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Duration of SARS-CoV-2 shedding and infectivity in the working age population: a systematic review and meta-analysis

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Key words: SARS-CoV-2; shedding; infectivity; working age population; occupational; return to work; meta-analysis; COVID-19

Abstract

Background: *During the COVID-19 pandemic, working age individuals have been implicated in sustaining the resurgence of SARS-CoV-2 infections, and multiple outbreaks have been observed in several occupational settings. In this regard, Occupational Physicians play a crucial role in the management of infected workers, particularly in the safe return-to-work of subjects after clinical resolution. To this end, knowledge of the duration of the infective phase in the working age population is essential, taking into account previous evidence suggesting that PCR positivity does not coincide with virus viability.* **Methods:** *A systematic review and meta-analysis, searching major scientific databases, including PubMed/MEDLINE, Scopus and Web of Science, were performed in order to synthesize the available evidence regarding the mean and maximal duration of infectivity compared to the mean and maximal duration of viral RNA shedding. A subgroup analysis of the studies was performed according to the immunocompetent or immunocompromised immune status of the majority of the enrolled individuals.* **Results:** *Twenty studies were included in the final qualitative and quantitative analysis (866 individuals). Overall, a mean duration of RT-PCR positivity after symptom onset was found equal to 27.9 days (95%CI 23.3-32.5), while the mean duration of replicant competent virus isolation was 7.3 days (95%CI 5.7-8.8). The mean duration of SARS-CoV-2 shedding resulted equal to 26.5 days (95%CI 21.4-31.6) and 36.3 days (95%CI 21.9-50.6), and the mean duration of SARS-CoV-2 infectivity was 6.3 days (95%CI 4.9-7.8) and 29.5 days (95%CI 12.5-46.5), respectively considering immunocompetent and immunocompromised individuals. The maximum duration of infectivity among immunocompetent subjects was reported after 18 days from symptom onset, while in immunocompromised individuals it lasted up to 112 days.* **Conclusions:** *These findings suggest that the test-based strategy before return-to-work might not be warranted after 21 days among immunocompetent working age individuals, and could keep many workers out of occupation, reducing their livelihood and productivity.*

Introduction

Since the declaration of the COVID-19 pandemic on 11 March 2020 [1], over 250 million people have been infected with SARS-CoV-2. In Europe, a region comprising almost a third of global cases, the vast majority of infections occurred in working age populations [2]. Indeed, similarly to

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other respiratory pathogens, SARS-CoV-2 spreads mainly through close human contact, particularly via the droplet/airborne route, and, accordingly, groups that have higher contact intensities are at increased risk of infection [3]. Working age individuals have been implicated in sustaining the resurgence of COVID-19 cases [4], and multiple outbreaks have been observed in several occupational settings, particularly in the healthcare and food packaging and processing [5]. In this regard, in application of a worker-oriented approach that can contribute to the wider public health, particularly after the full reopening of businesses and industries [6], Occupational Physicians play a crucial role. This regards not only the assessment of risks for susceptible workers, but also the adoption of a series of preventive measures aimed to protect the health of the employees. These include work adjustments, modifications in the fitness for work judgments, vaccinations, as well as the early identification and management of infected workers and close contacts, but also the health evaluation for a safe return to work of the affected workers after recovery. Concerning this last aspect, a fundamental and necessary information is represented by the duration of infectivity of this disease. During the first months of the pandemic, up to the end of March and beginning of April 2020, due to the lack of sufficient infectivity data and applying the "precautionary principle", the main international public health agencies related the end of infectious phase to the end of the viral RNA shedding detection, which can be promptly obtained through RT-PCR testing [7]. However, it is known that RNA can persist long after the end of the contagious phase for many viral diseases [8-13]. In fact, RNA shedding and infectivity intervals seldom coincide, due to the immune response neutralizing different parts of the virus (e.g., envelope) preventing subsequent infection and progressively reducing its replication, without however eliminating residual nucleic acid [14]. Therefore, RT-PCR testing cannot distinguish between the shedding of viable and potentially infective virus or of viral fragments. Attempts have been made to associate RT-PCR cycle threshold and viral load, as well as assessing genomic and subgenomic RNA presence as correlates of infective state, however without enough evidence to support their implementation [15]. To date, the reference standard for assessing viral infectivity is based on isolation of replication-competent virus on cell cultures [16]. Upon the emergence of evidence indicating that most infected individuals did not shed viable virus after 10 days following symptom onset and after clinical resolution, international public health institutions modified their recommendations accordingly, ending isolation of immunocompetent cases and discontinuing precautions after 10-13 days following clinical onset and 24-72 hours after resolution, enabling workers to return to work with no requirement of a negative RT-PCR result [17-19]. Concerning severe and/or immunocompromised cases, the agencies extended this interval to 20 days, with the possible indication of testing to determine the ability to return to work. For public health purposes, the Italian Ministry of Health followed suit and applied a 21-day limit from symptom onset, with the last 7 days free of clinical manifestations, after which long-term shedders can end isolation and discontinue precautions [20]; nonetheless, for return-to-work purposes [21], based on the "precautionary principle", the requisite of a negative antigen or RT-PCR test is still mandatory for these workers at the time of writing (January 2022). However, the application of this principle should be based on current state of science, taking into account up-to-date *corpus* of evidence [22]. In this regard, the current systematic review and meta-analysis aims to synthesize the available evidence in the literature, in order to inform occupational health professionals and policy makers with up-to-date scientific information on the duration of COVID-19 infectivity of working age populations.

