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Letter to the Editor

"Rapid reinfections with different or same Omicron SARS-CoV-2 sub-variants"

Dear Editor,

we read with great interest the letter by Nguyen et al. [1], that the number of reinfections in the omicron wave increased to 6,8%, but did not occur in BA1 to BA2. They further describe the installation of an automatic system, which, in accordance with the CDC recommendations for the probability of reinfections, detects reinfections after a period of at least 90 days.

We report 242 cases of rapid reinfection of <60 days with different or same Omicron sub-variants and have evidence for a second symptomatic course.

At the beginning of 2022 the Omicron wave started in Austria and an increasing number of people who had recently recovered from BA.1 infection reported to the Vienna health authorities that they fell ill again. We have surveyed these individuals in detail, found that they all have had low CT values again and complained about significantly more pronounced symptoms during the course of the second infection.

The recurrence of symptoms associated with low CT values made it necessary to assess whether these individuals should be quarantined again despite recent recovery. In this context, we would like to know whether these were prolonged courses or reinfections with the same or a different variant.

Very early on in the SARS-CoV-2 pandemic, Vienna implemented the "Alles gurgelt" [2] PCR test system, a large-scale screening program which was later used nationwide. The Vienna Healthcare department soon integrated mutation analysis into this strategy, to identify the circulating variants with a high degree of certainty using PCR melting curve analysis [3]. According to the ECDC recommendation from 2021, rapid reinfection with SARS-CoV-2 was highly unlikely within a very short period [4]. Accordingly, mutation analyzes were only performed for the first positive SARS-CoV-2 test result. Therefore, there is actually only one variant analysis for each infected person within the period of 90 days available. Furthermore, according to the adapted Austrian variant surveillance program, not every sample of the initial positive PCR tests was examined for a specific variant. The proportion of initially analyzed samples was reduced from 50% to 10%. To clarify the question whether the people who had fallen ill again showed a prolonged course or were reinfected rapidly, we examined our data for possible clues. Due to ECDC recommendation, based system settings, multiple melting curve analyzes should not have been performed within 90 days. However, some samples have randomly been analyzed due to a peculiarity of a technical interface. Therefore, we found 242 cases of rapid reinfection between Omicron sub-variants with a mean interval of 47.0 ± 7.56 days and multiple melting curve analyses [Table 1]. 66% received at least one negative PCR result between the two infections. Despite the system settings that would have prevented further variant analysis, we do have evidence of early reinfections <60 days with various or even the same sub-variants of omicron, as well as indications of a second symptomatic course. In these 242 cases, we see a slight increase in symptomatic courses in the second infection and low CT values again (Ct-value 2nd infection 24.38 ± 4.64). Out of 242 cases, 76% are unvaccinated, 24% are vaccinated (out of these 24% at least one dose vaccinated individuals, 79% received a second dose, 16% a third dose). The proportion of symptomatic to asymptomatic courses in the second infection is 1.25. Compared to the proportion symptomatic/ asymptomatic courses of 0.90 in the first infection, this is a slight increase of symptomatic courses reported by patients in early reinfections. Among the symptomatic cases of primary infection, the proportion of unvaccinated persons is increased by a factor of 4.9 compared to the proportion of those who were vaccinated at least once. With reinfection, this factor is reduced to 3.4. 0% of the symptomatic, vaccinated, first infected individuals were vaccinated three times. Of those re-infected, symptomatic, vaccinated individuals, only 4% were vaccinated three times. We share these results to stimulate a discussion on how to manage upcoming waves, in terms of quarantine and immunity assessment at the current rate of mutation and the diverse range of sub-variants.

Nguyen et al. has reported a drastically increased reinfection rate compared to previous variants, which seems to be a special feature of the Omicron variant. Due to present ECDC recommended system settings, this phenomenon might be underreported. Reinfections, whether caused by high infection pressure and/or high genetic variability, can represent a separate infection driver in the coming waves. Current evidence suggest a much faster rate of reinfection possible than 60 days, and further, that multiple infections do not necessarily result in asymptomatic courses. However, rapid reinfections occur mostly in unvaccinated or incomplete vaccinated individuals. In these randomly a second time analyzed samples, symptomatic courses generally seem to be somewhat more frequent in the case of a second infection. Although the vaccines show, in terms of the Omicron variant, a reduced effectiveness against an infection, they still seem to be able to prevent reinfections as well as symptomatic courses effectively. Nevertheless, with a high reinfection rate due to a high genetic variability within the Omicron variant, one cannot generally assume reduced infectivity in reinfected individuals. The detection and management of infected people should therefore be re-evaluated.

There are limitations to these findings of this study. Melting curve analysis is not able to identify the specific sub-variant. Therefore, reinfections can also be attributed to the genetic diversity among sub-variants. The cases presented are incidental findings and do not allow any conclusions to be drawn about the actual number of cases of reinfection. Only the number of vaccinations was taken into account, not the interval between

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Table 1
242 cases of rapid reinfection between 01/01/22–05/10/22. Negative test rates include only PCR results that took place in the interval between both infections. Variant analysis via PCR melting curve.

