ASPHER Report

COVID-19 is at a Crossroads in Europe in Summer 2021: Risks of the Third Wave and the need to anticipate scenarios considering pitfalls

How can we handle major risks such as increased undetected transmission between unvaccinated groups, with potential long term clinical sequelae and importation and spread of global variants with vaccine 'immunity escape'?

July 2021

Vasco Ricoca Peixoto[1,2,3], John Reid[1,4], Vladimir Prikazsky[1,5], Ines Siepmann[6], John Middleton[1,7,*]

[1] ASPHER COVID-19 Task Force
[2] NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Portugal
[3] Comprehensive Health Research Centre - Universidade Nova de Lisboa, Portugal
[4] Visiting Professort, University of Chester, United Kingdom
[5] Independent expert, epidemiologist
[6] ASPHER Young Professional
[7] ASPHER President
* Corresponding Author: John.Middleton@ASPHER.org

Abstract

European countries and most places in the world, are facing challenges of COVID transmission that highlight difficulties in controlling the pandemic. Strategies need to be updated. There are multiple risks and unknowns. These include the risks of transmission between young unvaccinated people, and onward spread to other unvaccinated groups; high under-ascertainment of infection, due to our definition of COVID infection being too narrowly focussed and our increasing reliance on inadequate rapid antigen tests creating the potential for large numbers of false negative cases; rapid importation and dissemination of variants with reduced vaccine effectiveness and finally the risk of sequelae for infected individuals with impact on future burden of disease. Inequalities in vaccine uptake and availability, and inequalities in risks of infection leave some communities exposed to higher rates of infection and higher long-term ill health.

The initial public health goals and message around the world to prevent hospitalizations and deaths needs to change to gain peoples' collaboration in prevention and control in places like Europe, where most older populations are increasingly fully vaccinated. The approach should include two main aspects: Firstly there are warning signs on the frequency of sequelae and health risks in the medium-/long-term that could increase the burden of disease of COVID-19 during the next decades, even for some younger individuals; Secondly the risks posed by new

variants in terms of higher transmission and lesser effectiveness of vaccines in use could put Europe's huge vaccine efforts in jeopardy. It is important to consider enhanced strategies of wider testing and contact tracing and public communication. Recent research shows that there is a broader range of COVID-19 symptoms, particularly in younger people, that are less frequently recorded, probably due to surveillance bias. While efforts to vaccinate the world population are still far off, we must consider the potential risks and benefits of an improved public health strategy that includes preparedness for the Third wave impact, with updated winter plans, and reducing imports and dissemination from countries with high transmission and significant new variants.

The Association of Schools of Public Health in the European (ASPHER) recognises that Europe is at a crossroads. We should ignore false calls for abandonment of still reliable measures. We should carry forward with rolling out vaccination while maintaining balanced public health countermeasures and communications that increase compliance, that add protection and allow us to steadily exit pandemic mode as safely as possible. Trying to exit too fast, may create real risks in the long run.

COVID-19 at the crossroads in Europe

We need international recognition that we are at a crossroads. There are risks of this summer becoming known for the invisible spread of new or as yet unknown variants among younger non-vaccinated populations in Europe and the world. These may make control more difficult next winter, with a real risk of further reducing vaccine effectiveness.

We need more research on the risk of COVID-19 sequelae, that include *long-COVID* syndromes and other COVID-associated medical conditions. We need to understand if it is enough to protect older people from severe disease, or if other relevant risks lurk ahead for many healthy younger people that have been, and will be infected.

Higher underascertainment of cases in a context of generalized loosening of preventive measures, increase mobility and increase in mass gatherings make control of the Delta and other variants difficult this summer. We are beginning to see a rise in cases in European countries, beyond the initial appearance in the United Kingdom and Portugal. Worst-case scenarios for next winter must be projected and their risks evaluated so we can understand and communicate to the people what are the trade-offs of a quick opening up, loosened border control, allowing for variant spread and eventual long-term health risks related to infection among many yet susceptible individuals.

Borders, dissemination of variants, genomic surveillance and immune escape to vaccination and prior infection

Variants that arise tend to spread long before they are found as surveillance and identification as variants of concern. Identification of new and existing variants requires the genetic sequencing of a large number of samples, that are hardly representative, before their clinical relevance in terms of transmission, clinical severity and immune escape potential can be assessed[1]. Genomic surveillance has limitations everywhere and is very heterogeneous in

Europe and the World[2]. Institutions and authorities need to understand this surveillance bias and delay if they are to grasp the meaning of reported data to be ahead of the curve. In addition there are high levels of case-underascertainment in COVID-19[3,4]. Outbreaks that are not recognized as new variant-related make it nearly impossible to control the spread of variants, especially if coordinated travel policies and quarantine are not put in place.

