Use of antivirals and antibiotics for COVID-19 in Mexico City: A Real-World Multicenter Cohort Study

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Abstract

We aimed to characterize real-world use of antivirals and antibiotics in patients with COVID-19 and their associations with mortality. We conducted a real-world retrospective cohort study in 688 primary-to-tertiary medical units in Mexico City; 395,343 patients were evaluated for suspected COVID-19 between February 24 and September 14, 2020. All patients with a positive RT-PCR for SARS-CoV-2 (n=137,012) were included; those receiving unspecified antivirals (n=137), excluded, and groups of antivirals with <30 patients (n=20), eliminated. Survival and mortality risk analyses were done for patients receiving antivirals, antibiotics, both, or none (exposition groups). 136,855 patients were analyzed; mean age 44.2 (SD:16.8) years; 51.3% were men. 16.6% received an antiviral (3%), antibiotic (10%), or both (3.6%). More symptomatic patients received antivirals and antibiotics more often. Antivirals studied were Oseltamivir (n=8414), Amantadine (n=319), Lopinavir-Ritonavir (n=100), Rimantadine (n=61), Zanamivir (n=39), and Acyclovir (n=36). Survival with antivirals (73.7%, P<.001) and antibiotics (85.8%, P<.001) was lower than no antiviral/antibiotic (93.6%) in the general population. Increased risk of death was observed with antivirals in ambulatory (HR=4.7, 95%CI:3.94-5.62) and non-critical (HR=2.03, 95%CI:1.86-2.21) patients; no benefit in hospitalized and critical patients. Oseltamivir was associated with increased mortality in the general population (HR=1.72, 95%CI:1.61-1.84), ambulatory (HR=4.79, 95%CI:4.01-5.75), non-critical (HR=2.05, 95%CI:1.88-2.23), and pregnancy (HR=8.35, 95%CI:1.77-39.30). Antibiotics were a protective factor in hospitalized (HR=0.81, 95%CI:0.77-0.86) and critical patients (HR=0.67, 95%CI:0.63-0.72), but a risk factor in the general population (HR=1.13, 95%CI:1.08-1.19) and children and adolescents

(HR=4.22, 95%CI:2.01-8.86). In conclusion, oseltamivir was associated with increased mortality or no benefit in all groups. Common antivirals for COVID-19 should be avoided. Antibiotics may increase survival in hospitalized and critical patients. Vaccination history and rapid differentiation of etiologic agent will be key to promptly initiate or avoid antivirals during the COVID-19-influenza season.

Introduction

The severe acute respiratory coronavirus 2 (SARS-CoV-2) is the etiologic agent of the coronavirus disease (COVID-19) pandemic, one of the most devastating infectious diseases of this century. Non-pharmacological interventions are the most effective means of limiting the impact of COVID-19 to date (1,2). However, several countries have not been able to contain the disease through such measures (3).

One of the main strategies for finding ways to combat COVID-19 has been drug repurposing since developing novel antivirals against SARS-CoV-2 may be protracted (4). Repurposing existing antivirals is an attractive approach due to their relative safeness and potential anti-SARS-CoV-2 mechanisms (5). Up to October 2, 2020 there were 369 registered studies to test antivirals for COVID-19, of which 360 were still active (6). The majority of trials in the World Health Organization (WHO) platform were for lopinavir/ritonavir (176), remdesivir (41), favipiravir (29), oseltamivir (18), and ribavirin (16) (7). Thus, comprehensive evidence for these antivirals may be available shortly. Other common antivirals are not being tested for COVID-19 but could be having widespread use in the community and hospitals since practice guidelines do not discourage or recommend most antivirals due to a lack of evidence (8,9), others advice against most (10-12), or recommend oseltamivir empirically during the influenza season (13) and when coinfection exists (14).

Real-world data studies may reveal valuable information not encountered in conventional interventional studies; while pragmatic clinical trials are designed to obtain answers for real-world problems, most other clinical trials are not, often having strict

selection criteria (15). Therefore, real-world studies have the potential to become into real-world evidence with immediate impact on policymaking (16,17).

In Mexico, epidemiologic surveillance of viral respiratory diseases started in 2006 and has expanded to include monitoring units representative of the Mexican population (18,19). Follow-up and reporting of cases, including monitorization of antivirals and antibiotics have been occurring since. This surveillance system was adapted to monitor COVID-19 and open datasets for Mexico (20) and Mexico City (21) were made available, the latter including use of antivirals and antibiotics.

In this study, we sought to characterize the use of antivirals and antibiotics in patients with laboratory-confirmed COVID-19 in Mexico City and their associations with mortality.

Methods

Study Design

We conducted a real-world multicenter retrospective cohort study in patients who received medical attention for suspected COVID-19 in any of the registered and accredited COVID-19 medical units in Mexico City, to evaluate mortality (main outcome) in those receiving antivirals, antibiotics, both, or none (exposition groups).

