Distress and Psychological Impact of Covid-19 Pandemic and Previous Outbreaks Review and Methodological Suggestions

Research Article

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Abstract

The current worldwide outbreak of the novel coronavirus Covid-19, originated from Wuhan (China), has spread to 6 continents, 213 countries and territories around the world. This paper aggregates and consolidates the state of the art about Sars Cov2 virology, molecular genetics, immunology, pathogenicity, epidemiology, explores the concept of crisis and psychological effects on population by the ongoing 2020 Covid-19 outbreak crisis vs previous pandemic impacts. The detailed description of this public health threat highlights the great uncertainty surrounding it. Uncertainty and confusion can amplify the psychological impact of this event on the general population. Results are summarized and discussed. Methodological suggestions are provided for studies aimed at investigating psychological effects of critical catastrophic and unexpected life events, such as a pandemic. The analyzed aspects have implications for healthcare professionals in their efforts to promote the psychological well-being of general population during critical unexpected events.

Keywords: CoVid-19, Pandemic, Psychological Impact, Distress.

Introduction

The present worldwide outbreak of the novel coronavirus Covid-19 (coronavirus disease 2019; pathogen: SARS-CoV-2) emerged in Wuhan (China) and has now spread throughout 6 continents, 213 countries and territories around the world, that have reported a total of 9,228,526 confirmed cases, and a death toll of 475,123 deaths (this information includes reports as of 24:00 on June 21st, 2020). COVID-19 epidemic can be considered a global health threat [1]. It has been described as the major outbreak of atypical pneumonia since the severe acute respiratory syndrome (SARS) in 2003. The number of cases and deaths quickly exceeded those of SARS [2, 3].

This work provides a detailed description of this public health threat and explores the distress response and psychological impact of recent epidemics (rare, unpredictable and disruptive events) on general population. The detailed description of COVID-19 highlights the great uncertainty surrounding this new disease. Uncertainty and confusion may play an important role in amplifying the psychological impact of this event on general population.

Coronaviruses (CoVs), a large family of single-stranded RNA viruses, can affect animals and humans, producing disease in tissues and organs [4]. CoVs are divided into genera alpha - coronavirus, beta - coronavirus, gamma-coronavirus and delta - coronavirus[5]. CoVs have been identified in several animal hosts [6, 7] all around the world. Six human coronaviruses have been identified: the alpha-CoVs HCoVs-NL63 and HCoVs-229E; the beta-CoVs HCoVs-OC43; the SARS. CoV, causative agent of the severe acute respiratory syndrome SARS [8]; the MERS-CoV, ethiologic agent of Middle East respiratory syndrome MERS [9]. CoVs phylogeny is very old, according to actual and stem natural reservoir animals, and a long host adaption period (25-50 million years) made most of them minor pathogens: they commonly affect hosts mildly or not at all. Also new mammalian CoVs are identified [10]. For example, a HKU2-related coronavirus of bat origin was responsible for a fatal acute diarrhea syndrome in pigs in 2018 [11]. Novel CoVs emerge also in humans, probably due to the worldwide distribution of CoVs and their ability to adapt viral genome to new hosts [12].

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COVID-19 etiologic agent: SARS-CoV-2

A novel Coronavirus is the causative agent of COVID-19. It has been isolated in patients' fluids and cells and its genoma has been fully sequenced [13]. The new virus was named SARS-CoV-2 (Severe Acute Respiratory Syndrome - Coronavirus - 2) and classified in the subgenus Sarbecovirus.

It has been hypothesized that SARS-CoV-2 may have been spread to humans through intermediate hosts, such as bats [14], though the actual route of transmission is still debatable.

Coronaviridae family viruses have a single-strand, positive-sense RNA genome ranging from 26 to 32 kilobases in length [15].

The new virus is more similar to two bat-derived coronavirus strains, bat-SL-CoVZC45 and bat-SL-CoVZXC21, than to any other known human-infecting coronaviruses, including the virus that caused the SARS outbreak of 2003. Nevertheless, although, SARS-CoV-2 is closer to bat-SL-CoVZC45 and bat-SL-CoVZXC21 at the whole-genome level, its receptor - binding domain falls within lineage B and is closer to that of SARS-CoV, enabling it to recognize and link the human ACE-2s receptors and fuse straightforward with cell membrane. The receptor-binding domain of SARS-CoV-2 is its most relevant spill over mutation [13]. The SARS-CoV-2 human pathogenicity relies mainly upon this mutated receptor-binding domain.