Opportunities for new mutations and the resultant spread of new variants may further reduce vaccine effectiveness. A reduction in vaccine efficacy for infection has been detected in Delta variant especially with only one vaccine dose[5]. Recently Israel reported that the Pfizer vaccine protected 64% of people against illness between June 6 and early July, down from a previous 94%. However effectiveness against hospitalization and death remained high[6]. The risk of spread of the Delta and other variants this summer was considered highly likely in an ECDC risk assessment[2]. This variant is dominant in many areas of the world only 6 months after vaccine rollout started. The variant was first detected in February in India and certainly appeared many months before its first detection. After this, in May 2021, there was a big surge in cases in the same country.

The frequency of transmission in some parts of the world make it virtually inevitable that mutations arise that create variants of concern. These variants have characteristics that hinder control efforts either by increased transmissibility or by immune escape. These characterisitics are related to changes in the viral Spike Protein and others[7,8]. These may not necessarily become less severe[9,10]. It is estimated that an infected person can carry 1 000 000 000 viral particles at the peak of the infection[11]. There is already some evidence of early reduction of vaccine effectiveness with the Delta variant[12]. These variants will either be more infectious, have some level of immune escape by presenting structural and functional variations of the Spike protein or intracellular replication mechanisms or other immune evasion mechanisms[13].

It is biologically plausible, and to be expected, that new relevant variants will soon be detected in Europe if stronger Schengen border control efforts and adequate public communication is not put in place. Interventions that can delay the importation and dissemination of such variants from high risk areas may prove worth the effort this summer, while vaccination of the world accelerates. Failure to do so may result in a worst case scenario: an earlier loss of effectiveness of vaccines[13], new waves of infection and hospitalized cases next winter. The acute consequences of infection that we already know will be accompanied by greater risks of sequelae, including in younger individuals. These we can no longer ignore.

EU institutions should draw up scenarios and assess these risks and trade-offs and make recommendations to ensure the effectiveness of border control measures. The isolation and testing of people newly arriving in countries seems to have obstacles: legal; administrative and enforcement and needs to be addressed head-on. There must be strong common European policy, harmonized and effectively implemented by each Member State. Border controls must be supported by the effective use of information technologies and by ensuring compliance with quarantines. Enhanced Genomic Surveillance and efforts to increase surveillance system sensitivity/reduce under-ascertainment/detection of infections must be broadly promoted as essential tools to protect our near, common future. There must be international agreement on minimum levels and standards for Genomic surveillance. Governments need to cooperate to support health systems to achieve this where the capacity does not yet exist.

Risk of increased under-ascertainment – Need to update and communicate age specific case definitions/criteria for testing – Symptom neglect – Dissemination of (self-administered) rapid antigen tests and PCR substitution and increase in false negative results

SARS-CoV-2 infection may present much more often with milder symptoms than initially thought[14,15] due to surveillance bias and under-ascertainment of mild cases[16] with symptoms that differed from cough, fever and anosmia[17,18]. There is also a large proportion of asymptomatic cases[19]. This has probably been responsible for huge under-ascertainment throughout the pandemic[3] and may become a bigger problem now that infection will tend to have higher incidence in younger people who may neglect mild symptoms especially if they are different from those initially used in testing guidelines and different from the ECDC case definition[20]. We only find what we test for and there are calls to expand the COVID-19 case definition to improve pandemic control[21] There is recent evidence for Delta variant infections presenting with symptoms more similar to a bad cold, with stuffy, runny nose, odynofagia, headache, myalgia and only mild cough with no fever[22]. Or is it that these symptoms are finally being tested for COVID-19 perhaps?

Testing for COVID-19 needs be extended to a broader range of suspicious symptoms. The vigilance and sensitivity of surveillance systems needs to be thoroughly evaluated and improved[23]. Public communications need to reflect this widening range of symptoms of COVID-19. The population needs to understand that they should be tested, even if their symptoms are mild, and even if people are keen to attribute symptoms to a different range of causes, from a colder breeze, to air conditioning to allergies to unkown allergens. It is also important to rethink the testing strategy as the systematic replacement of PCR tests by rapid tests has increased the risk of false negatives making it difficult to control transmission. These false negatives in symptomatic people may turn them into super-spreaders of SARS-CoV-2. Although the sensitivity in the context of symptoms is slightly higher (72.0% 95% CI 63.7% to 79.0%) it still allows for high under-ascertainment. Tests on asymptomatic people in low prevalence settings will lose 33% to 50% of infection cases[24].

