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Learning from the Experience of the COVID-19 Pandemic: A New Paradigm for Occupational Biohazard Assessment and Management

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Summary

The COVID-19 pandemic has affected workplaces in many different aspects. In this scenario, Occupational Physicians played a crucial role in assessing and managing the risk of SARS-CoV-2 infection and associated disease to guarantee workers' health and the safety of workplaces. However, the pandemic experience has drawn attention to several critical issues in overall biohazard prevention and management strategies, originating from important knowledge gaps in our scientific understanding. An extensive analysis of the relevant hurdles that have emerged in our medical field can bring valuable lessons for the post-pandemic future, not only in preparation for possible new pathogens with pandemic potential but also with principles and concepts applicable to managing all biological agents. In particular, a paradigm shift is needed to properly approach occupational diseases caused by infective agents, accurately define the "case", assess exposure and possible causal relationship with work appropriately, and effectively manage the specific risk through implementing appropriate preventive and protective measures. In this framework, the Occupational Physician should expand his contribution based on his unique expertise and specific competencies, confirming his role as the go-to consultant in all occupational health matters, but also in a multidisciplinary approach, considering different scientific expertise and evidence.

1. Introduction

Since the start of the COVID-19 pandemic in March 2020, the occupational setting has been implicated by clusters of cases occurring in different workplaces. In particular, workers in close physical proximity with other people (e.g., coworkers, patients, users), in enclosed or shared spaces are more exposed and at a higher risk of COVID-19 in the absence of effective prevention and protection measures. At the European level, a preliminary analysis by the European Centre for Disease Prevention and Control (ECDC) indicated that most of the occupational clusters reported in the first six months of the pandemic took place in the healthcare sector but also in settings not traditionally considered to be at risk for transmissible biological agents, such as food packaging and processing, in factories and manufacturing, as well as in offices [1]. In addition, although with fewer clusters, cases were also reported from the mining sector, a context well known in the history of occupational medicine to be at risk for transmissible diseases, particularly tuberculosis and ancylostomiasis.

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At the Italian level, data from the *National Institute for Insurance against Injuries at Work* (INAIL) updated to May 2023 report that since the beginning of the pandemic, more than 320,000 COVID-19 infections have been notified due to occupational exposures, accounting for about one-sixth of the total number of all occupational injuries since January 2020. Although about half of these events occurred in the first pandemic year, the emergence of the Omicron variant, still prevalent at the time of writing, globally with its various subvariants, resulted in more than one-third of the total infections in 2022. Furthermore, Italian data indicate that healthcare was the most affected setting, with about 75% of all notified cases, in particular consisting of nurses (31.3%), aides (16.1%) and physicians (9.4%). However, other professional categories, such as administrative workers and professional drivers, followed with a proportion of 5.8% and 1.2%, respectively. The development, rapid production, and availability of effective vaccines as of December 2020 have resulted in a gradual but drastic reduction in adverse health outcomes among the workforce, as also observed in the general population. INAIL reports more than 900 deaths caused by occupational exposure to COVID-19, about two-thirds of which occurred in the first pandemic year, about one-third in 2021, and only 1 in 100 cases in 2022. Concerning overall mortality, although healthcare personnel were once again the most affected category, accounting for one-fourth of all fatal injuries, the analysis of specific jobs showed that administrative workers presented the highest proportion of fatal injuries (10.1%), followed by transportation workers (8.3%). In comparison, nurses (6.0%), physicians (4.8%) and aides (3.6%) demonstrated lower proportions [2].

From the perspective of applying a worker-oriented approach that could contribute to broader public health, Occupational Physicians have played a crucial role in reducing the risk of infection and possible complications in the workplace [3]. This involved not only individual risk assessment for susceptible workers and their appropriate placement in the workplace but also taking a range of preventive and protective measures to reduce health risks to employees, such as work adjustments, appropriate fitness-for-work assessments, implementing workplace vaccinations, as well as early identification and management of infected workers and close contacts. Additionally, an important role was performed in health assessments for the safe return to work of affected workers after recovery, not to mention the collaboration in the risk assessment of different occupational settings.