We considered 395,343 patients for eligibility who had been evaluated for COVID-19 in 688 medical units (primary-to-tertiary care) between February 24, 2020 and September 14, 2020. All patients with a positive RT-PCR for SARS-CoV-2 were included to maximize the power and generalizability of the study. Patients treated with an unspecified antiviral were excluded. To perform reliable analyses, a cut-off value of 30

patients receiving the same antiviral was set and groups of antivirals with <30 patients were eliminated.

Source of Data and Management of Variables

We used the COVID-19 open dataset available in Mexico City Government's Open Data platform (21), collected and updated daily by the Secretariat of Health of Mexico City. Patients meeting criteria of suspected COVID-19 case have been included in this dataset starting on February 24, 2020 when the first suspected cases arrived in Mexico. Criteria for suspected COVID-19 case in Mexico included having at least two of three signs/symptoms (cough, fever, or headache) plus at least one other (dyspnea, arthralgias, myalgias, sore throat, rhinorrhea, conjunctivitis, or chest pain) in the last 7 days. This operational definition was changed on August 24, 2020 to increase sensitivity (22): at least one of four signs/symptoms (cough, fever, dyspnea, or headache), plus at least one other (myalgias, arthralgias, sore throat, chills, chest pain, rhinorrhea, anosmia, dysgeusia, or conjunctivitis) in the last 10 days.

For epidemiologic purposes, two strategies are outlined in the National COVID-19 Epidemiologic Surveillance Plan (22): 1. testing of 10% of ambulatory patients with mild symptoms of respiratory disease and 100% of patients with respiratory distress at evaluation in monitoring units of viral respiratory disease (USMER, for its acronym in Spanish), and 2. testing 100% of patients who meet diagnostic criteria of Severe Acute Respiratory Infection (defined as shortness of breath, temperature ≥38 °C, cough, and ≥1 of the following: chest pain, tachypnea, or acute respiratory distress syndrome) in non-USMER units.

Upon evaluating a patient suspected of having COVID-19, healthcare professionals are required to fill out a format (Supplementary Appendix 1) containing demographic, clinical, epidemiological, and treatment variables, later complemented with follow-up by accredited hospital epidemiologists (inpatients) and healthcare professionals in primary care units (ambulatory patients). For ambulatory patients, follow-up is performed daily for a minimum 7 days and patients are considered recovered 14 days after the onset of symptoms if alive and not hospitalized. For hospitalized patients, follow-up is done daily until death or discharge; follow-up time for patients discharged from hospital is highly variable since no consensus or requirements by authorities exist but may extend from 14 days to 3-6 months after discharge. Duration of follow-up for each patient is not provided in the dataset and cannot be calculated.

For every medical unit there is only one responsible authority who ultimately uploads data into the Respiratory Diseases Epidemiologic Surveillance System and is accountable for accuracy. Results of diagnostic RT-PCR for SARS-CoV-2 are directly uploaded by the diagnostic facility; accreditation of diagnostic procedures by the Mexican Institute of Diagnostics and Epidemiological Reference is required to upload results. Reporting of all deaths of COVID-19 suspected or confirmed cases is obligatory and must be done in the first 48 hours after occurrence; in cases of deaths occurring in patients who had completed follow-up, registries are matched to death certificates and updated. There have been concerns that patients tested more than once may be duplicated. Since no variables that could lead to identification of patients are released, we searched for patients with identical demographic variables and only one registry was kept.

Management of Variables

All categorical variables were classified as dummy variables (present/absent). Polytomous variables were created from frequencies of use of antivirals and antibiotics (no antiviral/antibiotic, antiviral only, antibiotic only, and antiviral plus antibiotic), type of antiviral with >30 patients, and the combination of every individual antiviral with antibiotics. These were considered as the exposition groups. Special populations for subgroup analyses were defined as: children and adolescents (<18 years), pregnancy, puerperium, and non-pregnant/puerperal adults (≥18 years). Further subgroups included ambulatory and hospitalized patients, as well as patients admitted to intensive care unit (ICU) and those requiring invasive mechanical ventilation (IMV). A variable of critical patients was built by grouping patients admitted to ICU and/or requiring IMV, whereas non-critical patients did not meet any of both.

Since it has been hypothesized that early use of antivirals in COVID-19 could diminish hospitalization rate (23) and detain disease progression (24), thereby decreasing mortality, we distinguished early (≤2 days from symptom onset to initiation of antivirals) from late (>2 days) use of antivirals, and studied their relation to hospitalization rates and mortality; only patients with complete dates for all three variables (symptom onset, hospitalization [if required], and initiation of antivirals) were included for analysis. Occupations were grouped as follows: technical services (laborers), education (students and teachers), healthcare (dentists, nurses, diagnostic laboratorian, physicians, and other healthcare workers), agricultural activities (peasants), commerce (drivers, informal

commerce, employees, and businesspeople), unemployed, stay-at-home (stay-at-home parents and retired/pensioners), and other occupations (others, and other professions).