As above mentioned, the phylogenetic analysis showed that bat-derived coronaviruses fell all within subgenera of the genus beta-coronavirus. Additionally, bat-derived coronaviruses fell in basal positions in the subgenus Sarbecovirus [16]. The previous data are consistent with a bat reservoir for coronaviruses, according to common RNA viruses and bats CCS (Critical Community Size) [17], and in particular for SARS-CoV-2. However, the role of bats as reservoir by itself cannot provide full satisfactory evidence for the acquisition of the mutated receptor-binding domain. Another peculiarity of SARS-CoV-2 genome is the presence of a RNA-dependent RNA polymerase out from ancient negative-strand RNA virus bat gene [18]. Otherwise inexplicable, this suggested that at least another source acted as an intermediate host between bats and humans.

Mutagenecity of SARS-CoV-2

As a typical RNA virus, SARS-CoV-2 shows its particular spontaneous mutagenicity. The average evolutionary rate for coronaviruses is roughly 10^{-4} nucleotide substitutions per site per year, with mutations arising during every replication cycle [15]. It is remarkable that the sequences of SARS-CoV-2 from different patients described during the emerging outbreak in Wuhan were almost identical, with a sequence identity greater than 99.9%[13].

This finding suggests that SARS-CoV-2 originated from one only source, within a very short period, and was quickly detected.

The reservoir and spillover of SARS-CoV-2

Mass media delivered the news that SARS-CoV-2 started in a wildlife market in Wuhan. Nevertheless, the source of the virus (an animal carrying this pathogen in its body) has not been identified so far, either in the market or somewhere else.

Two groups of coronaviruses related to the virus behind the human pandemic have been identified in Malayan pangolins smuggled into China [19], but none of these suspect species has been definitely shown to be involved in this outbreak [20].

Bats also host coronaviruses [17], which are even closer to the human virus, except in one genoma key area - the part that enables the virus to invade cells [10, 13].

The outbreak of SARS-CoV-2 was reported for the first time in late December 2019. During this season most bat species are hibernating in Wuhan. No bats were found at the Huanan market [13]. The sequence identity between 2019-nCoV and its close relative bat-SL-CoVZC45 and bat-SL-CoVZXC21 was less than 90%, which is reflected in the relatively long branch between them. Hence, bat-SL-CoVZC45 and bat-SL-CoVZXC21 are not direct ancestors of SARS-CoV-2 [13].

In Xiao et al.'s study [19], one coronavirus isolated from a Malayan pangolin showed high levels of amino acid identity with SARS-CoV-2 in the E, M, N and S genes (respectively, 100%, 98.6%, 97.8% and 90.7%). The receptor-binding domain within the S protein of the Pangolin-CoV is very similar to that of SARS-CoV-2, with one noncritical amino acid difference. According to the authors, results of comparative genomic analysis suggested that Covid-19 may have emerged from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus [19].

Nevertheless, to stay with the SARS-CoV example, it has been described that few alterations in the SARS-CoV spike protein, compared to related bat CoV, enabled binding to its host receptor ACE-2 and thus became capable of infecting humans [21]. All SARS-like-CoV viruses so far detected in bats lack these alterations and are, therefore, not predictable in their capacity of infecting humans [21]. At the nucleic acid level, the different function of proteins is key for the host range, even though strains might appear similar: the similarity is not enough to analyze viruses' potential to spill over and infect humans or to predict their virulence [18].

Regarding the hypothesis of a pangolin acting as the intermediate host needed to let the SARS-CoV-2 spill over to infect humans, the acquisition of its mutated receptor-binding domain cannot be explained by similarity, it has not been demonstrated, nor found in pangolin genetics [22]. Stem pangolins and bats shared the same habitat for ages, for over 30 million years [23]. In such a long time, a cross-host evolution of coronavirus, suggesting a rapid evolving process of viral proteins, in bat [10] and pangolin as well, has not been detected. Major genetic variations in some critical genes, particularly the spike genes, essential for the transition from animal-to-human transmission to human-to-human transmission, much like their adaptation in the human host [24], have not been reported yet.