Less disruptive measures such as reducing and minimizing risks in mass gatherings, maintaining mask wearing, scaling up testing and improving the effectiveness of contact tracing and isolation in different settings and making them free and easily available, maintaining remote work when possible can reduce transmission and should continue to be considered this summer.

A range of factors are combining to facilitate a mostly invisible dissemination of variants across the summer and creating the potential for higher numbers of COVID-19 sequelae and long-term symptoms of infection. The perception of lower risk of health system overload due to the vaccination of older people lowers our resolve to suppress the virus. The trending social policies towards increasing contacts, events and international travel actively promote the spread of COVID-19. Transmission is increasing among the younger, less vaccinated population. There is complacency over what current vaccination levels mean. In all countries vaccination is incomplete, there are breakthrough otubreaks of infection in unvaccinated groups and schools and there is transmission from fully vaccinated people[25].

Long COVID, or shall we call them COVID-19 associated medical conditions?

Despite the protection by vaccination of populations at higher risk for severe acute disease, evidence is accumulated that sequelaes and COVID-19 associated medical conditions are frequent even in younger individuals. Early data on the long-term risks of infection should not be neglected, even among those with mild symptoms[26].

A large representative population sample study in the UK[27] estimated that 1.69% of the population (more than one million people) reported long COVID. The proportion was 1.53% in 17-24 years and 1.79% in 25-34. After 12 weeks, in a group COVID-19 patients with infections of any severity, prevalence of any symptom was 14%; fatigue was 8.3% (95% CI: 6.7-10.3), headache 7.2% (95% CI: 5.9-9.0). The 25-34 age group presented the highest prevalence of symptoms after 12 weeks: 18.2% (95%CI 14.1-23.4). In this study the prevalence of any symptom at 12 weeks in the control group (without COVID-19) was 1.7% (95% CI: 1.4-2.1) with a clear difference between this group and the infected. About 80% of people who reported long COVID, reported impacts on working capacity and about 70% on family life. Other symptoms reported include neurological symptoms including "brainfog" (concentration difficulties)[28,29] and possible associations with mental health disorders[30]. A large cohort study using electronic health registries found increased risk for a wide range of neurologic (stroke, dementia, myoneuronal junction and muscle disease) and psychiatric outcomes (mood, anxiety and psychotic disorders), only 6 months after infection and the risk increased with time[26]. There is uncertainty about the mechanisms that lead to these symptoms. Hypotheses have been put forward that these symptoms are mediated by persistent autoimmune/inflammatory mechanisms, persistent "low-level" infection, and tissue injury in different target tissues including central nervous system[31] with recent evidence of possible loss of grey matter in specific brain areas[32] as well as evidence of increase risk for a broad range of neuropsychiatric outcomes associated with COVID-19 in large cohort study 6 months after the infection[26].

Fast efforts must be put in place for surveillance of COVID-19 sequelae and robust healthcare surveillance systems for COVID associated medical conditions and cohort studies are essential to detect early signals of longer term health risks of COVID-19 infection in various age groups and according to disease severity to inform policy. Health-care services must prepare to respond to COVID-19 associated medical conditions and COVID-19 long haulers. We suggest a taxonomy of COVID associated health outcomes which recognises:

- Acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks.[33]
- Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks.[33]
- Post-COVID-19 syndromes: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.[33]
- COVID-19 associated medical conditions: any medical diagnosis (acute or chronic) that someone infected with SARS-CoV-2 is at increased risk of being diagnosed in the months and years after infection.

International agreement on these would enable more consistent international surveillance comparison and provide an early warning of new risks of COVID-19 associated morbidity.

These sequelae and long-term health risks of chronic disease impact in terms of years of life lived with illness and disability (YLDs) which may produce worsening health and wellbeing indicators in the future[34]. These should be weighted when considering policies to protect younger, active, individuals from infection during the next months, through vaccination and non-pharmacological measures.

Understanding and communicating risks

Surveillance and research on COVID-19 risks is a priority because it is relevant for decisions now. It should be focused on COVID associated medical conditions and emerging variants. Relevant anonymized data from surveillance systems and health registries, (that no longer constitutes personal data[35]) must be made available for researchers in a timely manner. Genomic Surveillance and surveillance systems sensitivity limitations must be understood if they are to be improved in many countries.