Statistical Analysis

Descriptive data were calculated and are provided as frequencies, percentages, mean with standard deviation (SD) or median with interquartile range (IQR). Qualitative comparisons were made with χ^2 or Fisher´s exact test. Independent-samples t-test and ANOVA were used for quantitative comparisons. Survival was calculated for all treatment groups (antiviral only, antibiotic only, antiviral plus antibiotic, and no antiviral/antibiotic) and specific antivirals (acyclovir, amantadine, lopinavir-ritonavir, oseltamivir, rimantadine, and zanamivir) alone or combined with antibiotics; survival curves were created for general population, ambulatory, hospitalized, non-critical, and critical patients. Survival between groups receiving distinct treatments were compared through the Log-Rank test against patients not receiving antivirals/antibiotics. Cox regression models were applied for general population, ambulatory, hospitalized, non-critical, and critical patients to determine mortality risk in patients receiving any treatment compared to no antivirals/antibiotics (reference). Resulting hazard ratios (HR) were adjusted for demographic and clinical variables (sex, age, indigenous self-identification, diabetes, chronic obstructive pulmonary disease [COPD], immunosuppression, hypertension, human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS], cardiovascular disease, obesity, chronic kidney disease [CKD], smokers, unemployed, time from symptom onset to medical attention, fever, cough, sore throat, shortness of breath, irritability, diarrhea, chest pain, chills, headache, myalgias, arthralgias, abrupt deterioration, rhinorrhea, polypnea, vomit,

abdominal pain, conjunctivitis, cyanosis, and sudden onset of symptoms) that were considered as risk factors in the univariate analysis for every group; all variables with P<.1 were included in the final model using the Enter method. To account for multicenter variability, adjusted risk was calculated through generalized estimating equations (GEE), setting the medical unit with the lowest CFR and the highest number of patients for every subgroup as the reference value. Further subgroup survival analyses and multivariable Cox regression models were applied for special populations (children and adolescents, pregnancy, puerperium, and non-pregnant/puerperal adults), VMI, and ICU. To quantify the minimal association strength of an unmeasured confounding factor that could reduce the risk conferred by exposures in our study, E-values were calculated for the point estimate and lower limit of the confidence interval.

A two-sided P value <.05 was used to define statistical significance. Analyses and figures were created with SPSS software v.21 and GraphPad Prism v.8.0.1.

Results

No duplicated registries were found. After selection of eligible participants (Figure 1), 136,855 patients from all 688 medical units were analyzed. 97.83% (n=133,887) were residents of the Mexico City Metropolitan Area, conformed by 17 municipalities of Mexico City (83.29%, n=111,768), and 60 municipalities (16.71%, n=22,119) of the State of Mexico. The remaining 2.17% (n=2,968) sought medical attention from all other 30 states of the republic.

Of all patients, 10.0% (n=13,743) received antibiotics only; 3.0% (n=4,044), antivirals only; 3.6% (n=4,925), antivirals plus antibiotics, and 83.4% (n=114,143), none (Table 1).

More symptomatic ambulatory patients received antivirals and antibiotics more frequently (Supplementary Table 1); hospitalized patients with more signs/symptoms had greater use of antivirals, but less antibiotics (Supplementary Table 2).

Baseline and follow-up characteristics of survivors (91.47%, n=136,855) and non-survivors (8.53%, n=11,679) are shown in Supplementary Table 3. Case-fatality rates (CFR) in special populations were: 8.92% (95%CI:8.76-9.07%), for non-pregnant/puerperal adults; 1.72% (95%CI:0.66-2.77), pregnancy; 0.97% (95%CI:0-2.90), puerperium; and 0.69% (95%CI:0.48-0.90), children and adolescents. Of all deaths, 92.7% (95%CI:92.2-93.2) and 99.6% (95%CI:99.5-99.7) occurred by day 28 and 56, respectively.

Patients treated only with antivirals had a lower survival than those not receiving antivirals or antibiotics in the general population (Figure 2a), ambulatory (Figure 2b), hospitalized (Figure 2c), non-critical (Figure 3a), critical (Figure 3c), IMV (Supplementary Table 4), ICU (Supplementary Table 5) and non-pregnant/puerperal adults (Supplementary Table 6); for children and adolescents (Supplementary Table 7) and pregnancy (Supplementary Table 8) differences in survival were not significant, and there were not enough events for analysis in puerperal women. Increased survival with only antibiotics was observed in hospitalized, critical, and IMV, whereas decreased survival occurred in the general population, non-pregnant/puerperal adults, ambulatory, non-critical, ICU, and children and adolescents; there were no differences for pregnancy. Antivirals plus antibiotics resulted in decreased survival in the general population, ambulatory, non-critical, non-pregnant/puerperal adults, children and

adolescents, pregnancy, and ICU; increased survival, in hospitalized; and no differences, in critical and IMV groups.

