Proposal for complementary targeted public health anti-epidemic measures during the pandemics of COVID-19.

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During the virus disease COVID-19 pandemics healthcare systems of most countries in the world face an unprecedented challenge how to counteract the dramatic spread of the disease and at the same time how to reduce its high case fatality rate.

Anti-epidemic measures are currently of crucial importance since medicine does neither have causal therapy nor causal prevention in form of a vaccine. The experience from countries with mass fatal spread of COVID-19 (China, Italy, Spain, USA) together with experience with SARS-CoV-1 and MERS epidemics several years ago point out to several important and possibly causal associations revealed. However, only a few were addressed until now. Following facts deserve to be considered:

- Thanks to important restrictions in public and social life (ban on assembling) and mobility, large gathering of people were eliminated. This is important, since most of the known COVID-19 hotspots were locally preceded by massive gathering of up to 50 000 people (e.g. Wuhan marketplace – December 2019, several events in February 2020 - Milano San Siro stadium football match with Atalanta Bergamo, religious congregation in Mulhouse, France, football match in Lyon with Juventus Torino supporters as well as large manifestation on Women's day in Madrid, Barcelona and Bilbao in March 2020). Such mass gatherings created unfortunately very favourable conditions for simultaneous infection or large number of persons amplified by singing and shouting which exponentially increase viral transmission. Fortunately, replication of this explosive factor for virus spread is actually banned by measures forbidding people to assemble.

- It becomes increasingly evident that widespread, mostly subclinical infection of health care workers (HCW) in the hospitals of the hotspot regions was a crucial factor for rapid virus transmission to elderly population, especially those seniors with comorbidities (cancer, diabetes, cardiovascular diseases, chronic pulmonary disease etc.). Given the reported 20% prevalence of symptomatic HCW positive for SARS-CoV-2 in Italy (1) (and probably also in Spain and US), one has to admit several times higher occurrence of subclinical infections. In practice this equals to almost all HCW in hospitals and long-care facilities infected. Since elderly people frequently required medical visits for other conditions, a significant proportion of seniors was infected during contacts with medical staff.

- Severe forms of COVID-19 typically comprise 2 phases:
    - Initial phase of viremia triggering a "standard" immune response with general malaise and fever a symptoms of lower respiratory tract irritation (mainly cough)

- A second phase, frequently following a short period of clinical improvement, characterized with exaggerated hyperinflammatory response localized mainly in pulmonary alveoli (ARDS) as part of cytokine storm and generalized thrombophilia. This mechanism shares many common features with secondary haemophagocytic lymphohistiocytosis (sHLH). A scoring system to facilitate diagnosis of this syndrome was proposed in the past (2) and its possible utility for COVID-19 management suggested recently (3).

- These pathophysiological mechanisms are responsible for a fulminant disease exacerbation blocking gas exchange in the lungs which together with multiple tissue microthrombi result in profound tissue hypoxemia. In spite of applying respiratory support with ventilators in these critically ill patients, their 25-60% fatality rate can't be prevented.

Thus, for public healthcare policy an important question arises: can we identify in the early stages of disease patients with high risk of cytokine storm with adverse outcome? Analyses of large spectrum of laboratory parameters in SARS-CoV-2 infected patients allow for the hypothesis that selected biomarkers might have prognostic value for COVID-19 course. Patients with lethal outcome differed already in early stages of disease from those with benign course (4). Based on the current knowledge of mechanisms of ARDS and experience from COVID-19 patient population, following parameters are of significant interest:

- Clinical parameters (fever, hepato- and/or splenomegaly, heart failure, arrhythmias)
- Complete blood count (focusing on cytopenias, mainly lymphopenia and/or other lineages incl. thrombocytes)
- Inflammation markers - CRP, IL-6
- Serum albumin and globulins
- Hemocoagulation parameters - D-dimer, prothrombin, fibrinogen
- Markers of tissue damage
  - Myocardial (troponins, NT-proBNP)
  - Hepatic (LDH, transaminases, triglycerides)
- Parameter of secondary haemophagocytosis (ferritine plasma level)

The above-mentioned premises allow for the following proposal for novel anti-epidemic measures:

1. Need for continuous periodic PCR "pooled testing" (5) of at least all workers hospital and long-term care facilities where COVID-19 patients are/were treated. This testing should be realised in 7-days intervals with strict immediate quarantine of all SARS-CoV-2 positive persons. Thus, in practice 1/7 of all HCW in the country (at least those in health-care facilities exposed to COVID-19 patients) have to be tested on a daily basis allowing for all being tested once in a week. With PCR testing with swab pools from 10 persons, this target appears realistic. Of course, in the case of positive pooled test, all persons within the pool must be tested individually to identify the SARS-CoV-2 positive individual (-s). This measure would significantly contribute to the safety of providing of all health care services including those not related to COVID-19 and thus,

minimize also the collateral damage due to limited availability of such services during the pandemics.

2. Early targeted clinical examination of all symptomatic COVID-19 patients together with assessment of the abovementioned biomarkers with single venous blood drawing. In the case of positivity (quantified by means of a modified reactive haemophagocytic score HS – Table 1) patients would be admitted to hospital (even if only mild symptoms were present).. Appropriate follow-up with intensive supportive measures including anticoagulation therapy, glucocorticoid therapy, early non-invasive respiratory support would be offered to them for preventing potentially lethal fulminant course with multi organ damage. Most recent reports from Italy and US question the benefit of aggressive invasive ventilation therapy and propose "softer" respiratory support (like High Flow Nasal Cannula (HFNC), Continuous Positive Airway Pressure (CPAP) or Non Invasive Ventilation (NIV)) (6). Such approach should be preferentially applied to high risk elderly population with comorbidities.

Conclusion:

The proposed approach could be of help to achieve 3 goals of crucial importance:

- To minimize virus spread in health-care facilities which played a key role for transmission in the COVID-19 hotspots.
- To protect health care workers who were ravaged by the epidemics and are irreplaceable for controlling the pandemics.
- To identify vulnerable patients with COVID-19 who are on high risk for adverse, frequently lethal outcome.

Of course, this proposal represents only a complementary approach to general anti-epidemic measures (masks, respirators, intensive hand hygiene), social distancing and mobility restrictions. Available evidence, albeit limited, points out to its potential to contain and mitigate the current pandemics and improve its odd prognosis without long lasting draconian paralysis of economic life. In addition, it appears both as feasible and economically sustainable strategy in mid-term horizon.

References:

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	Number of points
Body temperature	
<38.4°C	0
38.4–39.4°C	33
>39.4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38

Number of cytopenias in complete blood count – definition:

1. haemoglobin concentration of ≤9.2 g/dL (≤5.7 mmol/L),

2. white blood cell count of ≤5000 WBC / mm^3,

3. platelet count of ≤110 000 platelets/ mm^3.

	Number of points
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate (not mandatory)	
No	0
Yes	35
Known immunosuppression	
No	0
Yes	18
Maximum score (points)	**337**
Proposed cut-off value for sHLH	**>169**

Table 1: Scoring system for facilitating the diagnosis of secondary haemophagocytic lymphohistiocytosis (sHLH) modified to evaluate hyperimmune response in COVID-19. (Modified from references 1 and 2) Scoring system is easily available as online tool (http://saintantoine.aphp.fr/score/) . The best cutoff value for HS score was 169, corresponding to a sensitivity of 93%, a specificity of 86%, and accurate classification of 90% of the patients. Obviously, current situation does not allow for routine bone marrow examination, which is not mandatory