Spread of variants of concern is being facilitated by undetected transmission among unvaccinated people due to the neglect of mild symptoms, symptoms not considered in testing guidelines and changes in testing strategies mostly with rapid tests. This is taking place in the context of opening activities and relaxation of prevention measures. It is further facilitated where there are no effective border controls. Some of these variants may have an impact on the effectiveness of vaccines and put in jeopardy the huge vaccination efforts that have been made. This can have consequences for public trust and vaccine confidence. It will also require the development of other vaccines with inevitable delays. The potential sequelae of COVID-19 in people with mild disease should not be considered irrelevant, either by individuals or by the authorities and may be associated with a potentially high burden of disease in the future.

The advance of vaccination of older age groups in Europe will greatly reduce the immediate risk of a fast growth in hospitalizations and deaths. As such, most young people may not have been informed clearly on why preventive efforts are needed and governments have had a hard time explaining why. The communication strategy must change from the message of protecting the health system capacity and the lives of older individuals to protecting young individuals health over the long-term due to the risk of sequelae. We must also protect our collective health in a not so distant future by preventing the importation of potentially fast, mostly undetected variants. These variants can make control much harder due to immune escape, of vaccination and prior infection, and faster spread, before vaccination efforts gain traction around the world. We are in a race between the virus variants and vaccine development and deployment. We follow behind in this race but we should change the mindset to try to be ahead of the curve.

Communication of the medium-term risks is essential to have acceptable levels of compliance in preventive efforts that must be understood by citizens. European countries, with good Democratic indexes, must count on the peoples collaboration if they are to succeed in controlling pandemics with minimal restrictions and social and economic disruption as well as negative health and well-being impacts of restrictive control policies[36]. Being ahead of a curve is proving to be a continuous challenge.

Acknowledgments

Prepared by the authors and agreed by the ASPHER COVID-19 Task Force, July 8th 2021. https://www.aspher.org/covid-19-task-force.html

We thank Professor Carla Nunes, and Professor Alexandre Abrantes of the the National School of Public Health, Nova University Lisbon for helpful comments.

References

1. European Centre for Disease Prevention and Control. Guidance for representative and targeted genomic SARS-CoV-2 monitoring – 3 May 2021. ECDC: Stockholm; 202. Accessed June 21, 2021. https://www.ecdc.europa.eu/en/publications-data/guidance-representative-and-targeted-genomic-sars-cov-2-monitoring
2. European Centre for Disease Prevention and Control. Implications for the EU/EEA on the spread of the SARS-CoV-2 Delta (B.1.617.2) variant of concern-23June2021. ECDC: Stockholm; 2021. Accessed June 30, 2021. https://www.ecdc.europa.eu/en/publications-data/threat-assessment-emergence-and-impact-sars-cov-2-delta-variant
3. Golding N, Russell TW, Abbott S, et al. Reconstructing the global dynamics of under-ascertained COVID-19 cases and infections. *medRxiv*. Published online July 8, 2020:2020.07.07.20148460. doi:10.1101/2020.07.07.20148460
4. Ricoca Peixoto V, Nunes C, Abrantes A. Epidemic Surveillance of Covid-19: Considering Uncertainty and Under-Ascertainment. *Port J Public Heal*. Published online April 9, 2020:1-7. doi:10.1159/000507587
5. Bernal JL, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. *medRxiv*. Published online May 24, 2021:2021.05.22.21257658. doi:10.1101/2021.05.22.21257658
6. Israel sees drop in Pfizer vaccine protection against infections | Reuters. Accessed July 7, 2021. https://www.reuters.com/world/middle-east/israel-sees-drop-pfizer-vaccine-protection-against-infections-still-strong-2021-07-05/
7. Koenig P-A, Schmidt FI. Spike D614G — A Candidate Vaccine Antigen Against Covid-19. Phimister EG, ed. *N Engl J Med*. 2021;384(24):2349-2351. doi:10.1056/NEJMcibr2106054
8. Aschwanden C. Five reasons why COVID herd immunity is probably impossible. *Nature*. 2021;591(7851):520-522. doi:10.1038/d41586-021-00728-2
9. Scientific American. How Will the Coronavirus Evolve? . Accessed May 11, 2021. https://www.scientificamerican.com/article/how-will-the-coronavirus-evolve/
10. ECDC - SARS-CoV-2 variants of concern as of 18 June 2021. Accessed June 21, 2021. https://www.ecdc.europa.eu/en/covid-19/variants-concern
11. Sender R, Bar-On YM, Flamholz A, et al. The total number and mass of SARS-CoV-2 virions in an infected person. *medRxiv*. Published online November 17, 2020. doi:10.1101/2020.11.16.20232009
12. Public Health England. *SARS-CoV-2 Variants of Concern and Variants under Investigation Technical Briefing 16 18 June 2021*.
13. Gómez CE, Perdiguero B, Esteban M. Emerging sars-cov-2 variants and impact in global vaccination programs against sars-cov-2/covid-19. *Vaccines*. 2021;9(3):1-13. doi:10.3390/vaccines9030243
14. Sohal A. Open letter to Chris Whitty and Susan Hopkins: Change covid-19 case definition in line with WHO to save lives. *BMJ*. 2021;372. doi:10.1136/bmj.n283