Decreased survival with oseltamivir was observed in the general population (Figure 2d), ambulatory (Figure 2e), non-critical (Figure 2d), ICU (Supplementary Table 5), non-pregnant/puerperal adults (Supplementary Table 6), children and adolescents (Supplementary Table 7), and pregnancy (Supplementary Table 8); no differences in survival occurred in hospitalized (Figure 2f), critical (Figure 3d), and IMV (Supplementary Table 4). Survival rates for amantadine, zanamivir, rimantadine, acyclovir, and lopinavir-ritonavir are shown in the same figures and tables as oseltamivir.

Unadjusted (Supplementary Table 9) and adjusted (Table 2) risk of death for the general population, ambulatory, hospitalized, non-critical and critical patients, as well as for other subgroups (Supplementary Tables 10-14) were calculated. E-values for statistically significant risk groups are provided in Supplementary Tables 15-16. After adjusting for center through GEE, we found no significant variability in risk for the use of antivirals, antibiotics, or both in all groups; oseltamivir presented variability in hospitalized and critical patients, with the largest increases in risk occurring in public hospitals.

Of all 8,969 patients receiving antivirals, 10% (n=903) had complete dates of initiation of antivirals; baseline and follow-up characteristics are available in Supplementary Table 17. 25.2% (n=227) were admitted to hospital. Most patients (n=783) initiated antivirals before receiving medical attention in accredited units; 211 of those were hospitalized. Median time from symptom onset to initiation of antivirals was 1 day (IQR:0-4) for both

ambulatory and hospitalized patients; time from symptom onset to ambulatory care in accredited units was 5 days (IQR:3-8) and 6 days (IQR:4-9) for hospitalization. Time from initiation of antivirals to hospitalization was 3 days (IQR:0-6). Time-to-initiation of antivirals and time-to-hospitalization for specific antivirals are shown in Supplementary Figure 1.

Early (≤2 days) and late (>2 days) initiation of antivirals occurred in 64.2% (n=580) and 35.8% (n=323) patients, respectively. Overall survival in early (91.3%) and late (88.9%) groups was not different (P=.2). Survival for early/late use of antivirals is shown in Supplementary Table 18. Oseltamivir was associated with increased risk of death in both early (HR=3.00, 95%CI:2.14-4.20) and late (HR=2.99, 95%CI:1.83-4.89) groups, as well as late use of lopinavir-ritonavir (HR=9.9, 95%CI:2.49-39.83); all other early/late antivirals did not reach statistical significance. There were no differences in hospitalization rates between early and late groups for every antiviral (Supplementary Figure 2).

Discussion

To our best knowledge, this is the first observational study evaluating amantadine, rimantadine, zanamivir, and acyclovir for COVID-19; no registered studies to evaluate these drugs exist (7). Only one study has evaluated risk of death for oseltamivir (25); lopinavir-ritonavir has been evaluated in clinical trials (26,27).

We hypothesized that antivirals and antibiotics could be having widespread use in real-world settings. Therefore, we studied mortality in laboratory-confirmed COVID-19 patients treated with antivirals and/or antibiotics in Mexico City. Most patients were not

treated with antivirals or antibiotics (83.4%), although a substantial proportion received antivirals alone (3.0%) or combined with antibiotics (3.6%) despite national guidelines explicitly advising against antivirals out of clinical trials (12). Patients receiving antivirals and antibiotics were overall more symptomatic, suggesting that florid clinical presentations and not evidence may be guiding decision to treat, especially since evidence does not support antivirals included in our study: oseltamivir (n=8,414), amantadine (n=316), lopinavir-ritonavir (n=100), rimantadine (n=61), zanamivir (n=39), and acyclovir (n=31). Only one patient received remdesivir, the only antiviral to have shown some uncertain benefit for COVID-19 (28,29); physicians in low-to-middle income countries may be opting for low-cost repurposed medications before costly interventions for COVID-19.

Of patients treated with antivirals, 10% had dates of initiation of antivirals. These patients received antivirals early after symptom onset (1 day, IQR:0-4) and well before seeking ambulatory (5 days, IQR:3-8) or hospital (6 days, IQR:4-9) care, which was expected since date of initiation of antivirals is only required to be registered for those treated before seeking medical care in accredited units. In Mexico antibiotics and most antivirals (i.e. oseltamivir, zanamivir, rimantadine) are sold under prescription. Private pharmacy-associated clinics are a rapidly growing sector in Mexico not included in our study where physicians tend to have lower experience, qualifications, compliance with regulations, and higher prescription rates, which could partially explain this (30-32). Self-medication with amantadine could be occurring since it is a widely available over-the-counter antiviral combined with antihistamines and acetaminophen.

We studied the use of antivirals and antibiotics in patients with COVID-19 under conditions not commonly explored in COVID-19 studies since most tend to study hospitalized patients and adults, leaving important populations like children and adolescents, ambulatory patients, and pregnant women largely understudied (33,34). Our results show no benefit for the use of common antivirals for COVID-19 in the general population and every subgroup; increased risk of death was observed in certain groups. Hospitalization rates were not different when antivirals were used early (≤2 days) vs late (>2 days).