Epidemiology and pathogenicity of SARS-CoV-2

According to the WHO [3], SARS-CoV-2 human-to-human transmission has been observed via virus-laden respiratory droplets. The average incubation period is estimated to be 5.2 days (3-20 days), with significant variation among patients and spread from

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asymptomatic patients is admitted [25]. The most frequent symptoms of infection include fever, chills, cough, diarrhea; coryza, breathing difficulty, fatigue, myalgia, nausea, vomiting are also reported. Other unusual symptoms include neurological syndromes (e.g.confusion, stroke and seizures) diminished sense of smell (anosmia) and taste (ageusia), heart and coagulation ailments [26]. Coronavirus hits females more than men: gender ratio 1.2-1.6 [27]. Older men with medical comorbidities are more likely to get infected, with worse outcomes. Severe cases can lead to cardiac injury, respiratory failure, acute respiratory distress syndrome, disseminated intravascular coagulation and death. The provisional case fatality rate by WHO is around 2%, but some researchers estimate the rate to range from 0.3% to 0.6% [3].

Aspects of immunity of SARS-CoV-2

SARS-CoV-2 is an obligate intracellular parasite: it does not live outside the cell but can keep its infecting ability in environment [3]. In the host extracellular viruses may be removed by humoral and cellular mechanisms, but the intracellular replicative steps of coronaviruses and virus-infected cells-that (or if) they have developed virus specified antigens on their surface-are the major targets for the host immune response. The infectious virions spread [28] via extracellular spread (released from the infected cell in the extracellular fluids and then eventually outside the host); intercellular spread (spread from cell to cell through cell fusion, without contact with the extracellular environment) [29]; vertical spread: the viral genome becomes integrated into the host genome and is passed from parent cell to progeny during meiosis. In this latter case many or all virus antigens are absent on the cell surface, so that the virus is undetectable by the host. The retroviruses genes usually adopt this mechanism.

In the host SARS-CoV-2 spread occurs both at a local level (mucosal surface or organ) or via the bloodstream, with subsequent dissemination through all organs.

SARS-CoV-2 spread mechanisms may limit exposure of extracellular virus to humoral or cellular host defense mechanisms. Moreover, virus serologic variants evolve, with minimal cross-reactivity among them. Camouflage and latency mechanisms in SARS-CoV-2 require further investigation [30]. These mechanisms could also enable a long or indefinite persistence of the SARS-CoV-2 in the host, with minimal or no clinical evidence, similarly to what happens for other viruses.

The COVID-19 pandemic and the lockdown

On March 11th, 2020, the WHO, declared COVID-19 a pandemic, considering that more than 118,000 cases had been detected in over 110 countries and territories and the risk of further global spread.

The WHO defines a pandemic [3] as the "worldwide spread of a new disease", though the specific threshold for meeting that criteria is not always obvious. The term was most often applied to new influenza strains, and the CDC affirms it is used when viruses "are able to infect people easily and spread from person to person in an efficient and sustained way" in multiple regions. The declaration refers to the spread of a disease, rather than the severity of the illness it causes.

In order to retard the spread of the virus, a lockdown was imposed in several countries: school were closed and the lockdown was extended to all non-essential activities. Many citizens have remained at home for various weeks, socially isolated, with important economical and psychological consequences. Previous research has revealed a wide range of psychosocial impact on people during outbreaks of infection. Individuals are likely to experience fear of becoming ill or dying, helplessness, and stigma [31].

Negative emotions are likely to appear with the shutdown of schools and business activities [32]. For instance, during the SARS disruption, several studies researched the psychological impact on the healthy community and significant psychiatric symptoms were found [33].

Additional considerations in the definition and concept of crisis

A crisis may be defined as a very " "rapid change (...) that provides an individual with a 'no exit' challenge (...) to alter her or his conduct in some manner" " [34]. A crisis is a physiological emergency and acts on the individual as the deprivation of oxygen. The concept of crisis is very influential in community mental health and preventive modalities of care. The term crisis comes from the Greek word"κρίνω", which means "to decide". The term is used to describe a point in the course of a disease, or an event during the life course, which is decisive for either recovery or death. The term means a critical turning point in the progress of some state or condition in which a decisive change, for better or worse, is essential and about to happen. The idea of a change can lead the individual to think and act differently, according to her/his relationship to the problem and implies an ability to cope with the distress. Additionally, a crisis is precipitated by a situation that disturbs prior adaptation. Theorists [35, 36, 37] postulate some essential features of a crisis. First it is a stressful or dangerous event requiring change: a hazardous life event. Hazardous or stressful life events can be classified as expected or unexpected. Unexpected events are those whose timing cannot be predicted. The possibility to consider any preventive action or position facing a crisis relies upon its features. A second characteristic of a crisis depends on the way the new problem affects the individual on her/his life: material and physical integrity (health), psychological resources, her/his family, social context or any other person who might play a role in the individual social support network.