Methods

The systematic review and meta-analysis were performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [23].

Search strategy and selection criteria

An extensive search strategy was designed (Appendix A) in order to retrieve all research articles

reporting the duration of shedding and infectivity of SARS-CoV-2 virus in various samples, from individuals between the age of 15 to 64 years of age, published from December 1, 2019 to September 10, 2021, in English and Italian language, through systematic searches of major scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, ProQuest, IngentaConnect, Nature Journals, BioMedCentral, ScienceDirect, DOAJ, using the UNO per TUTTO platform, a unique access point for scientific literature provided by the University of Genoa [24]. Each source was last searched or consulted on September 10, 2021. In addition, a manual screening of relevant references of the included studies was performed to obtain additional studies. Studies were eligible if they met the following PICO inclusion criteria: P (population): working age population (15-64 years per Organisation for Economic Co-operation and Development -OECD- definition) [25]; I (intervention): duration of SARS-CoV-2 viral shedding based on RT-PCR testing performed on respiratory specimens; C (comparator): duration of SARS-CoV-2 infectivity or viable virus shedding based on cell cultures of virus isolated from respiratory specimens; O (outcome): definition of COVID-19 infectious period. Review articles, modelling studies, animal studies, studies on environmental sampling and case reports were excluded. Additionally, case series with less than three participants were excluded in order to reduce bias inclusion. When it was not possible to make a decision on a study's inclusion or exclusion based on the title and/or abstract, the full text of the study was examined. A thorough outlook of inclusion and exclusion criteria is detailed in Appendix A.

Data extraction

Two authors (A.R. and B.K.V) screened independently and retrieved articles according to the eligibility criteria. Full-text articles were reviewed and selected to be included by three reviewers (A.R., B.K.V. and A.M.). From each eligible study, the following variables were extracted in a Microsoft Excel dataset: name of first author, year of publication, country, sample size, average age, gender ratio, prevalence of severe COVID-19 (as defined by the National Institutes of Health-NIH [26]), average time from symptom onset to viral clearance detected by RT-PCR, maximum time of viral shedding detected by RT-PCR, average time from symptom onset to viable viral infectivity detected by viral culture, and maximum duration of infectivity detected by viral culture. Studies were classified as immunocompetent/immunocompromised based on the immune status of the majority of the included sample (50%+1 threshold). A request of clarification or information was sent to the authors of the studies in case of doubt or lack of data. Quality assessment of included studies was performed independently by two authors (A.R. and G.D.) using the Joanna Briggs Institute Critical Appraisal Checklist tools, for the different study designs included in this review. A third author (A.M.) was involved to resolve disagreements regarding the quality grading.

Data analysis

For every study included, we calculated the mean duration of viral shedding and infectivity, with 95% Confidence Intervals (CI). The random-effects model was applied to estimate a pooled effect size. Forest plots were produced to represent all studies based on the effect size and 95% CI; if not reported, means and Standard Deviations (SD) were derived from sample size, median, Interquartile Range (IQR), minimum, and maximum values: data were checked for skewness from normality [27], and only if data were detected as normal, the estimates were calculated [28-30]. Heterogeneity between studies was assessed using the I^2 statistic, with a value higher than 50% considered as substantial heterogeneity [31]. To identify sources of variation, further stratification was performed relative to study quality. Sensitivity analyses were performed by excluding individual studies from the meta-analysis in order to assess the robustness of the results. It was assumed that immune status might have an impact on duration of virus shedding and infectivity, therefore, for this factor a subgroup analysis was performed. Potential publication bias was investigated visually inspecting the asymmetry of the funnel plot, and if present, the Duval and Tweedie's trim-and-fill analysis and

the Egger's regression test were performed [32,33]. When at least ten studies presented a specific covariate, we performed a weighted meta-regression with a random-effects model to assess the effect of moderators on the pooled effect size. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Prometa (version 3.0) software.