Oseltamivir was associated with increased mortality in the general population (HR=1.72, 95%CI:1.61-1.84), ambulatory (HR=4.79, 95%CI:4.01-5.75), non-critical (HR=2.05, 95%CI:1.88-2.23), and pregnant (HR=8.35, 95%CI:1.77-39.30) patients. Importantly, increased mortality was also observed in the cohort of 903 patients with both early (HR=3.00, 95%CI:2.14-4.20) and late (HR=2.99, 95%CI:1.83-4.89) use of oseltamivir. Antiviral drug-related heart damage is a concern since some antivirals may be cardiotoxic, aggravating myocardial damage caused by SARS-CoV-2 (35). It is unclear if cardiac adverse events after the use of neuraminidase inhibitors (i.e. oseltamivir, zanamivir) are increased or not due to high risk of bias of numerous influenza clinical trials; renal and psychiatric adverse events have higher occurrence with oseltamivir compared to placebo (36). Future studies should address if oseltamivir could be associated with cardiovascular and renal damage in COVID-19.

Through molecular docking studies, oseltamivir had been hypothesized to inhibit viral proteases involved in the degradation of polyproteins that control viral replication (37). Nonetheless, this potentially inhibitory activity was found to be weak through molecular

modeling, while inhibition of SARS-CoV-2 *in vitro* and reduction of symptoms in hospitalized patients failed (38). In one single-center study, oseltamivir was associated with decreased risk of death in COVID-19-hospitalized patients (HR=0.21; 95%CI:0.10-0.43) (25). Contrary to Liu et al., we found no benefit for oseltamivir in hospitalized patients (HR=1.07; 95%CI:0.99-1.15) which is consistent with studies of oseltamivir for SARS-CoV infection (HR=0.87; 95%CI:0.55-1.38) (39). Furthermore, combination of oseltamivir with antibiotics in hospitalized patients in our study resulted in decreased risk of death (HR=0.92; 95%:0.87-0.98), which could explain findings by Liu et al. since most patients in their cohort (87.7%) received antibiotics. Decreased mortality is most likely driven by antibiotics since hospitalized patients in our study receiving only antibiotics had lower risk of dying (HR=0.81, 95%CI:0.77-0.86) than antibiotics plus oseltamivir.

In the RECOVERY study, there were no differences in mortality risk between hospitalized patients receiving lopinavir-ritonavir vs placebo (HR=1.03, 95%CI:0.91-1.17) (27), which is consistent with our finding of no benefit for lopinavir-ritonavir in hospitalized patients. Notably, ambulatory and late (>2 days) use of lopinavir-ritonavir was a risk factor for death.

Paradoxically, antibiotics in the general population were a risk factor for death, but a protective factor in both ambulatory and hospitalized patients. Nonetheless, univariate models showed no overall effect of antibiotics in ambulatory patients; when adjusting only for demographic variables no effect persisted but was protective after adjusting only for clinical variables. This is explained by the fact that more symptomatic patients

received antibiotics more often. Supporting this conclusion, no benefit was observed for antibiotics in non-critical patients.

We observed benefit for antibiotics in hospitalized, IMV, and critical patients, suggesting that increased survival could be due to prevention or treatment of concomitant bacterial infections, thereby supporting current WHO recommendations (11).

For children and adolescents, antibiotics were a risk factor for death (HR=4.22, 95%CI:2.01-8.86). However, we did not differentiate ambulatory from hospitalized pediatric patients and current recommendations include using antibiotics in hospitalized patients with multisystem inflammatory syndrome (40). The lack of benefit from antivirals included in our study in pediatric patients supports current guidelines discouraging their use after the expected large number of patients treated needed to observe differences in mortality in both non-severe and severe COVID-19 which would not outweigh risks (41).

The main limitation of our study is that we were not able to assess cointerventions being studied for COVID-19 since only data for antivirals and antibiotics were available. Steroids have shown to increase survival in patients requiring oxygen administration and decrease survival in patients without supplementary oxygen (42,43). Under the assumption that treatment regimens tend to be similar by medical unit and hospital, we believe to have accounted for some of that variability by adjusting for center; lower risk for oseltamivir in hospitalized and critical patients receiving attention in private hospitals notwithstanding, increased risk of death with the use of oseltamivir occurred in most private and public hospitals. Furthermore, E-values aid the interpretation of our findings

by providing the estimated effect size that unmeasured factors in our study should have to reduce the reported risk to non-significant.

Categorization of antibiotics as a single category in this dataset limits our study since we were not able to evaluate individual antibiotics proposed as candidate drugs for COVID-19, like azithromycin. However, in vitro studies (44) and clinical trials (45,46) have failed to support an effect of azithromycin against SARS-CoV-2. Thus, generalized effects for the use of antibiotics is plausible.