The impact of life events and stressors on psychological health

Investigations focusing on personal life events of otherwise ordinary people, undergoing some kind of situational crisis, evidenced a higher than expected incidence of disorders [38, 39]. Holmes and Rahe [40] and Rade et al. [41] recognized that different events required different change and adaptation, affecting more or less each individual. In the following studies the term life event emerged and has been commonly used.

During an unexpected worldwide crisis, such as a pandemic, which leads several countries in the world to adopt extreme measures to contain the contagion, the exploration of distress response and psychological impact of this event on general population plays an important role in preventing psychological health emergencies, originating during or soon after the public health crisis. To this aim, our review focuses not only on the few data on psychological

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impact of the current pandemic, but also on the results of studies exploring distress and psychological symptoms in people of affected countries during previous outbreaks. These data may have important implications for healthcare professionals.

Materials and Methods

In order to be analyzed, the results from descriptive studies must be leaded to common - quantitative (numeric) or qualitative (e.g.categorical, continuous) - shape, able to identify variables and casual roles. Data analysis for any given outcome includes two possibility: univariate and multivariate analyses. Univariate analyses are used to identify individual predictors of the investigated outcome and to establish relationships among the dependent and independent variables. The relationship between categorical outcomes can be appropriately measured using the chi-square test or Fisher's exact test. In case of continuous outcomes (e.g. illness days) the relationship to continuous independent variables (e.g. age) can be assessed by examination of X-Y scatter plots; if that relationship is linear - or amenable to a linear one - it can be quantified using Pearson's correlation. If it is a not linear relationship, the computation must be estimated [42, 43].

It is also very important to plot the data in order to explore any relationships that might exist. According to many published data, in CoVid 19, the plots of death rate and morbidity show monotonic (not linear or not only linear) relationships with associated independent variables as age or time. In a monotonic relationship, the variables tend to move in the same relative direction, but not necessarily at a constant rate. In a linear relationship, the variables move in the same direction at a constant rate. The plot can help to get rid of how the variables move: linear relationships are frequently also monotonic.

We performed a systematic search for the available literature using PubMed, SCOPUS and Web of Science. The following key words were searched: psychological adjustment, psychiatric symptoms, coping, stress, outbreak, epidemic. Papers over the last 15 years (2005-2020) were considered for inclusion. Only studies in English and papers from peer-reviewed journals were included. Studies that included only health workers as participants were excluded. Studies that explored psychological adjustment, coping or stress responses without relating the concepts to epidemics were also excluded.

Results

We identified 22 studies from the database search, of which 9 were included in the review. Of the 9 included articles 3 were qualitative studies and 6 were quantitative studies. Overall, 4 studies focused on the SARS epidemic, 2 studies examined the Ebola epidemic, two studies covered the H1N1 pandemic and 1 study focused on the COVID-19 pandemic. The results of the different studies are presented below, according to the specific epidemic. The results are also summarized in Tables 1 and 2.

SARS epidemic

Cheng & Cheung [44] designed a prospective, multiple time-point study, assessing trait anxiety and coping flexibility in seventy-two Hong Kong undergraduates, who had been assessed in an earlier