Results

The initial systematic search resulted in a pool of 1177 potentially relevant articles. After deleting duplicates, we obtained a set of 1120 unique items. Screening titles and/or abstracts led to the exclusion of 986 items. A pool of articles was sought for retrieval and evaluated in full-text. After reviewing the eligibility criteria, 20 articles were included in the final qualitative and quantitative analysis (Figure 1).

Of the 20 included articles, 4 were performed in the United States, 3 in China and South Korea, and one in Australia, Austria, Canada, France, Germany, Hong Kong, Saudi Arabia, Singapore, Spain and Switzerland, respectively. Fifteen articles were published in 2020 and 5 in 2021. The majority

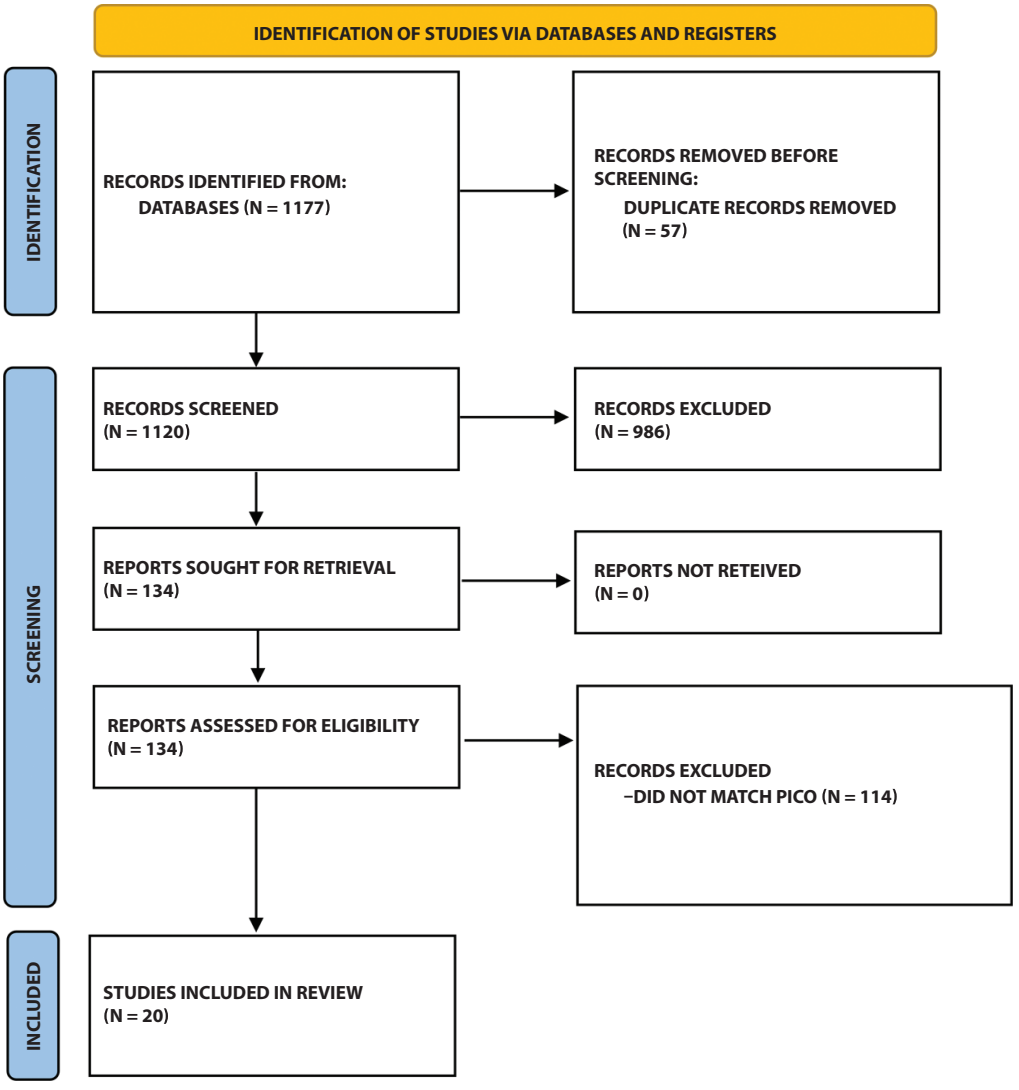

Figure 1. Study selection [23]; details of PICO inclusion and exclusion criteria are reported in Appendix A

of included articles were case-series (n=8), 7 were cohort studies, and the remaining 5 studies were cross-sectional. Concerning the immune status of the included sample, data of immunocompetent subjects was obtained from 17 studies, while data of immunocompromised individuals was available in 5 studies. The critical appraisal of the methodological quality of the included studies is reported in Appendix A.