Another potential limitation is that Mexico has a low diagnostic testing rate for SARS-CoV-2 (0.08 daily tests per 1,000 people) (47). However, health authorities require 100% of patients with severe disease to be tested. Since we only studied mortality, an outcome expected to occur in patients who progress to severe disease, our study feasibly included most events. Nonetheless, excess mortality rates suggest there could be an undercounting of deaths in Mexico City (47). These patients could have refrained from seeking medical attention or received medical care in non-accredited COVID-19 units where mortality, quality of care, and use of antivirals/antibiotics could be different.

Also, the number of ICU beds in Mexico City was relatively low in March 2020 (6.0 per 100,000 population) compared to most European countries (5 to 33.9 per 100,000) in the pre-pandemic period; this capacity was expanded to 29.5 ICU beds per 100,000 by September 2020 (48,49). Mortality rates, especially in patients younger than 60 years, are lower under high availability of ICU beds (48). Altogether, this means that mortality rates could have varied throughout our study period.

Although we were not able to determine duration of follow-up in our study, the mechanisms and resources used by epidemiologic authorities in Mexico are robust

enough to guarantee adequate matching of patients who had completed follow-up with death certificates. Thus, our finding that 92.7% (95%CI:92.2-93.2) and 99.6% (95%CI:99.5-99.7) of deaths occurred by day 28 and 56, respectively, could be important for the interpretation and design of COVID-19 clinical trials assessing short-term mortality.

In this study, we have obtained evidence to advise against the use of common antivirals (oseltamivir, zanamivir, amantadine, rimantadine, acyclovir, and lopinavir/ritonavir) for COVID-19 unless evidence from randomized controlled trials support their use in the future. Amantadine has been proposed as a candidate drug for COVID-19 (50), but our findings should discourage clinical trials to evaluate this drug.

During the COVID-19 and influenza syndemic, rapid differentiation of the etiologic agent will be of utmost importance since clinicians will have to differentiate patients with influenza who may benefit from neuraminidase inhibitors from patients with COVID-19 who may be harmed by them. Increasing vaccination rates against influenza will be a major challenge since only 20-30% of patients who presented with COVID-19 in our study had been vaccinated in the prior season. Mexican and international authorities should review treatment recommendations for patients with suspected viral respiratory disease since current guidelines recommend empiric use of oseltamivir before identification of the virus (13) or when coinfection exists (14).

Conclusions

Antivirals should be avoided for COVID-19 in the absence of evidence supporting their use. Oseltamivir was associated with increased mortality or no benefit in all groups.

Antibiotics may increase survival in hospitalized and critical patients. Amidst the upcoming combined COVID-19-influenza season, vaccination history and rapid differentiation of the etiologic agent will be key to initiate or avoid antivirals.

Ethical disclosures: This is a retrospective study using an open-source dataset of patients receiving medical care for suspected COVID-19 in Mexico City. The Secretariat of Health of Mexico approved the collection and publication of data.

Declarations of interest:

- Mancilla-Galindo: No competing interests.
- García-Mendez: No competing interests.
- Márquez-Sánchez: No competing interests.
- Aguilar-Aguirre: No competing interests.
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Author contributions

Kammar-García and Mancilla-Galindo had access to all data in the study and take responsibility for the integrity of the data and accuracy of analysis.

Concept and design: Kammar-García, Mancilla-Galindo

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: All authors

Critical revision of the manuscript for important intellectual content: García-Méndez, Rocha-González, Kammar-García

Statistical analysis: Kammar-García, Mancilla-Galindo

Administrative, technical, or material support: Kammar-García

Supervision: Kammar-García, Mancilla-Galindo

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Table 1. Baseline characteristics of patients with laboratory confirmed COVID-19 who were treated with or without antivirals/antibiotics, in 688 accredited COVID-19 medical units in Mexico City.