Indeed, workplaces have emerged as a critically important context of action as part of implementing and evaluating new preventive and protective strategies to counter the spread of SARS-CoV-2 infection. The rise in the appearance of new pathogens had raised the need for a paradigm shift in the management of biological risk, which, before the pandemic, was often considered to be of minor relevance to health and safety in the workplace of developed countries, restricting the focus mainly on the indisputable risk present in the healthcare, contact with animals and livestock and agricultural contexts. However, the pandemic experience has drawn attention to several critical issues in biohazard prevention and management strategies, stemming from important knowledge gaps which have severely limited the understanding of this phenomenon. A proper analysis of the significant concerns that have affected our medical field can bring valuable lessons for the post-pandemic future, not only in preparation for new emergencies of pathogens with pandemic potential but also with principles and concepts more broadly applicable to bio-risk management.

2. Case Definition of COVID-19

A crucial aspect that came into view immediately upon the emergence of this new pathogen was the case definition of COVID-19. From an initial clinical framing of severe respiratory infection, which led to the final naming of this new human coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), the rapid isolation of the virus meant that, within a few months, the sole necessary and sufficient criterion for pathological definition was the detection of viral material by RT-PCR [4]. The complete reliance of the diagnostics for COVID-19 on molecular identification of the virus effectively reduced the significance of

clinical evaluation to irrelevance, which, for millennia, had always been the foundation for any diagnostic approach in medicine [5, 6]. Although, on the one hand, this approach was necessary for the rapid containment of infection and prevent potentially infected persons from spreading the virus in different human settings, on the other, it expanded the very concept of infectious "disease", thus diluting its meaning to a certain extent, in grouping completely asymptomatic positive subjects (who, we might infer, are infected but not ill), with issues with clinical pictures of acute respiratory infection, up to the more severe but characteristic bilateral interstitial pneumonia, into one single nosological category. In turn, this resulted in apparent flaws in managing the disease, unconcerned with the specificities of individual cases. For example, initial treatments were recommended without a proper risk-to-benefit ratio, with no consideration for disease severity or risk of adverse outcome in the specific individual case (e.g., prescription of hydroxychloroquine, exaggerated corticosteroid dosing) [7]. Additionally, the lack of knowledge of a precise pathogenetic mechanism of infection determined by SARS-CoV-2, or a characteristic clinical picture with specific signs and symptoms, produced a proliferation of associated syndromes involving various systems of the human organism, from dermatological syndromes to neurological alterations, bringing forth the risk for this disease to be classified into the historical set of "Great Pretenders", as was the case with tuberculosis and syphilis in the premodern era of medicine [8]. Over time, however, the accumulation of evidence in the scientific *corpus* has led the various medical branches to gain a greater understanding of the disease, improving clinical definition and, at the same time, tailoring therapeutic management to the individual case specificities, gradually overcoming, therefore, the initial *one-size-fits-all* approach [9].

3. Diagnostic Approach

In Occupational Medicine, the mentioned test-based approach brought significant benefits in rapidly managing contacts with prompt identification and isolation of incident cases, enabling the containment of infectious risks in the workplace. And yet, the blanket use of diagnostic tests, deprived of a critical assessment of each patient's clinical picture, can potentially reduce this diagnostic activity to a mere bureaucratic task of notifying cases to various institutions, as required by national laws and regulations. As suggested by the above INAIL data, although the extensive nationwide vaccination campaign has significantly reduced the clinical expression of COVID-19 in infected individuals, the Institute has recognised a relevant number of notifications as occupational injuries based on diagnoses obtained by detection of genetic or antigenic material. Furthermore, in addition to defining the "disease" of interest in Occupational Medicine, it is fundamental to understand its cause in relation to work. Indeed, identifying an occupational disease requires the nosological framing of the pathology and the etiological link with the specific occupation [10]. In this regard, a key criterion for verifying the occurrence of an occupational disease concerns temporality, which, in the case of infectious diseases, should consider the contagious period, the incubation time, and the serial interval between points. In the case of COVID-19, we found that the infectious period started around 1-2 days before clinical manifestations, the incubation period was equal to 3-5 days, and the serial interval was 4-5 days [11, 12]. As tricky as this verification may be during a pandemic, where any human setting could be considered a source of contagion, the methodological rigour of our medical speciality would allow, in many cases, if not most, to distinguish occupational cases from those acquired by other causes. Despite this, idle compliance with standard procedures mandated by law has enabled the uncritical reporting of PCR-positive subjects that were recognised by agencies by "simple presumption" of their occupational category (e.g., a healthcare worker that has COVID-19 is considered *ipso facto* occupationally acquired). The inevitable consequence of this "presumptive" diagnostic approach has been translated into a paradoxical prevalence of COVID-19 injury and illness reporting to insurance institutions. In contrast, in the pre-pandemic years, injuries caused by biohazards, and even during the pandemic years for all agents other than SARS-CoV-2, have always been characterised by a submergence of the