Overall, the total sample size consisted in 866 individuals infected with SARS-CoV-2. Between studies, mean age ranged from 28.8 to 62.8 years; female gender ratio ranged from 0.0 to 73.0%; prevalence of severe COVID-19 patients ranged from 0.0 to 100.0%. The main characteristics of included studies are presented in Table 1.

Pooling results from 21 studies, including 824 individuals, it was found that the mean duration of RT-PCR positivity after symptom onset was equal to 27.9 days (95%CI 23.3-32.5; I^2 = 99.1%), with no evidence of publication bias (Figure S1, S2). The mean duration of successful virus isolation, based on 15 studies (197 individuals) was 7.3 days (95%CI 5.7-8.8; I^2 = 92.2%), however with presence of publication bias, identified by the visual inspection of the funnel plot, the Duval and Tweedie's trim-and-fill analysis, and a statistically significant Egger's linear regression test (intercept = 3.93, t = 3.55, p = 0.004) (Figure S3, S4).

Performing the subgroup analysis based on immune status, in immunocompetent subjects, the pooled mean duration of SARS-CoV-2 shedding (16 studies, including 775 individuals) resulted equal to 26.5 days (95%CI 21.4-31.6; I^2 = 99.3%), while the mean duration of SARS-CoV-2 infectivity (11 studies, including 172 individuals) was 6.3 days (95%CI 4.9-7.8; I^2 = 92.4%) (Figure 2). No evidence of publication bias was present (Figure S5, S6). At the meta-regression analysis, age (intercept = -7.64, slope = 0.29, p = 0.007) and severe COVID-19 (intercept = 4.44, slope = 0.08, p = 0.004) resulted moderators significantly associated with the duration of the infectivity (Figure 3). The maximum duration of viral RNA shedding was reported after 112 days, while the last evidence of viable virus was found after 18 days among mild cases (a 36-year-old woman with hypothyroidism), and 22 days after a severe case (still symptomatic at the time of specimen collection) (Table 2). After removing studies that selectively included only individual with prolonged viral shedding (at least 14 days after symptom onset), we found a pooled mean of shedding duration of 15.5 days (95%CI 12.5-18.5; I^2 = 97.0%).

Pertaining to immunocompromised subjects, the pooled mean duration of SARS-CoV-2 shedding (5 studies, 49 individuals) was found to be 36.3 days (95%CI 21.9-50.6; I^2 = 94.2%), while the mean duration of SARS-CoV-2 infectivity (4 studies, 25 individuals) was equal to 29.5 days (95%CI 12.5-46.5; I^2 = 84.8%) (Figure 4). No publication bias could be detected (Figure S7, S8). The maximum duration of viral RNA shedding was detected 189 days after symptom onset (52-year-old man with follicular lymphoma, on chemotherapy), while the maximum duration of viral viability was reported after 112 days (47-year-old man with follicular lymphoma, on chemotherapy) (Table 3).

Upon removing studies that included only prolonged shedders (≥14 days post-symptom onset), we found a pooled mean of RNA shedding duration of 31.1 days (95%CI 17.6-44.5; I^2 = 94.6%), and a pooled mean of infective period duration of 18.1 days (95%CI 12.4-23.8; I^2 = 0%).

Discussion

The findings of the present systematic review and meta-analysis demonstrate a notable difference between the duration of viral RNA shedding and infectivity among the investigated groups. Indeed, among the working age immunocompetent population, patients could shed viral genetic material for prolonged periods of time without any evidence of cytopathic effect (CPE) on cell cultures, surpassing the maximum infective period identified in the literature by an average of 10 days, up to 13 weeks. In this group, the average infective period of less than one week is in line with recommendations provided by international institutions [17-19]. Furthermore, the inclusion of five studies which had specifically selected patients with prolonged viral shedding (enrolled after at least 14 days had passed since first RT-PCR positivity) did not show evidence of

Table 1. Characteristics of the studies included in the current meta-analysis.

