

PRESS WORKSHOP

Sensitivity of Antigen Tests to the Omicron Variant

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Exemplary Analysis by the
Paul-Ehrlich-Institut (PEI), Robert Koch-Institut (RKI),
Bundeswehr Institute of Microbiology (InstMikroBioBw)

Manufacturer Inquiry by the BfArM

Cichutek, Nübling, Scheiblauer
Paul-Ehrlich-Institut
Presse-Workshop
Langen, 24.03.2022



Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich
des Bundesministeriums für Gesundheit.
The Paul-Ehrlich-Institut is an Agency of the
German Federal Ministry of Health.



AGENDA



Sensitivity of Antigen Tests

Exemplary Analysis by the Paul-Ehrlich-Institute,
Robert Koch-Institute, Bundeswehr Institute of Microbiology

- Structure of the exemplary experimental test
Prof Klaus Cichutek
- Results
PD Dr Micha Nübling
- Manufacturer information about test design
PD Dr Micha Nübling
- Discussion
Dr Scheiblauer et al.

Emergence and dominant circulation of the Omicron variant in Germany since early 2022



Omicron variant from Botswana and South Africa (Dec. 2021)

- > 30 mutations in the spike protein with amino acid exchange
 - Immune evasion, increased transmission rate, better reproductive capacity
- 4 amino acid changes in the nucleocapsid protein
 - 2 of which have already been seen in earlier circulating variants

Target antigen of antigen assays

98.8% nucleocapsid protein

1.2% spike protein or spike protein + nucleocapsid protein

Omicron detection put in question by current antigen testing?



Diagnostic tests and Omicron:

- **US FDA** (Dec 2021): possible impaired detection of Omicron
 - no data published on rapid antigen testing
 - no known regulatory consequences (March 2022)
- **Bekliz,..., Eckerle (2022):**
"Sensitivity of some Ag RDT reduced with Omicron"
 - Cell culture: Comparison of different SARS-CoV-2 variants (PFU)
 - Clinical samples (Delta/Omicron): 4/7 tests affected
- **Ostermann, ..., Keppler (2022): "Impaired Detection of Omicron"**
 - Cell culture: no impairment to detection
 - Clinical samples (Delta/Omicron): 10 to 100-fold impaired detection

Analyses for the detection of the Omicron variant by antigen testing - test procedure



- **Investigation** of an exemplary sample of 20 rapid antigen tests, representative of the sensitivity range of positively evaluated tests
 - Swab
 - Pools of Patient Swabs (RKI)
 - Delta versus Omicron variant
 - Cell culture supernatant
 - Beta-propiolactone inactivated (InstMikroBioBw)
 - Wuhan versus Omicron variant
 - **Transfer** of the results to further tests ("bridging" on the basis of similar test designs)



Clinical samples positive for Delta and Omicron are detected comparably well

Clinical samples (swab pools; RKI), visual reading of antigen test results

- 4x delta concentrations corresponding to Ct 24.4 to 32.1
- 4x Omicron concentrations according to Ct 23.2 to 32.6

		Rapid antigen test																		
	Test Nr.	1	2	3	4	5	7	8	9	10	11	12	12	14	15	16	17	18	19	20
Pool #	ct E-Gen	Delta																		
Delta 1	24,39	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	(+)	(+)	+	
Delta 2	25,59	+	+	+	+	+	+	+	+	+	+	(+)	(+)	+	+	(+)	(+)	-	+	
Delta 3	29,19	(+)	(+)	+	+	-	-	+	-	(+)	-	-	-	(+)	(+)	-	-	-	-	
Delta 4	32,07	-	-	-	(+)	-	-	-	-	-	-	-	-	-	(+)	-	-	-	-	
		Omicron																		
Omicr A	23,18	+	+	+	+	+	+	+	+	+	+	(+)	+	+	+	(+)	(+)	+	+	
Omicr B	25,77	+	+	+	+	+	+	+	+	+	+	(+)	+	+	(+)	+	-	(+)	+	
Omicr C	28,68	+	+	+	+	+	+	+	(+)	+	(+)	-	-	-	(+)	-	(+)	-	(+)	
Omicr D	32,63	(+)	(+)	+	+	-	(+)	-	-	(+)	-	-	-	-	(+)	-	-	-	-	