problem. The pandemic experience, thus, reminds us that the diagnosis must be approached not only based on instrumental and laboratory documentation but must take into account the careful, specific assessment of the individual worker and the precise job, besides analysing the peculiar clinical conditions and exposure history in the workplace. Molecular or antigenic detection of viral material, while representing important supporting tools in the logical diagnostic process made by the Occupational Physician, nonetheless, cannot replace the necessary clinical reasoning on the individual worker but must complement it.

A further limitation carried by the exclusive reliance on diagnostic tests was observed in the indication of the end of isolation of the infected person for a safe return to work. During the early months of the pandemic, due to the lack of sufficient infectivity data and in the application of the "precautionary principle", leading international public health agencies linked the end of the infectious phase to the end of detection of viral RNA shedding, readily obtained through the wide availability of RT-PCR testing [13]. However, it is known that RNA can persist long after the end of the infectious phase for many viral diseases. The RNA shedding and infectivity intervals rarely coincide due to the immune response that neutralises different parts of the virus, preventing subsequent infection and progressively reducing its replication but not eliminating residual nucleic acid [14]. Therefore, PCR tests cannot effectively differentiate between shedding viable and potentially infectious virus or viral fragments. To date, the gold standard for assessment of viral infectivity is based on replication-compatible virus isolation on cell cultures [15]. Following the publication of evidence indicating that most infected individuals could not spread viable virus ten days after symptom onset and after clinical resolution in April 2020 [16], international health institutions modified their recommendations accordingly, ending the isolation of immunocompetent cases and discontinuing precautions around 10 days after clinical onset, allowing workers to return to work without the requirement of a negative RT-PCR result [17]. For public health purposes, the Italian Ministry of Health followed suit and applied a more conservative limit of 21 days from the onset of symptoms [18], which was more recently reduced to 5 days [19]; however, for return to work, the requirement of a negative antigen or RT-PCR test is still mandatory [19, 20]. Through a systematic review and meta-analysis [21], we showed that in immunocompetent workers, the average duration of RT-PCR positivity after the onset of symptoms was far longer (around 27 days) compared to the mean duration of SARS-CoV-2 infectivity (around 6 days). This secondary research, based on studies that assess both *in vivo* and *in vitro*, could be important in informing the assessment and management of COVID-19 risk in the workplace, applied in practice not only when evaluating clinically recovered individuals before their return to the workplace, but also to better assess and manage possible residual biological risks, to protect the health of the entire workforce.

4. Biohazard Risk Assessment and Management

The requirement of multiple levels of evidence, including virological evidence, raises a second additional important lesson taught by the pandemic, namely the important role of the various scientific disciplines necessary for appropriate and effective biohazard assessment and management. Indeed, the establishment of multidisciplinary teams with diverse expertise are needed to develop new procedures and tools aimed at reducing pathogen transmission. Specifically, in addition to Occupational Physicians, infection prevention and control (IPC) specialists, and industrial hygienists, who are the traditional actors involved in the management of biological risks in the workplace, new key figures such as engineers and physicists specialised in the fluid dynamics of disease transmission have emerged as an integral part of resolving significant issues in the control of infective risk in the workplace.