Name	Study design	Country	Year	Immune status	Sample size (n)	Mean age (y)	Female (%)	Severe COVID-19 (%)	Mean shedding duration (d)	Last positive RT-PCR (d)	Mean infectivity duration (d)	Last viable virus (d)
Alshukairi AN[34]	case series	Saudi Arabia	2021	immunocompromised	7	51.3	42.9	57.1	15.9	26	16	16
Alshukairi AN[34]	case series	Saudi Arabia	2021	immunocompetent	6	55.3	50	66.7	14.8	24	9	11
Aydillo T[35]	case series	USA	2020	immunocompromised	20	59.5	45	55	49.8	78	13.8	61
Basile K[36]	cross-sectional	Australia	2020	immunocompetent	195	40	24.6	2.6	18.2	29	4.5	18
Benotmane I[37]	case series	France	2021	immunocompromised	16	61.9	12.5	12.5	26.9	39	19.1	38
Bullard J[38]	cross-sectional	Canada	2020	immunocompetent	90	44.6	51	NA	7.4	21	3	8
Gniazdowski V[39]	cohort	USA	2020	immunocompetent	46	57.3	47	22.8	16.7	51	9.3	22
Jeong HW[40]	case series	South Korea	2020	immunocompetent	5	60.6	33.3	80	15.4	30	13	15
Kim JY[41]	cross-sectional	South Korea	2021	immunocompetent	17	60	64.7	64.7	15.2	33	8.1	17
Kim JY[41]	cross-sectional	South Korea	2021	immunocompromised	3	43.7	0	0	34	47	24.3	44
Kujawski SA[42]	case series	USA	2020	immunocompetent	12	49.7	33	33	20.6	36	4.3	9
Laferl H[43]	cohort	Austria	2020	immunocompetent	15	43	73	0	34.8	58	NA	NA
Li Q[44]	cohort	China	2020	immunocompetent	38	62.8	NA	7.9	91.2	105	NA	NA
Lu J[45]	cross-sectional	China	2020	immunocompetent	84	28.8	48.3	0	25.3	46	NA	NA
Owusu D[46]	cohort	USA	2021	immunocompetent	109	35.5	48	2	21	38	NA	NA
Perera RAPM[47]	cohort	Hong Kong	2020	immunocompetent	16	39.7	34.3	0	NA	67	3.4	8
Pérez-Lago L[48]	case series	Spain	2021	immunocompromised	3	54	33.3	100	132	189	89	112
Sohn Y[49]	cross-sectional	South Korea	2020	immunocompetent	48	32.6	70.8	0	30.4	NA	NA	NA
Vetter P[50]	case series	Switzerland	2020	immunocompetent	5	40.6	0	20	12.6	19	6.3	7
Wang X[51]	cohort	China	2020	immunocompetent	22	59.8	45.4	45.4	77.8	112	NA	NA
Wölfel R[52]	case series	Germany	2020	immunocompetent	9	NA	NA	0	11.6	28	5.3	8
Young BE[53]	cohort	Singapore	2020	immunocompetent	100	46	44	20	16.7	48	7.3	14

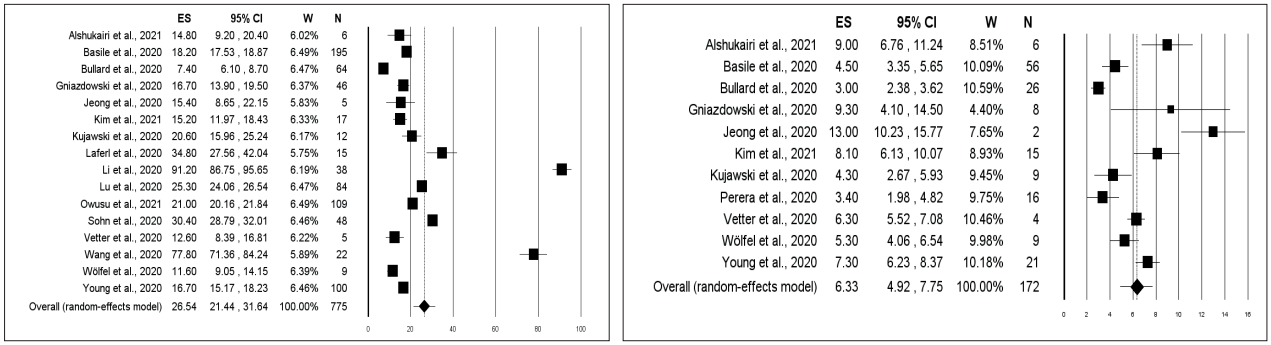

Figure 2. Pooled mean duration in days of viral RNA shedding (A) and viable virus detection (B) among immunocompetent individuals