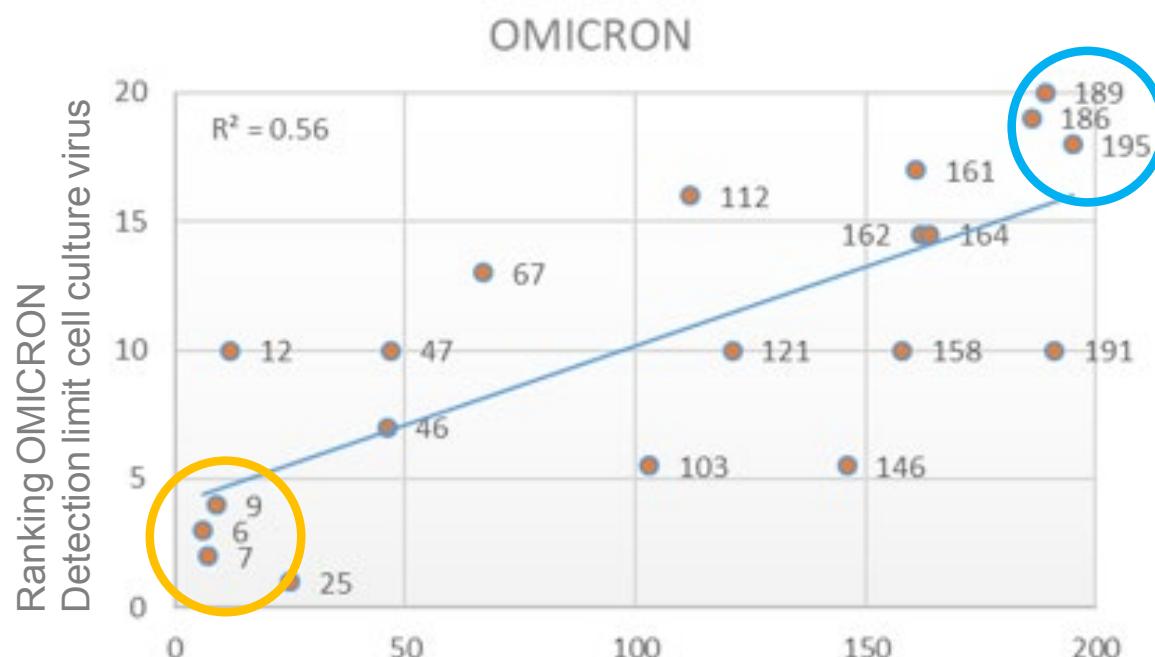
Cell culture samples positive for Wuhan and Omicron are detected comparably well

Cell culture samples (RKI, PEI, InstMikroBioBw), reading band intensity (scanner)

- 6 Wuhan concentrations corresponding to 10^8 to 10^4 virus particles
- 6 Omicron concentrations corresponding to 10^8 to 10^4 virus particles