	BA1/BA1	BA1/BA2		BA2/BA2		BA2/BA1	Total
	BA1/BA1	BA1/BA2	BA1/BA2+ORF3a:H78Y	BA2/BA2	BA2/ BA2+ORF3a:H78Y	BA2/BA1	
***N*=**	60	138	27	14	1	2	242
Mean Age ±SD	34,13 ± 14,37	31,22 ± 14,81	33,15 ± 13,71	33,29 ± 17,69	25 ± 0	32,5 ± 12,02	29,5 ± 14,72
Sex F/M	1,86	0,94	1,25	1,80	1,00	1,00	1,20
Mean Interval ±SD	45 ± 7,48	48 ± 7,40	48 ± 7,39	41 ± 6,47	42 ± 0	44 ± 4,24	47 ± 7,56
Negative PCR result	75%	57%	70%	50%	100%	100%	66%
1st mean Ct-value ±SD	25,23 ± 3,34	24,36 ± 5,69	24,03 ± 4,07	25,03 ± 3,69	22,7 ± 0	26,31 ± 1,39	24,58 ± 4,89
2nd mean Ct-value ±SD	24,37 ± 4,73	23,69 ± 4,83	23,99 ± 4,03	25,36 ± 3,74	25,92 ± 0	23,13 ± 1,96	23,99 ± 4,64
1st infection							
Symptomatic	19 (32%)	39 (28%)	9 (33%)	4 (29%)	0 (0%)	0 (0%)	71 (29%)
Asymptomatic	24 (40%)	46 (33%)	8 (30%)	1 (7%)	0 (0%)	0 (0%)	79 (33%)
Unknown	17 (28%)	53 (38%)	10 (37%)	9 (64%)	1 (100%)	2 (100%)	92 (38%)
Symp./Asymp. ratio	0,79	0,85	1,13	4,00	0,00	0,00	0,90
Ratio Unvacc./ Vacc. Symp.	3,8	4,6	9,0	3,0	0,0	0,0	4,9
% Symptomatic 1 dose	21%	18%	0%	33%	0%	0%	17%
% Symptomatic 2 dose	16%	19%	0%	33%	0%	0%	14%
% Symptomatic 3 dose	0%	0%	0%	0%	0%	0%	0%
2nd infection							
Symptomatic	22 (37%)	42 (30%)	10 (37%)	6 (43%)	0 (0%)	0 (0%)	80 (33%)
Asymptomatic	19 (32%)	38 (28%)	7 (26%)	0 (0%)	0 (0%)	0 (0%)	64 (26%)
Unknown	19 (32%)	58 (42%)	10 (37%)	8 (57%)	1 (100%)	2 (100%)	98 (40%)
Symp./Asymp. ratio	1,16	1,11	1,43	6,00	0,00	0,00	1,25
Ratio Unvacc./ Vacc. Symp.	3,6	3,7	4,0	2,0	0,0	0,0	3,4
% Symptomatic 1 dose	23%	21%	20%	33%	0%	0%	23%
% Symptomatic 2 dose	18%	17%	20%	33%	0%	0%	19%
% Symptomatic 3 dose	0%	0%	0%	17%	0%	0%	1%
Vaccination							
Unvaccinated	46 (77%)	109 (79%)	23 (85%)	6 (43%)	0 (0%)	1 (50%)	76%
1 dose	14 (23%)	29 (21%)	4 (15%)	8 (57%)	1 (100%)	1 (50%)	24%
2 dose	11 (18%)	23 (17%)	3 (11%)	8 (57%)	1 (100%)	1 (50%)	19%
3 dose	2 (3%)	3 (2%)	0 (0%)	4 (29%)	1 (100%)	0 (0%)	4%

infection and vaccination. In addition, no distinction was made between the vaccines. However, these immunizations are officially accepted in Austria.

The data was collected in the period from 1 January 2022 to 11 May 2022. Only cases with a second diagnosis date >30 and <60 days were considered. In addition, the Ct values had to be <30 at the second diagnosis. To make sure it is not a Delta to Omicron infection (after Delta was not fully replaced by Omicron yet), reinfections with only one melting curve analysis were excluded.

Ethical approval

The Municipal Department 15 - Public Health Services has legal permission to process confidential patient data for national surveillance of SARS-CoV-2. Therefore, individual patient consent is not required. After consultation with the Vienna Ethics Committee, Austrian law does not require approval by an ethics committee for the processed data.

Declaration of Competing Interest

The authors are employees of the Municipal Department 15 - Public Health Services and declare no conflicts of interest.

CRediT authorship contribution statement

Ihm Vera-Lise: Writing – original draft, Investigation, Formal analysis, Conceptualization, Visualization. **Ensle Dominik:** Investigation. **Reiter Elisabeth:** Investigation. **Huber Kerstin:** Investigation. **Förster Raffael:** Formal analysis, Data curation. **Barna Jusztina:** Writing – review & editing. **Jordan John-Hendrik:** Conceptualization, Supervision, Writing – review & editing, Investigation.

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