Indeed, the tools traditionally available for risk assessment and management, primarily following the hierarchy of controls, are important components of the well-known Anticipate, Recognize, Evaluate, Control, and Confirm (ARECC) reference model. This approach, however, was developed primarily for the control of chemical hazards and risks, thus

requiring to be adapted to the specific characteristics of infectious pathogens, such as SARS-CoV-2. The identification of hazards and assessment of risks differs when evaluating biological agents versus chemical and physical agents [22]. While such models have been successfully applied to the deliberate biological use in specific workplaces (for which the exposure is planned due to work processes, e.g., microbiological laboratories), attempts to adapt them to the potential biological risk (for which the exposure is unplanned but could be foreseen, e.g., healthcare personnel), and specifically to the control of infectious disease outbreaks, are still limited. Biological risk assessment is further complicated because of the high level of variability in exposures, limitations in sampling methods, differences in the susceptibility of exposed individuals, as well as the lack of epidemiological data to support the identification of specific occupational exposure limits (OELs) [23]. Indeed, while chemical and physical agents are often evaluated on a quantitative basis, a qualitative or semi-quantitative approach is generally used for biological agents, such as the classification into "risk groups" identified by Directive 2000/54/EC of the European Parliament and Council and Article 268 Legislative Decree 81/2008, depending on the level of individual and community infection risk [24]. However, as well observed in the evolution of the recent pandemic, the assessment based on the aforementioned "risk groups" has not been matched by the actual biological risk, which evolves over time due to the changing epidemiological characteristics of pathogen spread in the community, the contagiousness and virulence of the circulating variant strains as well as the pharmacological interventions available. In fact, although SARS-CoV-2 has been included in Risk Group category 3 by the Commission Directive of the European Union 2020/739 since 3rd of June 2020, during the last phase of the pandemic we have seen an overall reduction of risk of severe disease due to acquired immunity through vaccinations or natural infection. This is quite evident analyzing the data on hospitalized patients and deaths between different pandemic waves provided by the Italian National Institute of Health, as the pandemic reached the endemic dimension [25]. Furthermore, in the presence of methodological limitations in exposure sampling, the assessment of occupational biological exposure is typically limited to qualitative characterisation (e.g., low, medium, and high): therefore, for an effective exposure assessment, it is appropriate to consider the mode of transmission of the pathogen as a key variable. In the absence of OELs, the concept of occupational exposure banding (OEB) has been borrowed from chemical assessment [26]. This approach relies on hazard-based data to identify an agent's infective potential and establish an environmental concentration range to place pathogens in categories according to infectious potential, virulence, and particle size distribution. Industrial hygienists and other experts in the field are in the developmental stages for the definition of appropriate OEB, which may lead to qualitative and semi-quantitative exposure metrics in the near future. In the current scenario, where important exposure variables may be missing, researchers have developed the strategy of control banding, a qualitative decision tool that allows Occupational Health professionals to identify for a particular job or task the degree of exposure to a specific hazard, combined with some measure of its toxicity. Integrating the two would allow the professional to individuate the appropriate control band for the particular job/task, guiding the proper type and nature of controls for that band. Applying these principles to an infective biological agent such as SARS-CoV-2, the definition of exposure would involve two main components: concentration and time. Without an adequate explanation of the former, the likelihood of encountering infectious sources during work has been proposed as a surrogate. Similarly, without toxicological data on specific pathogens, Risk Group could be used as a surrogate for toxicity. Combining these two variables can provide a control banding matrix that can effectively stratify the appropriate measures for different levels of exposure in different working groups and tasks [27].

From this perspective of controlling hazards and risks, it has been necessary to act on the multiple factors in the "chain of infection" to prevent viral transmission in occupational settings [22]. Indeed, pathogen exposures can be controlled within a framework that borrows from the classic industrial

hygiene hierarchy of controls, particularly from the pathway-based approach applied to noise and radiation exposure, as suggested by Sietsema et al., who developed the conceptual model of "source, pathway, and receptor" [28]. At each of these levels, occupational health professionals can assess and manage risks based on the specific characteristics of the biological agent and disease, enacting control measures in order of efficacy at the source, at the pathway and finally at the worker level. During the pandemic, particularly in the early stages, many difficulties were met in rapidly identifying asymptomatic (or presymptomatic) infectious individuals, which comprise the source level. As detailed in studies published in the Journal, contagions have often occurred in the workplace from infective subjects with no clinical presentation, possibly due to low-risk perception, particularly during work breaks [29].