study, five months earlier. They reported their anxiety and coping at four time points during the outbreak, during the four-week study period. Fluctuations in state anxiety were detected across time points. Results from hierarchical linear modeling revealed that trait anxiety and the situation-appropriate coping strategies of avoidance and personal hygiene practice accounted for changes in state anxiety. Trait anxiety assessed 5 months earlier could predict initial levels of state anxiety, but the positive association between trait and state anxiety was only present at the initial time points: individual differences in state anxiety became minimal at the following time points. Situation - specific coping strategies of personal hygiene practice and avoidance could also predict fluctuations in state anxiety: results showed that personal hygiene practice and avoidance played a stronger role in explaining state anxiety. The authors found that individuals who used more avoidance experienced less state anxiety during the four-week period. The authors hypothesized that the use of avoidant strategies, which can be defined as efforts to escape from the stressful event [45], may have had a role in easing anxiety during the outbreak, as SARS outbreak was a stressful event perceived as uncontrollable. Yu and coworkers [46] focused on depressive symptoms and emotional distress before and during SARS outbreak in a sample of Hong Kong midlife women (n=126). As expected, they found higher levels of depressive symptoms and emotional distress during the epidemic. Using logistic regression analysis, the authors identified three factors significantly associated with emotional distress during SARS: feeling scared, restless sleep and financial loss. The latter was the only factor independently related to the increase in stress level. Additionally, personal perception of risk of infection was correlated with psychological distress.

Peng and colleagues [47] explored the post-crisis psychological distress four months after the resolution of the SARS outbreak in Taiwan (n=1278). In particular, the authors explored variables comprised perceptions and attitudes towards SARS, behavior and SARS-related experiences and psychological distress. About 9% of the participants reported that their perceptions of life became more pessimistic following the SARS crisis and the prevalence of psychiatric morbidity was around 11%. The authors found a number of major predictors of higher levels of pessimism after the SARS outbreak: demographic factors, perception of SARS and preparedness, knowing people or having personal experiences of SARS-related discrimination, individual worries and psychiatric morbidity.

Main and colleagues [48] analyzed SARS related stressors (participants' experience of SARS-related stressful events, such as having had a family member suspected of having SARS) coping strategies, psychological symptoms, perceived general health and life satisfaction in a sample of 381 undergraduate students recruited from universities of Beijing (China). As hypothesized by the authors, experience of SARS-related stressors was positively associated with psychological symptoms. Participants' use of avoidant and seeking social support coping positively predicted psychological symptoms, while active coping positively predicted life satisfaction. Additionally, significant interactions between coping and stressors, able to predict perceived general health, were detected for the three coping strategies (active, avoidant, and social support seeking coping).

The authors found a stress buffering effect of coping: notwithstanding the type of coping, the number of SARS-related stress-

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Table 1. Details of the studies included in the review (year of the epidemic, epidemic, country, investigated variables, instruments, sample size and gender distribution).

Paper	Year of the epidemic	Epidemic	Country	Variables	Instruments	N	Males
Cheng &Cheung,, 2004	2003	SARS	Hong Kong	Anxiety; coping responders; Situation-specific coping strategies.	State-Trait Anxiety Inventory; Coping Flexibility Inventory; ad-hoc questionnaire assessing strategies for coping with SARS.	72	31
Yu et al., 2005	2003	SARS	12	Depressive symptoms and emotional distress before and during SARS.	Center of the Epidemiological Study of Depression Scale (CES-D) and Perceived Stress Scale (PSS).	126	0
Rabelo et al., 2016	2014-15	Ebola	Liberia	Mental health distress during treatment at Ebola Treatment Unit; Coping strategies to overcome mental health distress in Ebola Treatment Unit; mental health distress after discharge from Ebola Treatment Unit; coping strategies after discharge from Ebola Treatment Unit.	Focus group.	17	8
Schwerdtle, 2017	2014-15	Ebola	Liberia, Sierra Leone.	experiences of Ebola survivors (causes of distress, sources of resilience).	Semi-structured interview.	25	0
McCauley et al., 2013	2009	H1N1	United States, New England.	psychological processes of cue convergence and associative priming; stress and coping.	Focus group.	46	17
Taha et al., 2014	2009	H1N1	Canada	H1N1 experience; intolerance of uncertainty; Appraisal of ambiguous situations; stress appraisal measure; Self-evaluation questionnaire / state anxiety.	Ad-hoc questionnaires; The stress appraisal measure; State-Trait Anxiety Inventory.	316	59
Main et al., 2011	2003	SARS	China	SARS related stressors, coping strategies, psychological symptoms, perceived general health, life satisfaction.	Ad hoc checklist measure to assess participants' experience of SARS-related stressors; Nine subscales from the Coping Inventory; 90-item Symptom Checklist (SCL–90); Ad hoc single-item self-rating of perceived healt; The 5-item Life Satisfaction Scale.	381	162
Peng et al., 2010	2003	SARS	Taiwan	Perceptions and attitudes towards SARS; Behavior and SARS-related experiences; Psychological distress 4 months after SARS epidemic resolution.	Ad hoc questionnaires; a single question related to participant's change in perception of life plus the five-item Brief Symptom Rating Scale (BSRS-5).	1278	643
Wang et al., 2020	2019-20	COVID-19	China	physical symptoms; contact history with COVID-19; knowledge and concerns about COVID-19; precautionary measures against COVID-19; additional information required with respect to COVID-19; the psychological impact of the COVID-19 outbreak; mental health status.	Ad-hoc questionnaires; Impact of Event Scale-Revised (IES-R); Depression, Anxiety and Stress Scale (DASS-21).	1210	396