	All patients n=136855	No antiviral / antibiotic n=114143	Antiviral only n=4044	Acyclovir n=36	Amantadine n=319	Lopinavir-Ritonavir n=100	Oseltamivir n=8414	Rimantadine n=61	Zanamivir n=39	Antibiotic only n=13743
Sex										
Women	66683 (48.7)	56999 (49.9)	1813 (44.8)	19 (52.8)	182 (57.1)	31 (31)	3407 (40.5)	28 (45.9)	17 (43.6)	6000 (43.7)
Men	70172 (51.3)	57144 (50.1)	2231 (55.2)	17 (47.2)	137 (42.9)	69 (69)	5007 (59.5)	33 (54.1)	22 (56.4)	7743 (56.3)
Age, mean (SD)	44.2 (16.8)	43.1 (16.6)	50.5 (16.5)	46.9 (14.9)	43.9 (14.8)	56.9 (15.9)	51.8 (15.9)	46 (15.1)	50 (14.1)	48.3 (16.8)
Age categories										
0-19 years	7558 (5.5)	6963 (6.1)	57 (1.4)	0 (0)	12 (3.8)	1 (1)	97 (1.2)	2 (3.3)	0 (0)	483 (3.5)
20-29 years	20098 (14.7)	18027 (15.8)	375 (9.3)	6 (16.7)	38 (11.9)	2 (2)	638 (7.6)	5 (8.2)	3 (7.7)	1379 (10)
30-39 years	29434 (21.5)	25586 (22.4)	707 (17.5)	6 (16.7)	86 (27.0)	10 (10)	1286 (15.3)	16 (26.2)	7 (17.9)	2437 (17.7)
40-49 years	29553 (21.6)	24683 (21.6)	837 (20.7)	10 (27.8)	71 (22.3)	21 (21)	1780 (21.2)	14 (23)	8 (20.5)	2966 (21.6)
50-59 years	24928 (18.2)	20011 (17.5)	852 (21.1)	5 (13.9)	63 (19.7)	23 (23)	1895 (22.5)	15 (24.6)	10 (25.6)	2906 (21.1)
60-69 years	15070 (11.0)	11441 (10.0)	632 (15.6)	7 (19.4)	32 (10)	18 (18)	1515 (18.0)	3 (4.9)	6 (15.4)	2048 (14.9)
70-79 years	7183 (5.2)	5213 (4.6)	418 (10.3)	2 (5.6)	14 (4.4)	17 (17)	855 (10.2)	5 (8.2)	5 (12.8)	1072 (7.8)
80-89 years	2594 (1.9)	1902 (1.7)	146 (3.6)	0 (0)	2 (0.6)	8 (8)	292 (3.5)	1 (1.6)	0 (0)	389 (2.8)
90-99 years	419 (0.3)	303 (0.3)	20 (0.5)	0 (0)	1 (0.3)	0 (0)	56 (0.7)	0 (0)	0 (0)	59 (0.4)
≥100 years	18 (0.01)	14 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.03)
Indigenous self-identification	713 (0.5)	537 (0.5)	37 (0.9)	0 (0)	2 (0.6)	1 (1)	79 (0.9)	0 (0)	2 (5.1)	92 (0.7)
Occupation										
Technical services	1916 (1.4)	1527 (1.3)	70 (1.7)	0 (0)	3 (0.9)	3 (3)	145 (1.7)	0 (0)	1 (2.6)	237 (1.7)
Education	10006 (7.3)	9129 (8)	105 (2.6)	1 (2.8)	24 (7.5)	1 (1)	187 (2.2)	2 (3.3)	0 (0)	662 (4.8)
Healthcare	17281 (12.6)	14910 (13.1)	655 (16.2)	3 (8.3)	47 (14.7)	9 (9)	1029 (12.2)	7 (11.5)	2 (5.1)	1274 (9.3)
Agricultural activities	302 (0.2)	232 (0.2)	5 (0.1)	0 (0)	0 (0)	0 (0)	19 (0.2)	0 (0)	0 (0)	51 (0.4)
Commerce	50450 (36.9)	42625 (37.3)	1078 (26.7)	15 (41.7)	111 (34.8)	36 (36)	2569 (30.5)	27 (44.3)	12 (30.8)	5055 (36.8)
Other	24630 (18)	19906 (17.4)	911 (22.5)	6 (16.7)	63 (19.7)	20 (20)	2021 (24)	9 (14.8)	6 (15.4)	2599 (18.9)
Unemployed	5685 (4.2)	4747 (4.2)	277 (6.8)	1 (2.8)	5(1.6)	2 (2)	463 (5.5)	3 (4.9)	7 (17.9)	457 (3.3)
Stay-at-home	26585 (19.4)	21067 (18.5)	943 (23.3)	10 (27.8)	66 (20.7)	29 (29)	1981 (23.5)	13 (21.3)	11 (28.2)	3408 (24.8)
Last-season flu vaccination	27087 (19.8)	22972 (20.1)	695 (17.2)	9 (25)	85 (26.6)	9 (9)	1244 (14.8)	13 (21.3)	4 (10.3)	2751 (20)
Special populations										
Pregnancy	583 (0.9)	530 (0.9)	12 (0.3)	0 (0)	2 (1.1)	0 (0)	16 (0.5)	0 (0)	0 (0)	35 (0.6)
Age during pregnancy, mean (SD)	29.8 (7.4)	29.5 (6.9)	30.3 (5.2)	-	32 (4.2)	-	30 (5.9)	-	-	34.8 (12.4)
Last-season flu vaccination	161 (27.6)	153 (28.9)	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)	7 (20)
Pregnancy age group										
Early adolescent (≤14 years)	2 (0.3)	2 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Late adolescent (15-19 years)	34 (5.8)	33 (6.2)	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)	0 (0)
Normal age (20-34 years)	404 (69.3)	373 (70. 4)	9 (75)	0 (0)	1 (50)	0 (0)	12 (75)	0 (0)	0 (0)	18 (51.4)
Advanced maternal age (≥35 years)	143 (24.5)	122 (23)	2 (16.7)	0 (0)	1 (50)	0 (0)	3 (18.8)	0 (0)	0 (0)	17 (48.6)
Trimester of pregnancy										
First trimester	114 (19.6)	102 (19.2)	5 (41.7)	0 (0)	1 (50)	0 (0)	5 (31.3)	0 (0)	0 (0)	6 (17.1)
Second trimester	177 (30.4)	161 (30.4)	3 (25)	0 (0)	0 (0)	0 (0)	4 (25)	0 (0)	0 (0)	12 (34.3)
Third trimester	292 (50.1)	267 (50.4)	4 (33.3)	0 (0)	1 (50)	0 (0)	7 (43.8)	0 (0)	0 (0)	17 (48.6)
Puerperium	103 (0.2)	64 (0.1)	2 (0.05)	0 (0)	0 (0.0)	0 (0)	7 (0.2)	0 (0)	0 (0)	32 (0.5)
Days of puerperium										
1 day	33 (32)	21 (32.8)	1 (50)	0 (0)	0 (0)	0 (0)	3 (42.9)	0 (0)	0 (0)	9 (28.1)
2-7 days	33 (32)	16 (25)	1 (50)	0 (0)	0 (0)	0 (0)	3 (42.9)	0 (0)	0 (0)	14 (43.8)