5. Modes of Transmission of SARS-CoV-2

At the pathway level, in the specific case of SARS-CoV-2, the main modes of transmission that have been studied over the years are the following, in order of epidemiological significance: i) inhalation of very fine respiratory droplets and aerosol particles, ii) deposition of respiratory droplets and particles on exposed mucous membranes of the mouth, nose, or eyes through direct splashes, and iii) contact with mucous membranes of hands contaminated either directly by respiratory fluids containing the virus or indirectly through surfaces. In this regard, one of the main lessons learned from the recent pandemic relates to the first two modes of transmission mentioned through the airborne pathway. Indeed, droplet and aerosol transmission should not be considered mutually exclusive but rather represent a spectrum in continuity that includes so-called close-range aerosol or short-range airborne transmission [30]. During the pandemic, the historic but still persistent concept of dichotomous separation between droplets and droplet nuclei using the 5-micron cut-off stood out as an important hurdle: although only particles smaller than 5 microns can reach the *alveoli*, this is of questionable relevance when considering that pathogens, such as SARS-CoV-2, can enter cells and also replicate in the upper tract of the respiratory system. In addition, it has been shown over the years that larger particles can remain suspended in air for varying lengths of time in a cloud of turbulent gas travelling well over the 1-to-2-meter limit which public health institutions initially adopted and that smaller droplets can rapidly evaporate in midair [31], effectively becoming *droplet nuclei*. There may have been a practical advantage in dividing the transmission routes of respiratory infections into droplets or aerosols using the 5-micron/1-meter cut-offs for public health considerations.

Nonetheless, many experts in the field have expressed criticism and concern about the rigid categorisation of particles, and several studies have shown the spread of the disease over wider distances. Some authors suggested that the reduced R0 base reproduction number of SARS-CoV-2 could be used as an indicative parameter of transmission by droplet and not aerosol [32]: although the mode of transmission is one of the components that contributes to the successful spread of a specific pathogen, there are many other factors to consider, including pathogenic mechanism, cell entry, and infectious dose. For example, if one were to compare *pertussis* and *tuberculosis* on the basis of R0 alone, one might think that the former is airborne and the latter by droplets. In fact, the only true "typical airborne pathogen" evidence that is missing for SARS-CoV-2 is the so-called long-range transmission. However, this does not rule out short-range aerosol transmission, especially in specific circumstances such as crowded and inadequately ventilated spaces. Indeed, mechanistic models have suggested that in close proximity to an infected person, the risk of exposure is greater for the short-range airborne route than for the classic droplet route [33]. Thus, airborne transmission has been progressively recognised as a significant mode of transmission of SARS-CoV-2, particularly considering these types of settings.

6. Protective Equipment

From a worker protection perspective, this acquired knowledge is diriment in defining which protective equipment is needed to warrant the protection of workers. One of the main preventive and

protective measures taken during the COVID-19 pandemic has been using respiratory protective equipment. Several types of masks are available (N95/FFP2 respirators, surgical masks, and cloth masks), varying in filtering effectiveness, fluid resistance, and wearability. The scientific community of Occupational Physicians in Italy has contributed to their comparative analysis through numerous studies [34-38]. More recently, an important update on the topic has been published on the specific aspect of concern to the field of Occupational Medicine, aggregating, for the first time, evidence obtained from RCTs to compare the protective efficacy in the healthcare setting between filtering facepieces and surgical masks [39]. Previous updates had not identified RCT studies on face masks and SARS-CoV-2 infection in healthcare settings. In this study, surgical masks were found to be non-inferior to N95 concerning the risk of PCR-confirmed SARS-CoV-2 infection based on a prespecified noninferiority margin up to a doubling of risk. This update undoubtedly represents the synthesis of the highest quality evidence on the specific topic of the protective efficacy of different types of respiratory protective equipment.