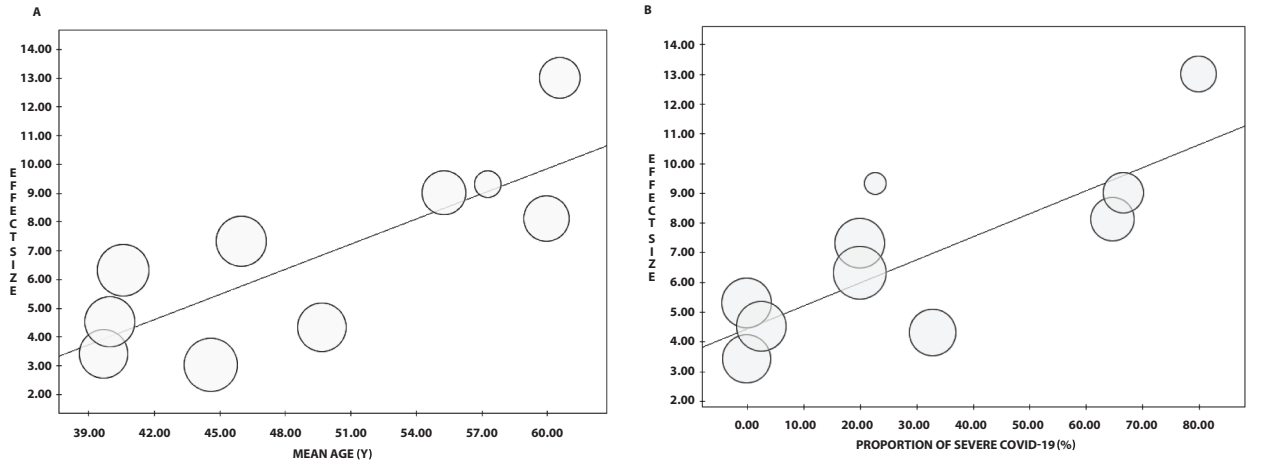

Figure 3. Meta-regression analysis for mean age in years (A) and severe COVID-19 case proportion (B) showing positive associations with mean duration of infectivity in days, among immunocompetent individuals

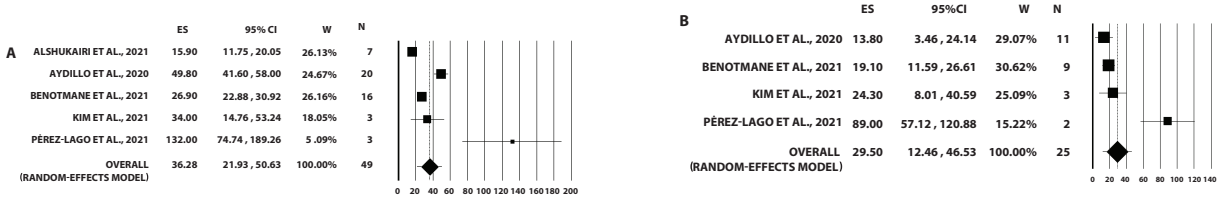

Figure 4. Pooled mean duration in days of viral RNA shedding (A) and infectious virus detection (B) among immunocompromised individuals

culturable virus, indirectly supporting an earlier end of the infectious phase [43-45, 49, 51]. However, effects of aging and COVID-19 severity on the duration of infectivity suggest that these conclusions might not be sufficient for everyone. Particularly, caution should be paid concerning the longer virus viability reported by several studies in subjects with previous severe disease, even after clinical resolution [39, 54].

After complete clinical resolution, the longest contagious period of 18 days post-symptom onset was detected before the 21-day limit provided for by Italian law. Based on this evidence, the "precautionary principle" of further requiring a negative

Table 2. Maximum duration of viral shedding and infectivity in studies with immunocompetent population. When available, details of patients are reported.