			Rapid antigen test																			
		Test Nr.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Nr	Verd	Virus-RNA	Wildtyp-Virus (Wuhan)																			
1	8	$3,5E+07$	336	359	385	387	185	308	179	212	287	158	70	157	139	216	130	194	82	160	225	114
2	32	$8,8E+06$	231	278	287	279	88	158	87	68	86	73	44	44	41	33	16	43	18	71	102	18
3	128	$2,2E+06$	40	162	143	189	41	48	13	7	12	13	16	11	6	5	7	4	14	11	9	
4	512	$5,5E+05$	8	17	25	52	5	9	2	0	0	0	4	4	0	2	2	0	0	4	2	
5	2.048	$1,4E+05$	2	3	6	8	0	0	2	0	0	0	0	0	inv	0	0	0	0	0	0	
6	8.192	$3,4E+04$	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
LoD RNA			$2,1E+05$	$1,4E+05$	$8,5E+04$	$7,3E+04$	$3,8E+05$	$2,7E+05$	$7,0E+05$	$1,3E+06$	$9,6E+05$	$9,3E+05$	$4,4E+05$	$4,4E+05$	$1,4E+06$	$1,1E+06$	$1,1E+06$	$1,3E+06$	$1,8E+06$	$4,4E+05$	$7,3E+05$	$7,8E+05$
Nr	Verd	Omicron																				
1	8	$1,9E+07$	333	340	381	352	194	350	249	270	293	296	135	193	159	190	232	154	107	178	133	46
2	32	$4,7E+06$	211	269	333	277	121	152	102	87	77	91	60	67	37	60	60	64	16	100	37	9
3	128	$1,2E+06$	88	158	160	182	32	40	18	8	14	16	12	7	4	5	7	7	4	16	5	4
4	512	$2,9E+05$	14	41	49	24	3	5	4	0	3	0	2	3	0	1	2	2	0	3	0	1
5	2.048	$7,3E+04$	5	3	7	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	8.192	$1,8E+04$	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
LoD RNA			$5,1E+04$	$7,3E+04$	$4,2E+04$	$6,0E+04$	$2,9E+05$	$2,1E+05$	$2,4E+05$	$6,2E+05$	$2,9E+05$	$4,6E+05$	$3,8E+05$	$2,9E+05$	$9,5E+05$	$7,3E+05$	$4,7E+05$	$4,7E+05$	$9,5E+05$	$2,9E+05$	$8,2E+05$	$8,8E+05$

Ranking of individual antigen test sensitivity to Omicron corresponds to the ranking determined against Wuhan



No evidence of decreased sensitivity of antigen tests to Omicron



- Investigations by the Paul-Ehrlich-Institut do not indicate reduced sensitivity of rapid antigen tests to Omicron
 - Sensitivity to Omicron analogous to that of previous SARS-CoV-2 variants (Wuhan, Delta)
 - confirmed by other publications
- **Results of the Paul-Ehrlich-Institut study can be applied to further tests of similar designs**

Further investigations confirm Omicron detection by antigen tests



- Nielsen et al (Statens Serum Institut Copenhagen, DK)
 - 9 different Ag RDTs, different variants (cell culture)
- Goderski et al. (RIVM, NL)
 - 7 different Ag RDTs, Omicron versus Wuhan (cell culture)
- UK Health Security Agency
 - 5 different Ag RDTs, Omicron versus Wuhan (cell culture)
- WHO Prequalification Workshop (02/2021)
 - no known reduced sensitivity in pre-qualified tests
- Deerain J. et al. 2021.
 - 10 Ag RDTs similar for Delta and Omicron
- Molenkamp, R & Igloi, Z.
 - 3 Ag RDTs Omicron vs Delta
- Barbara L Goodall (2022)
 - Omicron comparable to evaluations with other SARS-CoV-2 strains



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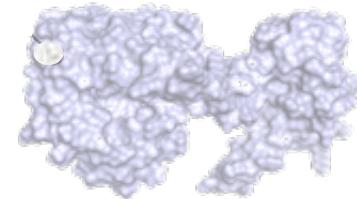
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Mutations in the nucleocapsid protein of SARS-CoV-2 variants

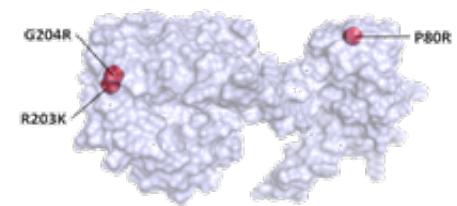
- Design of most antigen tests aims at N-protein recognition -