Nonetheless, it is essential to note that, in more than three years since the beginning of the pandemic, and in consideration of the fact that healthcare personnel were the only occupational category adequately studied, only one randomised clinical trial and four observational studies have been able to provide evidence considered to be of sufficient quality. The classical approach of Evidence-Based Medicine (EBM) has demonstrated many limitations in the practical and timely application of evidence-based policies over time, as could be witnessed during the pandemic [40]. A heated scientific debate has opened within medical epistemology on whether the scientific method should be adapted to the new awareness of the complex systems present in reality, moving beyond the dogma of the hierarchy of probabilistic, clinical and epidemiological medical evidence, with systematic reviews/meta-analyses of randomised clinical trials at the top and case studies at the base, towards the inclusion of mechanistic evidence that studies and analyses the causal mechanisms of events. This new integrated, multi-disciplinary approach, called EBM+, involves the recognition and inclusion in biomedical research of evidence derived from *in vitro* experiments, biomedical imaging, animal experiments, aerosol science, engineering research, and simulations selected based on the specific questions. According to this new paradigm, vaccine efficacy of a new preparation is answered with the classical biomedical model involving the randomised clinical trial; otherwise, interventions that generate outcomes in complex systems require a new paradigm with designs that can capture dynamic changes, accommodate nonlinearity, and accept uncertainty: studying the efficacy of an instrument designed and produced with an engineering approach, whose efficacy can be for measured directly, needs the integration of mechanistic evidence. The mechanisms of respirator function are established and well understood. Certification systems, standards and occupational protocols for respirators are robust and minimise exposure to occupational hazards for millions of workers worldwide. For this reason, an RCT comparing respirators with devices of lower filtering efficacy, such as surgical masks, would not be reasonable to "prove" the value of protecting against chemical hazards. Similar paradoxes could not be considered for seat belts, parachutes or umbrellas. In application of this integrated approach, the IPC Working Group of the Italian National Institute of Health updated the technical note providing recommendations for the appropriate use of personal protective equipment against SARS-CoV-2 infection in healthcare and social care, indicating the use of respirators for all healthcare providers, based on the risk assessment of specific job/task/individual [41].

Finally, as a fundamental control applied at the receptor level, the vital role of vaccinations in reducing SARS-CoV-2 infections and COVID-19 worldwide should be underscored: up-to-date evidence demonstrate that COVID-19 vaccine-induced immunity and hybrid immunity provided by vaccinations and the natural infection offer the highest degree of protection to the individual workers [42, 43]. This impressive result was obtained thanks to the rapid clinical development and on-field availability of new pandemic vaccines based on mRNA and viral vector-based technology, reaching very

high vaccination coverage among the target population during the first semester of 2021 in developed countries. It is worth highlighting the important role played by Occupational Physicians to jumpstart the national vaccination campaign in workplaces, closely collaborating with Public Health Authorities and employers for the first time in Italy. This activity contributed to protecting individual workers exposed to the pandemic agent in different occupational settings, particularly the healthcare sector, and reduced its transmission within the broader community.

As an example of the impressive achievement obtained in the occupational setting, the most recent vaccine coverage data registered among healthcare workers in the European region, updated to November 2023, indicates that 90.4% were administered with the primary vaccination course and two thirds (67.0%) with the first booster dose [44]. However, only a minority (11.9%) reported a second booster dose, which should remind us not to lower the guard and continue being vigilant for possible new incident cases in the workplace.

7. Conclusions

Learning from these lessons, the Occupational Physician should rethink his role in the workplace, expanding his contribution from the minimum required by law, which often reduces the profession to bureaucratic functions, but instead draw on his expertise and specific competencies, acting as the go-to consultant in all matters of occupational health [45], to maintain and promote workers' health and wellbeing, as well as their work capacity. Additionally, it must be stressed that effective prevention of risk factors for workers' health further requires a multidisciplinary and integrated approach (i.e., between technologists and occupational physicians) during all phases and the decision-making process implicated in work [46]. In this endeavour to provide sound scientific reasoning in all his activities, particularly in the identification of occupational disorders caused by biological hazards, the Occupational Physician should remember, as crystallised in Bradford Hill's nine Points of View [47], that no single piece of evidence is sufficient, but that the different types of evidence should be combined to support the case for causation, as real-world circumstances often differ from those presented in scientific studies. Only through evidence-based practice approaches for assessing and characterising biological risk will improve, as data emerge and enhance our understanding of exposure and risk management, potentially in all occupational settings.

Declaration of Interest: Paolo Durando declares he was a member of the Working Group on Infection Prevention and Control established at the Italian National Institute of Health (ISS). The other Authors declare no conflict of interest.

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