ors was positively associated with perceived general health only at low levels of coping. The authors commented on this result hypothesizing that when stressors are large-scale and perceived as severe and out of control, any type of coping could be helpful in reducing distress.

H1N1 outbreak

McCauley and colleagues [49] performed an exploratory qualitative study on the psychological processes of the associative priming, through which many people likely merged the news of the H1N1 epidemic with prior cognitive scripts that blamed Latino immigrants for various social problems. The authors used a transactional model of stress andcoping to analyze the transcripts from focus groups, in order to examine the ways in which a group of American residents evaluated the H1N1 threat, processed information about stereotypes and stigmas and developed individual strategies to cope with these stressors. Participants in all focus groups reported similar processes of stress and coping in reaction to H1N1 threat; individual responses varied by ethnicity. This study highlighted some of the ways in which epidemics can be relevant sources of individual and social stress. Ilness-related stress

Table 2. Statistical methods and quantitative results.

Paper	Statistical method	Quantitative results (when where as available)
Cheng & Cheung, 2004 - SARS	Hierarchical linear modeling	20% of the variance in state anxiety over time was attributable to interindividual differences, 80% of the variance was attributable to intra-individual differences across time points. This result indicates that the state anxiety reported by participants varied across the 4-weeks period. The test statistic for the linear model against the baseline model was w2(3) 5 24.07, p <.001, whereas the test statistic for the quadratic model against the linear model was w2(4) 5 40.78, p <.001.
Yu et al., 2005 - SARS	Univariate analysis: ANOVA p Value; binary logistic regression	Factor associated with the mild depression and emotional distress OR positively related to "Felt scared" and "Financial losses", p< .05.
Rabelo et al., 2016 - EBOLA survivors	Qualitative study	--------
Schwerdtle 2017 - EBOLA survivors	Qualitative study	--------
McCauley et al 2013 - H1N1	Qualitative study	--------
Taha et al 2014 - H1N1	Descriptive statistics; Pearson correlations; Hierarchical regression analysis	Stressfulness increases according to appraisals of ambiguous life events and less to appraisals of viral threat. Pearson correlations among stressfulness of life events, anxiety and intolerance to uncertainty are evidenced, p <.01.
Main et al.,, 2011 - SARS	Zero order correlations; Descriptive statistics; Multiple Regression analyses	The relations of stressors and coping suggested that the number of stressors and use of avoidant coping strategies positively predicted psychological symptoms, p <.01. Support seeking behaviors positively predicted psychological symptoms, p <.001.
Peng et al 2010 - SARS	Descriptive statistics; Multivariate logistic regression	Age equal or > 50, perceived survival rate have been quaranteened and education level positively correlated to higher score in OR for psychiatric morbidity (prevalence 11.7%).
Wang et al 2020 - COVID-19	Descriptive statistic; Percentages of response; Linear regression	Associations between demographic variables and psychological impact of COVID-19 were investigated. Associations were found present between all independent and dependent variables, p <.05 - .01.

was shown to lead to the stigmatization of marginalized social groups, as well as to anxiety about personal and family health and to troubles in working and social relationships.

A different study on H1N1 outbreak was developed in Canada. In the spring following the H1N1 peak, when the pandemic was visibly diminishing, but vaccination was still available, Taha and coworkers [50] analyzed H1N1 experience, uncertainty intolerance, ambiguous situation appraisal, stress appraisal and anxiety in a sample of 316 adults. The participants were presented with several scenarios regarding viral threats. They reported moderate anxiety, regardless of the specific viral threat (familiar vs. unfamiliar), considered the threats moderately stressful and believed that they would have control in this situation. Nevertheless, high levels of anxiety accompanied the viral threat in individuals with high intolerance of uncertainty, with the mediation of appraisal aspects (i.e. control and stressfulness). Additionally, participants used to appraise ambiguous life events as stressful, the viral threat appraisals were accompanied by even higher levels of anxiety.

Ebola outbreak

The studies on Ebola emerged from our bibliographic research were both focused on Ebola survivors. Rabeloet al. [51] analyzed mental health distress during treatment at a Liberian Ebola Treatment Unit (ETU), coping strategies to overcome mental health distress in ETU and mental health distress after discharge from ETU in a qualitative study. Using focus group technique, the authors found that post traumatic stress reactions and symptoms of depression were common among the Ebola survivors exposed to death in the ETU and stigma in the communities. The main stressors during the hospitalization were the daily exposure to corpses, the patient's isolation from family and worries about his/her well-being; sometimes, also the perception of disrespect by

ETU staff could generate relevant distress. The support of family, friends, and prayer, when available, allowed the survivors to cope with their psychological distress. Psychosocial counseling and the survivor's network helped those excluded from society, because of the stigma and fear of contagion, give a meaning to life after Ebola.

Causes of distress and sources of resilience were the focal points of Schwerdtle and colleagues' study [52]. Using focus group, they involved 25 participants in Liberia and Sierra Leone and identified two main themes: "causes of distress" and "sources of resilience." Each main theme comprised two further sub-themes, respectively: the "multiplicity of death," "abandonment," "self and community protection and care" and "coping resources and activities."

Covid-19 pandemic

A recent study investigating psychosocial impact of SARS-CoV-2 in Chinese population found that, during the initial phase of the COVID-19 outbreak, 53.8% of the respondents (n=1210) rated the psychological impact of the outbreak as moderate-to-severe, 28.8% reported moderate - to - severe anxiety, 16.5% reported moderate to severe depressive symptoms and 8.1% reported moderate to severe stress levels [53]. Most respondents were worried about their family members contracting the virus (75.2%). Female gender, student status, specific physical symptoms and poor self-rated health status were significantly associated with a greater psychological impact ofthe outbreak and higher levels of stress, anxiety, and depression. Specific up-to-date and accurate health information and particular precautionary measures were associated with a lower psychological impact of the outbreak and lower levels of stress, anxiety, and depression.

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Discussion

The descriptive or observational studies that investigate distress and psychological symptoms in general population during epidemics have focused on very different variables and used varied study designs, leading to mixed results.

The uncertainty produced by an unexpected, uncommon and threatening event, such as an epidemic, may play an important role in modulating the distress and psychological response of general population.

Higher levels of depressive symptoms and emotional distress [46] and fluctuations in state anxiety [44] have been highlighted during the outbreaks.

Moderate to severe psychological impact related to the outbreak and anxiety seems common [53], whereas less participants reported moderate to severe depressive symptoms stress levels.

It is not easy to analyze these variables in a sudden outbreak condition, because of the lack of previous time points analyses, before the beginning of the epidemics. This may suggest the importance of continuous monitoring of psychological parameters in samples from general population, in order to have a baseline in case of unexpected events which may put general psychological health at risk.

Many of the studies considered in this work analyze the factors which may have a role in mediating the effect of stressors on individual psychological well-being.

Feeling scared, restless sleep and financial loss were associated with emotional high stress during SARS [46], experience of SARS-related stressors was positively associated with psychological symptoms and use of avoidant and seeking social support coping positively predicted psychological symptoms [48]. Nevertheless, coping had a stress buffering effect: notwithstanding the type of coping, the number of SARS-related stressors was positively associated with perceived general health only at low levels of coping [48].

Uncertainty tolerance has also an important role: individuals with high intolerance of uncertainty have been shown to be more likely to appraise a virus as being more stressful and less controllable and to experiment high anxiety, whereas an optimism bias seems to protect most individuals from feeling anxious about new hypothesized viral threats [50].

Epidemics can increase not only individual, but also social stress: as McCauley and colleagues [49] showed in their study on H1N1 epidemics, illness-related stress can lead to the stigmatization of marginalized social groups, to anxiety about personal and family health and to troubles in working and social relationships.