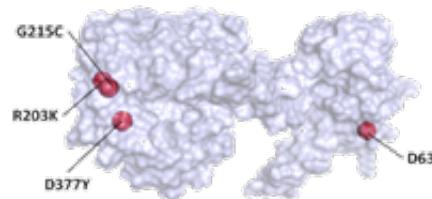
Wuhan – December 2019



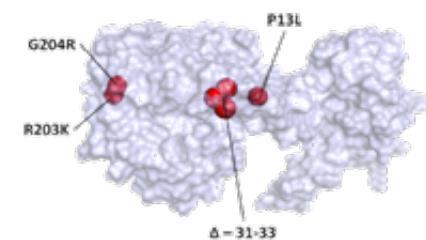
Gamma - December 2020



Mutations in the nucleocapsid protein
Various SARS-CoV-2 variants



Delta - December 2020

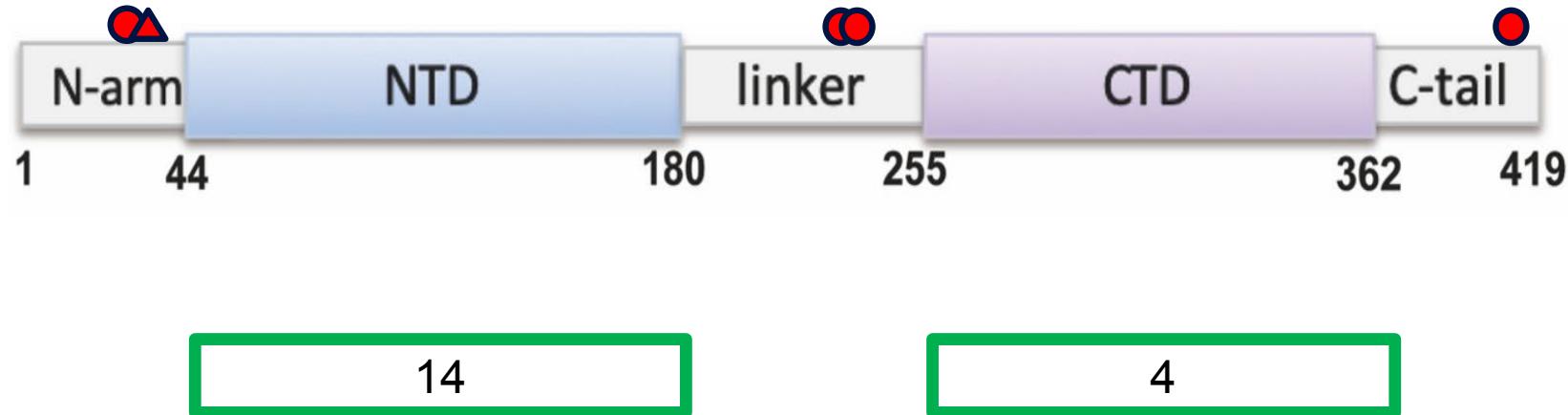


Omicron - November 2021

The tests evaluated on an exemplary basis at the Paul-Ehrlich-Institut
use conserved regions of the nucleocapsid protein