Study	Maximum duration of viral shedding (days since symptom onset)	Maximum duration of infectivity (days since symptom onset)
Alshukairi AN et al., 2021	24	11
Basile K et al., 2020	29	18
Bullard J et al., 2020	21	8
Gniazdowski V et al., 2020	51 in severe case (45 in mild case)	22 in severe case, still symptomatic (16 in mild case)
Jeong HW et al., 2020	30 in severe case	15 in severe case
Kim JY et al., 2021	33 in severe case (28 in mild case)	17 in severe case (12 in mild case)
Kujawski SA et al., 2020	36	9
Laferl H et al., 2020*	58	none (first sample was at minimum 19 days after symptom onset)
Li Q et al., 2020*	105	none (two subjects excluded due to age)
Lu J et al., 2020*	46	none (first sample was at minimum 16 days after symptom onset)
Owusu D et al., 2021	38	none (first sample was at minimum 12 days after symptom onset)
Perera RAPM et al., 2020	67	8
Sohn Y et al., 2020*	NA	none (first sample was at minimum 20 days from symptom onset)
Vetter P et al., 2020	19	7
Wang X et al., 2020*	112	none (first sample was at minimum 50 days from symptom onset)
Wölfel R et al., 2020	28	8
Young BE et al., 2020	48	14

Table 3. Maximum duration of viral shedding and infectivity in studies with immunosuppressed population.

Study	Maximum duration of viral shedding (days since symptom onset)	Maximum duration of infectivity (days since symptom onset)
Alshukairi AN et al., 2021	26	16
Aydillo T et al., 2020	78	61
Benotmane I et al., 2021	39	38
Kim JY et al., 2021	47 in a patient with Acute Myeloid Leukemia	44 in a patient with Acute Lymphocytic Leukemia
Pérez-Lago L et al., 2021*	189 in a patient with Follicular Lymphoma on treatment with rituximab	112 in a patient with Follicular Lymphoma on treatment with rituximab-bendamustine

**Studies that specifically included only prolonged viral shedders.*

antigen or PCR test should be overcome and informed with evidence-based decision making. This is not only scientifically sound, but in accordance with the main international public health agencies indicating that a symptom-based, rather than a test-based, strategy for ending isolation and return to work should be preferred for most individuals [18]. Releasing recovered individuals solely based on a non-test-based strategy could potentially introduce still infectious subjects back into the community, increasing the risk of onward transmission; however, several studies have shown that this risk is marginal after 10 days from symptom onset [55, 56]. Moreover, potentially restricting workers for over 3 months can lead to limitations in work ability, with clear consequences from a productive, economic and social point-of-view. Among the population with a weakened immune system, results showed protracted duration of viral shedding and infectivity, particularly among individuals affected by hematological malignancies [48]. Although with conflicting evidence in the literature [57, 58], patients might not be able to control the infection due to impaired B-cell immunity or T-cell impairment, not effectively mounting a robust adaptative immune response or only with a short-term memory response, increasing the risk of becoming chronically infected. The variability of immune responses in terms of efficacy and durability in this group of patients can increase the probability of the emergence of immune-pressure escape mutations [59-61]. Among these patients, the evidence concerning a definite end of infectivity is still not conclusive, therefore the requirement of a negative RT-PCR before return to work, based on the "precautionary principle", is reasonable and could be maintained.

Overall, these data may be absolutely important to inform COVID-19 risk assessment and management in workplace settings. Indeed, Occupational physicians can apply these findings into practice not only when assessing fully clinically recovered individuals before their return to the workplace, taking into consideration each individual's clinical characteristics, treatment and comorbidities, but also in better evaluating and managing the possible residual biological risks, with the goal of protecting the health of the overall workforce, while assuring a suitable re-opening of businesses and industries.

To the Authors' knowledge, this systematic review and meta-analysis is the first to specifically study and synthesize the shedding and infectious duration among the working age population infected with SARS-CoV-2, with the goal of providing updated evidence for the early and safe return to work of affected workers. The strengths of this study comprise of the comprehensive and rigorous methodological approach adopted in the literature search and study quality assessment, the definition of the infectious period as the duration of viral culture on Vero E6 cells, considered as the reference standard for the detection of replication-competent virus [16], and the focus on the possible implications that this information may have on relevant occupational health outcomes. However, this study presents some limitations as well: firstly, few high quality studies have assessed the infective period among immunocompromised working age individuals, with fewer specifying the immunosuppressive treatments adopted (e.g., dose and duration of corticosteroid treatment, treatment with biologics such as tumor necrosis factor - alpha (TNF-α) inhibitors or B cell–depleting agents such as anti-CD20 monoclonal antibodies), resulting in a limited pooled sample size and subsequent reduction in the generalizability of the findings. Furthermore, the quantitative analysis identified substantial heterogeneity, suggesting ample differences between included study populations, particularly in the clinical characteristics and the settings of the included patients, the variability of laboratory methods concerning timing and sensitivity of testing [16,62]. Finally, the conversion of durations from median and interquartile ranges to means and standard deviations, required by the meta-analysis, might have introduced further imprecisions, although appropriate strategies were implemented to reduce this error. Further studies improving on these limitations are needed in order to conclusively define the infectious period of this communicable disease, particularly in light of the possible effect of COVID-19 vaccinations and the emergence of more transmissible variants of concern.