15. Change covid case definition | The BMJ. Accessed June 21, 2021. https://www.bmj.com/content/371/bmj.m4851/rr-4
16. Vasco Ricoca Peixoto, André Vieria, Pedro Aguiar, Alexandre Abrantes. Retrato Epidemiológico: 1 mês em tempos de Covid-19 Barómetro Covid-19 | ENSP-NOVA . Accessed June 5, 2020. https://barometro-covid-19.ensp.unl.pt/politicas-e-intervencoes/Resultados/
17. Mahase E. Covid-19: Sore throat, fatigue, and myalgia are more common with new UK variant. *BMJ*. 2021;372:n288. doi:10.1136/bmj.n288
18. ECDC - Clinical characteristics of COVID-19. Accessed November 1, 2020. https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical
19. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *JAMA Netw Open*. 2021;4(1):e2035057-e2035057. doi:10.1001/JAMANETWORKOPEN.2020.35057
20. ECDC - Case definition for coronavirus disease 2019 (COVID-19), as of 29 May 2020. Accessed November 6, 2020. https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition
21. Crozier A, Dunning J, Rajan S, Semple MG, Buchan IE. Could expanding the covid-19 case definition improve the UK's pandemic response? *BMJ*. 2021;374:n1625. doi:10.1136/BMJ.N1625
22. COVID Symptom Study. Accessed June 30, 2021. https://covid.joinzoe.com/data
23. European Centre for Disease Prevention and Control. Data quality monitoring and surveillance system evaluation – A handbook of methods and applications. Stockholm: ECDC; 2014. Accessed July 7, 2021. https://www.ecdc.europa.eu/en/publications-data/data-quality-monitoring-and-surveillance-system-evaluation-handbook-methods-and
24. Dinnes J, Deeks JJ, Berhane S, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev*. 2021;2021(3). doi:10.1002/14651858.CD013705.pub2
25. Kustin T, Harel N, Finkel U, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. *Nat Med 2021*. Published online June 14, 2021:1-6. doi:10.1038/s41591-021-01413-7
26. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry*. 2021;8(5):416-427. doi:10.1016/S2215-0366(21)00084-5
27. Office for National Statistics - Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK . Accessed May 10, 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021
28. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. *J Neurol*. 2020;267(6):1573-1576. doi:10.1007/s00415-020-09896-z
29. Graham EL, Clark JR, Orban ZS, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers." *Ann Clin Transl Neurol*. 2021;8(5). doi:10.1002/acn3.51350
30. Mohammadian Khonsari N, Shafiee G, Zandifar A, et al. Comparison of psychological symptoms between infected and non-infected COVID-19 health care workers. *BMC Psychiatry*. 2021;21(1):1-9. doi:10.1186/s12888-021-03173-7
31. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615. doi:10.1038/s41591-021-01283-z
32. Douaud G, Lee S, Alfaro-Almagro F, et al. Brain imaging before and after COVID-19 in UK Biobank. *medRxiv*. Published online June 15, 2021:2021.06.11.21258690. doi:10.1101/2021.06.11.21258690
33. Overview | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE.

34. Nurchis MC, Pascucci D, Sapienza M, et al. Impact of the burden of COVID-19 in italy: Results of disability-adjusted life years (dalys) and productivity loss. *Int J Environ Res Public Health*. 2020;17(12):1-12. doi:10.3390/ijerph17124233

35. Obel C, Obel C, Olsen J, Jensen UJ. Use of Existing Health Data in Epidemiologic Research–Issues of Informed Consent Under Normal Circumstances and at a Time of Health Crises. *Clin Oncol Res*. 2020;2020(6):1-4. doi:10.31487/j.cor.2020.06.09

36. Viner R, Russell S, Saulle R, et al. Impacts of school closures on physical and mental health of children and young people: a systematic review.