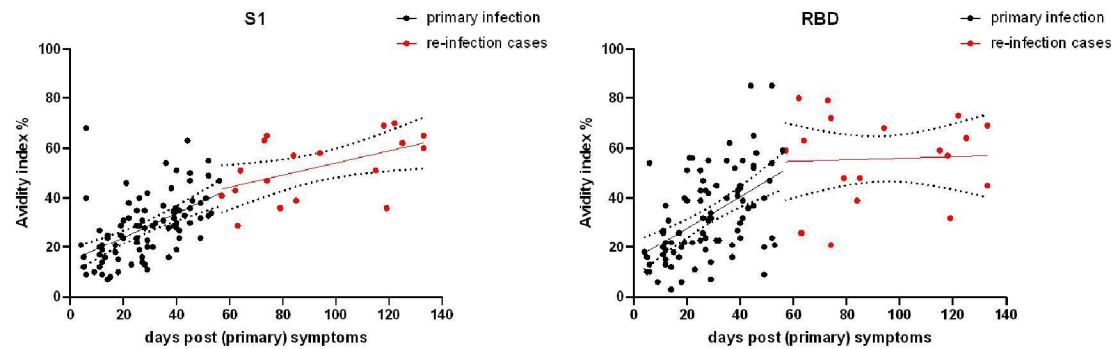
	Sensitivity%	95% CI	Specificity%	95% CI
> 28.75	89,47	68,61% to 98,13%	85,00	63,96% to 94,76%
> 31.30	89,47	68,61% to 98,13%	90,00	69,90% to 98,22%
> 33.00	84,21	62,43% to 94,48%	90,00	69,90% to 98,22%
> 35.51	78,95	56,67% to 91,49%	90,00	69,90% to 98,22%
> 38.01	78,95	56,67% to 91,49%	95,00	76,39% to 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

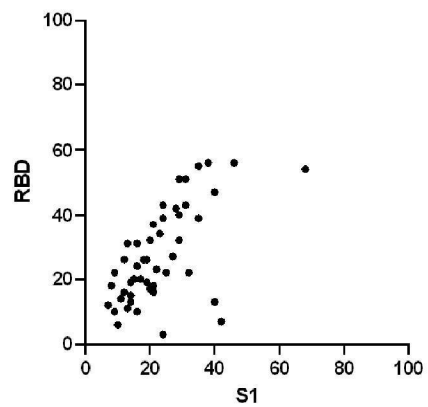
- IgG avidity supports discrimination between recent and past Cov-2 infection
- Correlation between IgG (MIA) and NT
(additional primary FFX/NT data required to support correlation)
- One exceptional case at day 4 with very high IgG (IgM) and low avidity
- Framework pub
 - (clinical) case description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

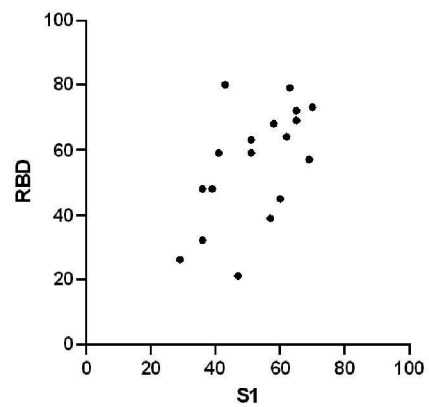
IgG avidity index primary and re-infect cases
time/disease relationship according to "first episode"



AI primary day 1-30 (S1 versus RBD)



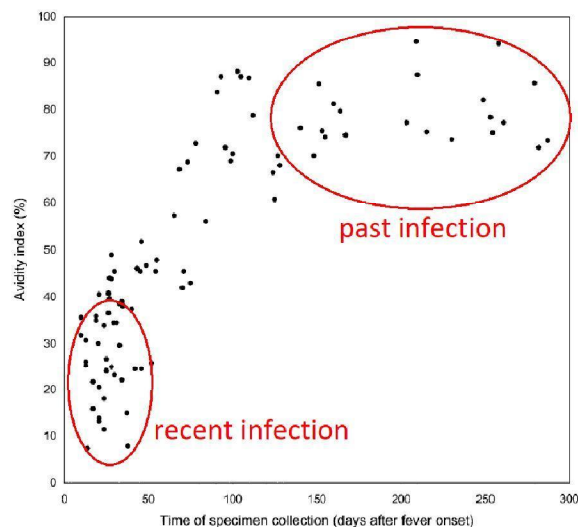
AI re-infect (S1 versus RBD)



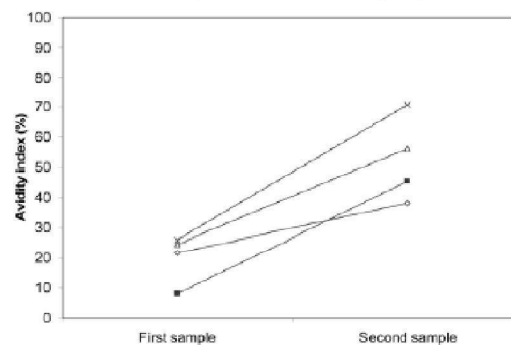
Antibody Avidity Maturation during Severe Acute Respiratory Syndrome–Associated Coronavirus Infection

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