Conclusions

This systematic review with meta-analysis provides detailed information on the duration of viral shedding and infectivity in the working age population. Infectious potential was detected for shorter intervals compared to RNA shedding, and, among immunocompetent cases after clinical resolution, no infective case has been reported after 18 days from symptom onset. These findings suggest that, in this group of subjects, the test-based strategy before return-to-work might not be warranted after 21 days, but on the opposite could keep many workers out of occupation, reducing their livelihood and productivity. Conversely, for immunocompromised workers, the test-based strategy could be useful in reducing the risk of introducing a possible contagious individual in the workplace. This information could be used by both occupational health professionals and policy makers in the development of updated recommendations, and in the implementation of appropriate preventive policies, preserving a safe and healthy workplace.

Supplementary Materials: The following are available in the online version: Figure S1: Forest plot of pooled mean duration in days of viral RNA shedding among all included studies; Figure S2: Funnel plot for duration of viral RNA shedding among all included studies; Figure S3: Forest plot of pooled mean duration in days of viral infectivity among all included studies; Figure S4: Funnel plot for duration of viral infectivity among all included studies; Figure S5: Funnel plot for duration of viral RNA shedding among immunocompetent subjects; Figure S6: Funnel plot for duration of viral infectivity among immunocompetent subjects; Figure S7: Funnel plot for duration of viral RNA shedding among immunocompromised subjects; Figure S8: Funnel plot for duration of viral infectivity among immunocompromised subjects.

Declaration of Interest: The authors declare no conflict of interest.

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Appendix A: Search strategy and critical appraisal of included studies

Search strategy	Details
Search query	("SARS-CoV-2"[All Fields] OR "COVID-19"[All Fields]) AND ("infectiv*"[All Fields] OR "infectious*"[All Fields] OR "contagious*"[All Fields] OR "transmiss*"[All Fields] OR "live virus"[All Fields] OR "viable virus"[All Fields] OR "viral cultures"[All Fields]) AND ("shedding"[All Fields] OR "PCR positive"[All Fields] OR "viral clearance"[All Fields])
Databases	PubMed/MEDLINE, Scopus, Web of Science, ProQuest, IngentaConnect, Nature Journals, BioMedCentral, ScienceDirect, DOAJ
Time filter	December 1, 2019 - September 10, 2021
Language filter	English and Italian
Inclusion criteria	P (population): working age population (15-64 years) I (intervention): duration of viable SARS-CoV-2 detection/growth on Vero E6 cell cultures, since symptom onset C (comparator): duration of SARS-CoV-2 shedding detected by RT-PCR on respiratory samples, since symptom onset O (outcome): definition of COVID-19 infectious period Study type and design: primary research, all study designs
Exclusion criteria	Studies not matching the defined PICO criteria; studies on pediatric population; studies on geriatric population; animal studies; reviews; editorials; comments; case-reports; case series with less than 3 included cases

Critical appraisal of case-series studies included in the present systematic review and meta-analysis.

Study	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Domain 8	Domain 9	Domain 10
Alshukairi AN et al., 2021	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
Aydillo T et al., 2020	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
Benotmane I et al., 2021	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes
Jeong HW et al., 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	No	Yes
Kujawski SA et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pérez-Lago L et al., 2021	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
Vetter P et al., 2020	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
Wölfel R et al., 2020	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes

Critical appraisal of cross-sectional studies included in the present systematic review and meta-analysis.

Study	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Domain 8
Basile K et al., 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Bullard J et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim JY et al., 2021	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Lu J et al., 2020	Yes	Yes	Yes	Yes	No	No	No	Yes
Sohn Y et al., 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Critical appraisal of cohort studies included in the present systematic review and meta-analysis.

Study	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Domain 8	Domain 9	Domain 10	Domain 11
Gniazdowski V et al., 2020	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Laferl H et al., 2020	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Li Q et al., 2020	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes
Owusu D et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Perera RAPM et al., 2020	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Wang X et al., 2020	Yes	Yes	Yes	No	No	Unclear	Yes	No	No	No	Yes
Young BE et al., 2020	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes