Can early home administration of azithromycin with zinc help prevent severe COVID-19 disease progression and long-COVID?

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Abstract

Introduction

The effects of the SARS-CoV-2 pandemic continue to disrupt health systems worldwide, leading to population lockdowns in many countries. Preventing hospitalisation, death and long-COVID with repurposed drugs remains a valuable research goal. To respond to this priority, the use of azithromycin (AZM) is one of the most common treatments worldwide, in combination with hydroxychloroquine (HCQ) or as standalone molecule. With the aim of decentralizing early treatment to family practitioners, we address the question: *Can early home administration of AZM with zinc help prevent severe COVID-19 disease progression and long-COVID*?

Methodology

We conducted a scoping review of articles published from 31 December 2019 to 5 November 2020 in the PubMed, Google Scholar, MedRxiv, and BioRxiv databases, and a review of ongoing clinical trials published in the Clinicaltrial.gov database.

Results

Many studies report on outpatient treatment with a combination of AZM + HCQ versus AZM alone, and a few studies propose the addition of zinc (Zn) to AZM. Studies using HCQ were not considered in this review. We failed to identify any study reporting results of home-based utilisation of AZM administrated by family practitioners. In addition, we identified seven

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clinical trials currently recruiting individuals for early outpatient treatment with AZM, but results have not yet been published.

Discussion

The antiviral, anti-inflammatory, immunomodulatory benefits of AZM + Zn make this drugs combination a good candidate therapy to treat flu-like COVID-19 and atypical pneumoniae. The antibacterial action of AZM is expected to disrupt the poorly-documented bacteria-virus cooperation. Considering the pros and cons of macrolide use (including antimicrobial resistance), we call for further research on the early use of this therapy by family practitioners for the home treatment of individuals presenting mild or moderate symptoms to prevent hospitalisation, death and long-COVID.

Keywords: COVID-19; azithromycin; early treatment; family practitioners

Introduction

The novel SARS-CoV-2 belongs to the *Betacoronavirus* family and contains a single-stranded positive-sense RNA genome. Similar to the two other coronaviruses, SARS-CoV-1 and MERS-CoV, SARS-CoV-2 is also likely to have originated in bats, which serve as established reservoirs for various pathogenic coronaviruses [1]. Although it is still unconfirmed, the most commonly admitted hypothesis suggests that SARS-CoV-2 is transmitted from bats to humans via an unidentified intermediate host species (zoonotic transmission). Then, the rapid human-to-human transmission through airborne aerosols occurs, which has been confirmed widely. The first case of COVID-19, which is the disease caused by SARS-CoV-2 [2], was reported in the province of Wuhan, China, on 7th January 2020. On 30th January, following the recommendations of the International Health Regulations (2005) Emergency Committee, the General Director of the World Health Organization (WHO DG) declared the outbreak a Public Health Emergency of International Concern (PHEIC)[3]. At that time, there were 7,818 reported confirmed cases, out of which 7,736 were in China and 82 were in 18 other countries [4]. On 9th March, the WHO DG declared that 'the threat of a pandemic has become very real'. As of 5 November 2020, over 48 million confirmed cases and 1.2 million deaths had been reported by the World Health Organisation in 215 countries, with high disparities among regions and countries and even at the sub-national level. At that date, the five most affected countries (classified by total number of reported deaths) were the USA, India, Brazil, Russia, and France.

In the absence of effective treatment, only reinforced prevention coupled with early treatment of coinfections with repurposed drugs can disrupt viral transmission. Azithromycin [5], a macrolide antibiotic with antiviral, anti-inflammatory, and antibacterial properties has appeared as a valuable treatment candidate. We reviewed studies published from 31 December 2019 to 5 November 2020 addressing the question: *Can early home administration of AZM with zinc help prevent severe COVID-19 disease progression and long-COVID*?

Five steps of COVID-19 disease progression

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The genome of the novel SARS-CoV-2 has been rapidly sequenced to study its host adaptation, viral evolution, infectivity, transmissibility, and pathogenicity [6]. Disease progression has been well described by many authors [6-9]. For the purpose of our study, we have drawn on the classification system proposed by Siddiqi et al. [10] to characterise the infection cycle as follows: Stage 1 – person-to-person infection via respiratory droplets produced when an infected individual coughs or sneezes (airborne transmission). Stage 2 – viral penetration to host cells via two receptors: angiotensin-converting enzyme 2 (ACE2) and CD147 [11]. Stage 3 – SARS-CoV-2 inhibits and evades the innate immune response and drives pathogenesis (Viral replication provokes localised inflammation in the lung, leading to viral pneumonia; there is no clear boundary between the viral and inflammatory stages and they may overlap. At this stage, most patients need to be hospitalised for close observation and treatment). Stage 4 – progression to acute respiratory stress associated with increased production of proinflammatory cytokines. Stage 5 – the patient must be admitted to the intensive care unit as he/she is most likely to develop a cytokine storm and autoimmune disorders that can lead to death.

Duration of infectiousness and symptoms

The duration of infection from symptom onset to recovery is approximately ten days in non-severe cases [12]. As reported by Matheson and Lehner [13], '20% of patients deteriorate 7 to 10 days after symptom onset'. A viral peak appears in the upper respiratory tract within the first week of symptom onset, and later in the lower respiratory tract in both asymptomatic and symptomatic infected individuals. Viral load clearance occurs faster in asymptomatic than in symptomatic patients. Generally, individuals recover within three weeks. However, the post-recovery course of the disease, including its physical and psychological sequelae, presents many unknowns. Around 10% of the patients who tested positive for the SARS-CoV-2 virus remained unwell for more than three weeks, and a small proportion did so for months [14]. Prolonged COVID-19 can induce long-term pulmonary disorders and have adverse effects on the heart, kidneys, digestive tract, and neural system. The most important determinants of disease progression are age, comorbidities, history of smoking, length of hospitalisation, severity of the acute disease (such as the need for ICU admission), and the type of medications administered (such as antiviral or corticosteroid therapy) [15]. In addition, the consequences on mental health are underestimated [16].

Preventive strategies and therapy

In stage 1, in an epidemic context, defining the basic reproduction number is essential. This ratio represents the expected number of secondary cases caused by an infected individual [17, 18]. Estimating the R_0 at the country level can be difficult, and studies have reported huge variations in the ratio among regions and countries [19]. From this ratio, the formula $R_0 = \beta.c.d$, where β = probability of transmission of the virus; c = number of contact cases; and d = generation interval [20], can help decision-makers to take appropriate measures to stop viral transmission:

- β can be reduced by basic protection measures such as regularly washing hands, covering the mouth and nose when coughing and sneezing, not shaking hands, and wearing a mask [21-23]

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- ! c can be reduced by physical distancing, massive testing, contact tracing, and isolation of positive cases [24, 25]
- ! d can be reduced with antiviral treatment and immunization.

As of 5 November 2020, no study has demonstrated the real added value of any of the experimental treatments, while many clinical trials are underway. Ending the SARS-CoV2 epidemic with antivirals and/or a vaccine remains a global priority. In the meantime, however, it is essential to reinforce the 'therapeutic toolbox' for controlling the epidemic, to avoid relying only on '! ' and 'c' measures that have proven to be effective in partially controlling the spread of the epidemic by disrupting person-to-person transmission.

In stage 2, there is a need to develop drugs that can potentially block the host cell receptors ACE2 and CD147. AZM presents this capacity [11]. The combination of (hydroxychloroquine) HCQ + AZM has an *in vitro* synergic inhibitory effect on the replication of SARS-CoV1 and SARS-CoV2. This can be beneficial in the early stage of COVID-19 infection by reducing the viral load [26]. AZM occupies the ganglioside-binding domain of the spike protein and neutralises virus binding to lipid rafts, while HCQ covers the ganglioside surface and prevents virus-membrane interaction through a complementary mechanism [27].

In stage 3, efforts have focused on blocking viral replication with antiretroviral drugs such, as those used against human immunodeficiency virus (HIV) or Ebola virus (e.g., Remdesivir!). The most commonly tested drugs were inhibitors of RNA polymerase, such as Darunavir! , Liponavir! and Ritonavir! , targeting the transcription of the viral genome, and inhibitors of regulatory proteins, such as Remdesivir, Ribavirin! , or Favipiravir! , which target the translation of viral proteins. At the date of this review, only Remdesivir had shown limited efficacy in reducing the length of stay in the ICU from 15 to 11 days. However, on 19 November 2020, due to the high number of reported adverse effects and its high cost, the WHO stated that Remdesivir should not be used to treat hospitalised patients with COVID-19, regardless of disease severity [28]. In parallel, whether corticoid therapy should be initiated to stop the inflammatory process that could be concomitant with viral replication is still unclear. Steroids are considered corrective, anti-inflammatory interventions to be administered later in the diseases course. Thus, the WHO [29] expressed its concern about early steroid use, as there was little or no evidence of its effectiveness at this stage.

In stage 4, it is important to the limit the production of cytokines, particularly interleukin 6 (IL6), and of interferons. Anti-inflammatory drugs, such as IL6 inhibitors, corticosteroids, or Tocilizumab! , may potentially remediate severe damage and prevent a cytokine storm. During the SARS-CoV-1 outbreak, an intensive activation of proinflammatory cytokines and chemokines was observed, and researchers used steroids to effectively control the rapid deterioration of clinical conditions by attenuating the immune response [30]. Even if a meta-analysis did not demonstrate a clinical benefit, glucocorticoids have been widely used in syndromes closely related to Covid-19, including SARS, Middle East respiratory syndrome, severe influenza, and community-acquired pneumonia [30]. The RECOVERY open-label trial [31] rapidly proposed to treat COVID-19 hospitalized patients with dexamethasone at a dose regimen of 6mg daily for up to ten days. On June 2020 preliminary results [32] announced that dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14). Although dexamethasone proved an effective remedy against COVID-19, some severe side effects are associated with

corticosteroids use. This should lead physicians to use a risk-benefit ratio and recommend corticosteroids to severely ill COVID-19 patients only.

Why is azithromycin a good candidate therapy?

AZM, a macrolide antibiotic, has a well-known safety profile, it is easily produced at a low cost as a generic drug, and has been declared an essential medicine by the WHO [33]. It is distributed worldwide, making it compliant with the WHO's policy for drug repositioning [34]. AZM is effective against gram-positive bacteria, some gram-negative bacteria, and many atypical bacteria. Common side effects include nausea, vomiting, diarrhoea, and upset stomach. Allergic reaction, such as anaphylaxis, QT prolongation, or diarrhoea caused by *Clostridium difficile,* is possible. In the search for a safe and effective treatment for early mild or moderate COVID-19, AZM seems to be the most promising option, if administrated early enough.

AZM has antiviral, immunomodulatory, and clinical effects in the treatment of COVID-19 [35, 36]. In stage 2, AZM can occupy the ganglioside-binding domain of the spike protein and neutralise virus binding to lipid rafts. It also interferes with the ligand CD147 receptor interaction (antiviral action). In stages 4 and 5, AZM can reduce the synthesis of proinflammatory cytokines, and thus reduce the length of stay or the need for respiratory support during hospitalisation (immunomodulatory effect).

Finally, there is a paucity of literature on coinfection with bacterial species in COVID-19 patients. The most frequently isolated species are, in descending order, *Mycoplasma pneumoniae, Staphylococcus aureus, Legionella pneumophila, Haemophilus spp., Klebsiella spp., Pseudomonas aeruginosa, Chlamydia spp., S. pneumoniae,* and *Acinetobacter baumannii* [37]. The respiratory symptoms of patients with COVID-19 pneumonia admitted to the hospital with fever and dry cough can mimic those of atypical bacterial pneumonia. This makes it difficult to distinguish COVID-19 pneumonia from hospital-acquired and ventilator-associated pneumonia. Antibiotic treatment should be designed considering the possible side effects (e.g., QT prolongation, diarrhoea), the local epidemiology of drug resistance, and the impact of drug resistance on the patient [37]. Macrolide antibiotics, particularly AZM, remain an interesting option in specific conditions.

Why consider treatment with zinc?

Zinc (Zn) is well tolerated and is known for its antioxidant, anti-inflammatory, immunomodulatory, and antiviral activities. Elderly people have an increased probability of zinc deficiency. In the elderly, low Zn status (serum Zn values <0.7 mg/L) represents a risk factor for pneumonia [38]. Inadequate Zn supply may predispose individuals to infectious diseases of the upper and lower respiratory tracts. Although the therapeutic effects of Zn are inconsistent, evidence-based data indicate the efficiency of Zn supplementation in preventing pneumonia and its complications due to the anti-inflammatory properties of zinc [39, 40]. Recently, *in vitro* results indicated that low zinc levels favor viral expansion in SARS-CoV2 infected cells [41].

Why promote ambulatory care?

With the continuous expansion of the pandemic and the resurgence of a second wave in Europe, health systems are facing many disruptions worldwide. In many countries, this situation has led to public lockdowns. To decongest hospitals, McCullough et al. [42] have proposed focusing on early treatment at home's patient with patients combining drugs, self-quarantine for the control of contagion, and house aeration to reduce self-reinoculation. In addition, frontline health workers and family practitioners can play key roles in triage, early detection, and early treatment of patients with mild and moderate symptoms [43]. Only the most vulnerable patients at risk of severe disease progression should be referred to the hospital.

Methodology: The review

We adopted Arksey and O'Malley's [44] five-stage framework for a scoping review: identifying the research question, identifying relevant results, selecting studies, charting data, and reporting results. We defined the following research question: *Can early home administration of AZM with zinc help prevent severe COVID-19 disease progression and long-COVID*?

The scientific literature review was conducted by searching the online databases of PubMed and Google Scholar using the following search terms and Booleans: (COVID-19 OR SARS-CoV-2 OR coronavirus) AND (azithromycin OR Zithromax) AND (outpatient OR ambulatory OR "early treatment"). Preprints were selected from the bioRxiv, and medRxiv platforms. We accessed grey literature using the Google search engine. Materials published from 31 December 2019 to 5 November 2020 were searched. One researcher (PL) independently searched the databases and conveyed his findings to the co-authors. We also performed an advanced search using the Clinicaltrials.gov database using the keywords COVID, SARS-CoV-2, azithromycin, and Zithromax.

Findings

1. **Articles**

A total of 350 articles were identified, of which 19 (17 peer-reviewed articles and two preprints) were selected for full review (Figure 1). The inclusion criteria were outpatient or ambulatory treatment, home treatment prescribed by general practitioners, use of AZM alone or with Zn, and AZM treatment duration! ! 5 days. We failed to identify any study fulfilling all these criteria, either from both the peer-reviewed literature or preprints, because none of these studies involved family practitioners. Most articles focused on the *in vitro* action of AZM, reviewing opinions, and the properties of AZM. We paid particular attention to two articles presenting a research protocols [45, 46] and one article in which the author [47] recommended formal clinical trials after having successfully treated more than 50 patients presenting flu-like symptoms, with AZM (500 mg on day 1 + 250 mg for the remaining five days). Clinical improvement was observed in all patients 24–48 hours after treatment initiation.

Many excluded articles (peer-reviewed studies, preprints, commentaries, letters, editorials, and so on) reported the effectiveness of a combination of HCQ + AZM administered to patients at different stages of the disease, from outpatient treatment to ICU care. Gautret et

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al. [48] were the first to highlight the effectiveness of dual therapy, showing better results with HCQ + AZM than with HCQ alone, under rigorous cardiological surveillance, in reducing hospitalisation and mortality. Many other studies concluded that given the efficacy of HCQ + AZM in early outpatient treatment, the evidence on the use of HCQ alone or HCQ + AZM in inpatients is irrelevant to its use in high-risk outpatients in early stages of the disease [49, 50]. In addition, triple therapy with HCQ + AZM + Zn improved the outcomes and reduced the duration of hospitalisation [51]. However, most of these studies had a small sample size, non-robust methodology, different measures of the primary endpoint, and inconclusive results. HCQ was at the centre of many debates until the WHO [52] concluded in October 2020 that repurposed drugs such as Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens appeared to have little or no effect on hospitalized COVID-19.

2. **Protocols for clinical trials**

We identified a total of 3,904 NIH registered clinical trials on the ClinicalTrials.gov database for COVID-19. Through an advanced search, we selected 121 studies, out of which 88 were on going. We identified 12 clinical trials on the effect of AZM, with at least one arm comprising patients treated with AZM alone for a minimum duration of five days, and one clinical trial proposing a single dose of AZM. Five trials were hospital-based, and six focused on ambulatory care. In addition, we focused on the PRINCIPLE trial [53], which is a community-based trial in which multiple treatments for the same disease are tested simultaneously, including a AZM arm. This study is registered at the ISRCTN registry [54].

We selected the latter six trials + the PRINCIPLE trial (Table 1).

ACTION: This is the most innovative clinical trial on home self-treatment using mobile phones for follow-up. However, in the cohort study, AZM was administered as a single dose. This trial did not study the acceptability and adherence to a six-day home self-treatment regime (AZM 500 mg on day 1 + 250 mg for the five following days).

ATOMIC2: The AZM dose regimen and duration of treatment were similar to those recommended in the UK for Lyme disease (500 mg daily for 14 days).

HyAzOUT: This study involved individuals aged 44 years or older who presented to the hospital. This study aims to compare the benefits of HCQ and AZM.

AMBU-COVID: The Clinicaltrial.gov website has not been updated since the announcement of this trial, and we did not find further information on the PubMed, Google Scholar, medRxiv or bioRxiv databases. Further, the sample size may not allow us to conclusively answer the research question.

PROTECT: This clinical trial provided relevant information from low- and middle-income countries. However, the primary endpoint was a negative PCR results on day 7, which may not be the most relevant endpoint, as HCQ and AZM may delay virus clearance to more than 28 days after symptom onset [55]. This delay in viral clearance is correlated with older age.

Clarithromycin versus azithromycin in treatment of mild COVID-19 infection: This study has been completed. The low size of the AZM arm, AZM dose regime (500 mg), duration of treatment (seven days) and primary endpoint (time to complete resolution of fever) do not allow this study to respond to our research question.

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PRINCIPLE: This randomized trial targets people in the community aged ! 65, or ! 50 with comorbidity, with a suspected or confirmed SARS- CoV-2 infection. In this study, azithromycin is administered at a dose regimen of 500 mg once daily for three days, to patients with symptoms that appeared between t=0 and t=14 days (zero to 14 days after infection). However, even if PRINCIPLE RCT is conducted out of the hospital, the results might partially answer our research question, if they are not desegregated by date of treatment initiation after symptom onset. Only results from treatment administrated less than seven days after infection should be considered to answer our research question. Furthermore, the trial team conducts the enrolment of and follow-up with participants by telephone, with no involvement of family practitioners.

These trials have proposed different AZM dose regimens, from a single dose to ten days of treatment. If one or more trials provide evidence of AZM's efficacy or the absence of evidence in a particular population or setting, further studies will be needed to provide conclusive data on the population, settings, and dose regimens [45]. Furthermore, none of these trials involved family practitioners. Hence, we did not find information on the added value of decentralising early detection and care to family practitioners, who best know their patient's habits, behaviours, comorbidities, and so on. Further, the trials had different primary outcomes. Hence, the results cannot be compared. Finally, to the best of our knowledge, these trials did not provide information on the prevalence of coinfections before initiating the treatment and/or after recovery.

Discussion

We outlined five stages of COVID-19 disease progression. COVID-19 response strategies should consider these stages and propose appropriate strategies, such as testing, contact tracing, isolation of confirmed cases with home-based early treatment, hospitalisation of severe cases, and immunisation. In parallel, in the long run, it is essential to maintain a focus on preventive measures in the long run. These include washing hands, covering the mouth and nose when coughing and sneezing, refraining from shaking hands, wearing a mask, and physical distancing. In this discussion, we will focus on early home treatments that could significantly reduce the number of infected patients needing hospital-based care. Early action and home-based care are the two essential aspects considered to prevent major disruptions in the health system. Treating patients with COVID-19 as soon as possible and before the seventh day of symptom onset is essential for any potential action of azithromycin.

He Z. et al. [56] analysed 2,034 COVID-19 studies registered on ClinicalTrials.gov as of 18 June 2020 and reported that the five most frequently tested drugs were HCQ (n = 148), AZM (n = 46), tocilizumab (n = 29), lopinavir (n = 20), and ritonavir (n = 20). We did not conduct a deep review, but of the 3,904 registered trials, as of 5 November 2020, a quick scan showed that HCQ and AZM were still highly preferred, with 262 records mentioning the use of HCQ alone or in combination with AZM. Despite being a promising medication, there is a paucity of data on the use of AZM alone in treating COVID-19. Thirteen studies proposed the use of AZM alone: seven focused on the hospital inpatient level, and six, on the outpatient level. Results of those studies will be deeply scrutinised, once published.

Scientific knowledge of COVID-19 has been increasing rapidly, but as of 5 November 2020, there was still no antiviral with proven efficacy; hence, the world is placing its hope on a vaccine. Press releases announced the start of trials on promising vaccines produced by

Pfizer/BioNTech [57], Moderna, Spoutnick, and Sinovac. However, considering the uncertainties of long-term efficacy, the level of protection by age (e.g., protection in older people with a deficient immune response), reactogenicity and side effects of mRNA vaccines, and logistical conditions (e.g., cold storage, production), it is too early to consider these vaccines a 'magic bullet'. Vaccines and early treatment are complementary and necessary tools in a comprehensive package of prevention aimed at preventing hospitalisation, death, and long-COVID. In Europe, and particularly in France, the response strategy for the COVID-19 epidemic failed to involve frontline health workers. A paradigm change is urgently needed to shift from a 100% hospital-based approach to a family practitioner-based strategy to avoid further disruption of the health system and lockdowns. In addition, recent data suggests focusing on those with long-COVID, also termed as 'COVID long-haulers' [58]. The long-term physical and mental consequences of the disease are still unknown.

Dry nose, loss of taste and/or smell, and muscle pain are frequent complaints of COVID-19 patients who visit their family practitioners [59, 60]. Meanwhile, hospitalised patients [6] usually complain of fever, dry cough, dyspnoea, chest pain, fatigue, and myalgia. Almost 95% of infected people present mild or moderate symptoms that do not necessitate hospital-based care. Approximately 5% of the patients with COVID-19 and 20% of those hospitalised experience severe symptoms necessitating intensive care [61]. Therefore, family practitioners should play a central role in triage, early treatment of patients with mild and moderate symptoms, and referral to the hospital when early treatment fails and for most-at-risk vulnerable individuals. However, this approach presents two major challenges: the need for a drug with proven effectiveness and early detection of COVID-19 symptoms for early care. As mentioned, HCQ + AZM is the most common drug therapy used for early treatment. However, when decentralising early care to family practitioners, it might be opportune not to consider HCQ because i) while its efficacy is still controversial, it seems to work only when administered early enough [62], and ii) it can have adverse effects requiring close monitoring. Clinical trials of HCQ or HCQ + AZM arms usually enrolled patients and initiated treatment at very early stages of infection. If administrated to patients in more advanced stages of COVID-19 with mild or moderate symptoms, the use of HCQ could be counterproductive, given its immunomodulating effect. When prescribed at an advanced stage of the disease, dual therapy has little effect; at this stage, only strong anti-inflammatory and/or anticoagulant treatments can help the patients [63]. In addition, in these late stages, the HCQ + AZM combination can be toxic in patients whose cardiac status is compromised [64]. HCQ appears to be the main driver of cardiac toxicity and not AZM itself. This is consistent with evidence that macrolides are not associated with an increased risk of cardiac events [35].

For these reasons, it is appropriate to focus on AZM only, which is considered to be effective if administered less than seven days after viral infection. Moreover, it shows no adverse effects that cannot be monitored at the family practitioner level. In France, several groups of family practitioners, known as the 'Laissons les médecins prescrire' and 'Azithro d'hospitalisation' alliances, claim to have obtained encouraging results with a small number of COVID-19 patients referred to the hospital after AZM treatment. These alliances recommend the involvement of family practitioners and the use of AZM under rigorous scientific guidance. To support these groups of doctors, we (BE) introduce a therapeutic algorithm (Figure 2) based on findings from the literature [35, 36, 42, 65-68]. In parallel, the Association for the Prevention and the Management of Sanitary Crisis (UGPS), which represents individuals who have recovered from COVID-19 or are affected by it, supports

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these alliances. UGPS is advocating for clinical trials to be designed with the necessary scientific rigour by a research institution. Such a clinical trial would show whether early treatment with AZM significantly reduces i) the number of people infected by SARS-CoV-2 who need to be hospitalised; ii) of these hospitalised people, the number of fatal events; and iii) the number of infected people who suffer from a long-COVID disease. Secondary outcomes could focus on the satisfaction of both, the patient and the family practitioner.

We need to be aware of new data that can be applied to the early ambulatory treatment of COVID-19. The role of *Mycoplasma pneumoniae* (MP) remains unclear. Lansbury et al. [69] do not recommend the routine use of antibiotics in the management of confirmed COVID-19 infections, because the level of MP–SARS-CoV-2 coinfection is too low. Nicolson and de Mattos [70] suggest that the severity of signs and symptoms in progressive COVID-19 patients could be partly due to MP and other bacteria. We recommend considering the role of MP–SARS-CoV-2 coinfection and the need to address it to prevent severe disease progression [71]. As demonstrated in a previous study (by CE, who obtained the patent EP0349473b1), certain mycoplasmas contribute to the explosive amplification of the replication of certain RNA viruses, such as the respiratory syncytial virus (RSV), *in vitro*. Bacteria such as *Chlamydia pneumoniae (CP)*, *MP*, *Borrelia burgdorferi (BB),* and *Legionella pneumophila (LP)* are generally present in the pulmonary microbiota, hidden intracellularly in a quiescent state [72]. They participate in the development of local immune disorders, leading to superinfection. Studies on the prevalence of *MP, CP, BB,* and *LP* present contradictory findings, considering the difficulty of isolating *MP*. In studying the seasonal distribution of *MP* among patients presenting with mild acute respiratory symptoms caused by the influenza virus A or B or RSV, Layani-Milon et al. showed [73] the co-circulation of *MP* and viral strains of influenza A or B or RSV (Figure 3). The authors noted that every year, at least one peak of MP infection is observed in late autumn (October to December), varying in duration and intensity. Therefore, *MP* can superinfect patients presenting with viral infections, either in the early stage of infection (the first three days) or in the late stage during the recovery of respiratory cells. To conclude, this hypothesis constitutes a reliable avenue for further research and favours early treatment of COVID-19 patients with AZM.

Many authors have described the SARS-CoV-2 cell penetration via ACE2 receptors, and the endocytosis facilitated by spike proteins. The viral spike protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) via the receptor-binding domain (RBD). In this process, the potential antiviral action of AZM to block ACE2 receptors is well documented [6, 8, 10, 14, 61, 74]. However, building on the hypothesis of bacteria-virus cooperation, we think that AZM antimicrobial action is preponderant even if AZM antiviral action cannot be neglected. In our previous work, we (CE) showed that HIV and RSV colonize intracellular bacteria such as mycoplasma *in vitro* through a bacteriophage-like mechanism. SARS-CoV-2 could develop a similar bacteriophage-like mechanism to colonize *MP* and other intracellular bacteria [75]. In such a case, it is essential to block the bacteria RNA polymerase responsible for the viral amplification with AZM. Further, Zn can inhibit RNA synthesis activity *in vitro* of several RNA viruses, including SARS-CoV at the initiation phase of this synthesis. It probably directly affects the enzyme that drives the SARS-CoV-2 genome-encoded RNA-dependent RNA polymerase in RNA replication and transcription [76, 77]. If a similar mechanism applies to SARS-CoV-2, it explains why Zn deficiency favours COVID-19 disease progression. Consequently, addition of Zn can enhance the action of AZM, leading to an augmented blockage of viral replication with the association of AZM + Zn.

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AZM is known to induce antimicrobial resistance at variable levels in different countries and regions [78], and antimicrobial resistance (AMR) is a matter of major concern [79]. The use of AZM and other antibiotics in the management of COVID-19 should be balanced against the risk of AMR. The paucity of available data makes it difficult to predict the impact that this pandemic may have on antimicrobial stewardship programmes and long-term rates of AMR [80]. The deaths from COVID-19 may overtake the deaths from AMR for 2020, but the estimated annual number of deaths from AMR of 10 million by 2050 may be higher than the death toll from the entire COVID-19 pandemic [81]. We encourage adopting a positive approach and considering the impacts of both COVID-19 and AMR. For instance, behavioural interventions, including physical barriers, to prevent the spread of SARS-CoV-2, will likely decrease the spread of other infections and the use of antimicrobials [81]. Such interventions focusing on hand hygiene may have a considerable impact on AMR if adopted in the long term by individuals in their daily lives and health workers in health facilities worldwide. Family practitioners can promote this. In addition, the high number of hospitalised SARS-CoV-2 infected individuals colonised with *carbapenemase-producing Enterobacteriaceae (CPE)/VRE/MRSA/Clostridioides difficile* increases the risk of nosocomial transmission within hospitals [80]. Early home treatment with AZM will inevitably reduce the risk of hospital transmission and the future consumption of antibiotics. This risk assessment should be addressed in collaboration with veterinary doctors and patient associations, as AMR is also caused by the overuse of antibiotics in agriculture, and animal and human health. Key monitoring indicators and information must be collected are to be rapidly defined. Considering the interrelated emergencies resulting from COVID-19 and AMR, it may be opportune to involve veterinary doctors and representatives of patient associations in the national task forces that monitor the COVID-19 response at the country level.

Strengths and limitations

The document selection was conducted by only one researcher (PL), who might have missed or misclassified a few articles; thus, the entire body of research may not be reflected. Nonetheless, we believe we have applied a systematic and rigorous search strategy to retrieve relevant articles responding to the research question. As a result, as per 5 November 2020, we believe we have selected enough relevant articles to draft an overview of the state of utilization of azithromycin at the early stage of disease progression, and that we have been able to answer the research question.

Conclusion

Our scoping review did not reveal evidence of early home treatment with AZM alone or associated with zinc to be a reliable option to prevent severe COVID-19 disease progression, and long-COVID. We failed to identify studies involving family practitioners as frontline healthcare workers administering AZM treatment.

Countries were not prepared to face the SARS-CoV2 pandemic, and a large part of humanity has been or is still locked down. To date, strategies to control the pandemic are mainly based on preventive and restrictive measures, while hope has been pinned on herd immunity acquired through the mass immunization of the population. In the meantime, even if scientific knowledge is evolving at an unprecedent pace, little is known about the long-term health

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outcomes among people infected by SARS-CoV-2, even for asymptomatic people. It is also too early to assess the extent to which immunization will prevent the occurrence of long-COVID. Persistent symptoms or the development of new symptoms weeks after infection are not well documented but are an evolving problem that could appear as a future public health issue.

With the second wave of the COVID-19 pandemic in Europe, we suggest shifting from a hospital-based approach to a family practitioner-based approach with early home treatment that prevents disease progression to hospitalization and death. In parallel, such an approach could potentially decrease the risk of developing post-COVID-19 symptoms and prevent a future epidemic of chronic disability by reversing the curve before it becomes established. AZM shows the potential to respond to both health issues: mitigating the disruptions of the health system while vaccines are deployed and preventing a new epidemic of 'COVID long-haulers'. We urge research institutions to provide the necessary support to develop clinical trials in collaboration with family practitioners in providing early home treatment with AZM +/- Zn under rigorous guidance.

Such research studies would benefit from the involvement of veterinary experts through a 'one health' approach that includes research components on both antimicrobial resistance and bacteria-virus cooperation. We call for national task forces managing the COVID-19 response and research institutions at the country level to consider the insights of family practitioners, associations of COVID-19 patients who have recovered, and veterinary doctors to develop an appropriate response to COVID-19 and pave the way to prevent the next epidemic.

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