The condition of survivors who have experienced the illness appears quite different from that of general population, as the studies about ebola epidemics showed: the support of family, friends, prayer, psychosocial counseling had an important role for the survivors to cope with their psychological distress [51]. Multiplicity of death and abandonment were the main causes of distress, whereas self and community protection and care and coping resources and activities were the key aspects for resilience according to Schwerdtle and colleagues' study [52].

The need to find and to measure the relationship between multiple variables, a feature common to the aim of all the studies analyzed in this review, is the basis of the type of analysis most frequently used by researchers.

The analysis of variance or multiple regression procedure is in fact the most commonly used quantitative approach to observe the behavior of a dependent variable X which is identified on the basis of the nature of the phenomenon being studied. It is worth to summarize some considerations about this type of statistical analysis methodology.

The relationship that link a dependent variable X_1 to the other variables X_2, X_3, ..., X_n (independent variables or regressors) expresses the way in which X_1 varies with the change of the other variables. The factors that can affect X_1 are many and not all quantifiable. For this reason, it is essential to select, for the analysis purposes, only the regressors that are truly relevant for the research purposes. There will therefore be factors (known and unknown variables) excluded from the selection, and all of these are collected in one common variable, indicated with the Greek letter ε, as in equation 1.

All the studies analyzed show - in some way - the role that different circumstances - stressors or life events - played in determining the stress / crisis effect. The stressors are the independent variables (X_n) and the crisis the dependent variable X_1. The relationship that links to each other is represented by function 1, which describes the law of dependence, and is noted in the form(1):

$$X_1 = f(X_2, X_3, ...,X_n, \varepsilon). \tag{1}$$

The trend of the function of X_1 in equation 1 is crucial to understand the relationship between the variables that represent the facts. The regression coefficient would be unique if X_1 depended only on one variable (X_2), it would be indicated by the Greek letter β, and the equation would be written as follows (2):

$$X1 = \beta_1 + \beta_2 X_2 + ...\beta_n X_n + \varepsilon \tag{2}$$

However, the number of experimental observations (both known and unknown) can often be greater than the number of parameters and an estimate able to cumulate many regression coefficients must be obtained according to the experimental data, these based on the samples. It is indicated with the Latin letter b, and the equation is transformed as follows (3):

$$X_1 = b_1 + b_2 X_2 + ... b_n X_n + \varepsilon \tag{3}$$

The choice of variables must be accurate enough to verify the need to include in the equation only the variables that, when their value changes, provide a factual contribution to the variation of the dependent variable X_1. An increase in the number of variables enclosed in the regressive analysis does not consequently increase the efficiency of the analysis itself.

The selection of which variables to insert has, therefore, the crucial role in the analysis results. There are procedures to conduct

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this choice in the most correct way, starting either from the significance of each single regression coefficient, discarding the less significant ones (backwards procedure), or by selecting as the first independent variable the one that has the highest simple correlation coefficient with the dependent variable X_1, until finding the highest correlation coefficient between variables (onward procedure) until there are no more variables to insert or remove. For a complete discussion of these techniques, see their detailed statistical description [54].

There is no perfect method for choosing variables, more than ever during the exploratory phase of a study, and practical decisions need to be made. Sometimes some variables do not show significant partial regression coefficients, but have a relevant logical significance, and so must be maintained. In other case variables must be removed which have a high significance of their partial regression coefficient but would not have any logical sense.

The discussion conducted so far has to be applied during the design phase of any research that intends to provide a concrete contribution to the eventuality and strength of a relationship between active factors in producing psychological effects and measures of the investigated effect itself.

Highlighting and measuring the possible relationship between stressors or life events and crisis conditions or psychopathological effects, requires the careful selection and clear measurement of the characteristics and dimensions of the variables under investigation for - and only for - the purpose of the condition towards which the effect of this relationship is supposed to operate.

This review suggests that future research on the correlation between stressful events and psychopathological consequences - like any correlation research that uses regressive analysis - should always be preceded, since its planning and design phase, by the selection and quantitative validation of independent variables to select, in order to avoid uncertainty or biased conclusions.

The analyzed aspects also have important implications for healthcare professionals: a particular attention should be paid to the promotion of psychological well-being of general population during critical and unexpected events. Available public psychological healthcare may help prevent the development of more serious psychopathological symptoms after the outbreaks are over.

For future research, it may be important to carry out follow-up studies to measure the effects over time, since it is reasonable that after a period of time has passed from the start of the outbreak different re-adaptation responses may appear.

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