Omicron (BA1, BA2): Mutations in the nucleocapsid protein



Information on the test design allows for an assessment of Omicron detection



Inquiry of the BfArM on the design of all rapid antigen tests

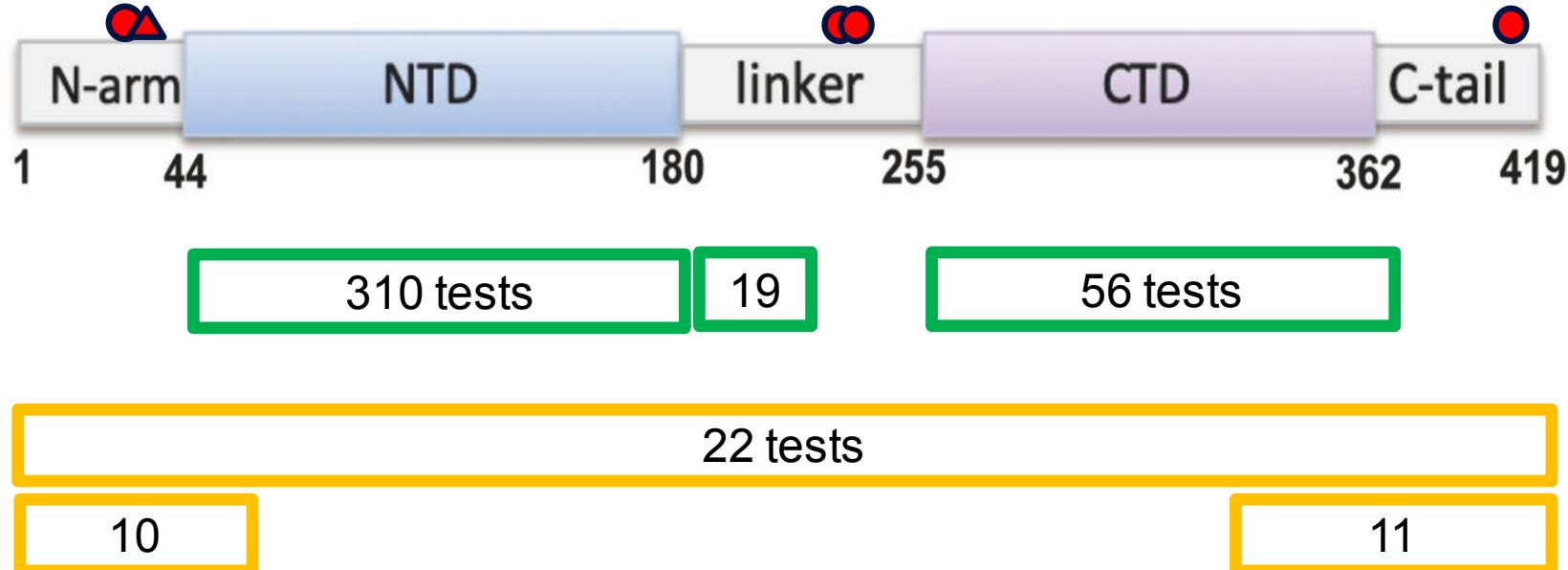
- Antibodies (usually mAb; capture, detection)
 - Binding region of antibodies
- 428 evaluable answers (23/03/2022)
 - **385** tests (90%) with Ak binding region without Omicron mutations
 - **43** tests (10%) may be affected by Omicron mutation
 - Validation of Omicron detection by manufacturers

Information on the test design allows for an assessment of Omicron detection



Transfer to further tests ("bridging" based on similar designs)

Omicron (BA1, BA2): **Mutations** in the nucleocapsid protein



Evaluating antigen tests for Omicron detection

- Conclusions -



- Investigations by the Paul-Ehrlich-Institut do not indicate reduced sensitivity of rapid antigen tests to Omicron
- BfArM inquiry provides information on test design (antibody target regions in N)
 - Antibody binding region outside of mutated regions
 - on BfArM list; reimbursable
 - Antibody binding region (potentially) overlapping with mutations
 - Manufacturer validation of Omicron detection
 - Removal of tests without reliable information
- BfArM list (recoverable antigen tests): information on test design now included
 - Bridging: 'yes' = target region of the antibodies used outside mutated N regions



The information on Omicron detection has been included
on the BfArM list since 23.03.2022.



Antigen-Tests auf SARS-CoV-2 zur professionellen Anwendung

die Gegenstand des Anspruchs nach §1 Satz 1 Coronavirus-Testverordnung (TestV) sind („Schnelltests“)



Test-ID	Handelsname	Evaluierung PEI	Omkron-Erkennung entsprechend der Bridging-Prüfung des PEI	Hersteller		Europa	
				Name ↑=	Stadt	Land	Name
AT025/22	SMARTTEST SARS-COV-2 NASOPHARYNGEAL ANTIGEN RAPID TEST	Nein	Nein	A PLUS DIAGNOSTICS LAB.SAN.TIC.A.S.	Ümraniye/istanbul	TR	
AT005/20	Panbio™ COVID-19 Ag Rapid Test Device (Nasopharyngeal)	Ja	Ja	Abbott Rapid Diagnostics Jena GmbH	Jena	DE	
AT116/21	Panbio™ COVID-19 Ag Rapid Test Device (Nasal)	Ja	Ja	Abbott Rapid Diagnostics Jena GmbH	Jena	DE	

Future regulation of SARS-CoV-2 diagnostics- Outlook -



- New **IVD regulation** with stricter regulations enters into force on 26.05.2022
- **Certification of new SARS-CoV-2 diagnostics only after**
 - appraisal by Notified Body
 - Laboratory testing by an EU reference laboratory
- **Transitional provisions** permits previously (self) certified SARS-CoV-2 diagnostics until May 2025

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Im Mittelpunkt steht die Gesundheit

Our Focus is on Health