8-42 days	37 (35.9)	27 (42.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	9 (28.1)
Age during puerperium, mean (SD)	31.9 (9.7)	31.1 (9.2)	33.5 (3.5)	-	-	-	31.1 (2.7)	-	-	33.6 (11.5)
Last-season flu vaccination	22 (21.4)	14 (21.9)	14 (21.9)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	7 (21.9)
Children and adolescents (<18 years)	5791 (4.2)	5336 (4.7)	40 (1)	0 (0)	9 (2.8)	1 (1)	67 (0.8)	2 (3.3)	0 (0)	376 (2.7)
Age, mean (SD)	10.9 (5.2)	10.9 (5.2)	10.9 (5.9)	-	13.4 (4.5)	-	11 (5.8)	14.5 (3.6)	-	9.9 (5.9)
Last-season flu vaccination	1213 (20.9)	1113 (20.9)	4 (10)	0 (0)	1 (11.1)	0 (0)	9 (13.4)	0 (0)	0 (0)	90 (23.9)
Non-pregnant/puerperal adults (≥18 years)	130378 (95.3)	108213 (94.8)	3990 (98.7)	36 (100)	308 (96.6)	99 (9)	8324 (98.9)	59 (96.7)	39 (100)	13300 (96.8)
Age, mean (SD)	45.7 (15.5)	44.7 (15.3)	50.9 (16.1)	46.9 (14.9)	44.8 (14)	57.5 (15.1)	52.1 (15.6)	47.1 (14.1)	50 (14.1)	48.5 (15.7)
Last-season flu vaccination	25691 (19.7)	21692 (20)	690 (17.3)	9 (25)	84 (27.3)	9 (9.1)	1233 (14.8)	13 (22)	4 (10.3)	2647 (19.9)
Comorbidities										
Diabetes	18229 (13.3)	13458 (11.8)	910 (22.5)	2 (5.6)	36 (11.3)	35 (35)	2007 (23.9)	8 (13.1)	6 (15.4)	2677 (19.5)
COPD	1741 (1.3)	1273 (1.1)	119 (2.9)	0 (0)	3 (0.9)	2 (2)	212 (2.5)	2(3.3)	1 (2.6)	248 (1.8)
Asthma	3035 (2.2)	2561 (2.2)	96 (2.4)	1 (2.8)	13 (4.1)	4 (4)	165 (2)	0 (0)	3 (7.7)	288 (2.1)
Immunosuppression	1758 (1.3)	1368 (1.2)	84 (2.1)	0 (0)	7 (2.2)	3 (3)	145 (1.7)	0 (0)	0 (0)	235 (1.7)
Hypertension	22185 (16.2)	16799 (14.7)	1074 (26.6)	10 (27.8)	40 (12.5)	35 (35)	2211 (26.3)	12 (19.7)	5 (12.8)	3073 (22.4)
HIV/AIDS	573 (0.4)	462 (0.4)	168 (4.2)	0 (0)	0 (0)	2 (2)	47 (0.6)	0 (0)	0 (0)	62 (0.5)
Cardiovascular disease	2724 (2.0)	2064 (1.8)	153 (3.8)	2 (5.6)	4 (1.3)	5 (5)	277 (3.3)	2 (3.3)	0(0)	370 (2.7)
Obesity	23848 (17.4)	18924 (16.6)	837 (20.7)	12 (33.3)	83 (26)	18 (18)	1817 (21.6)	5 (8.2)	6 (15.4)	2983 (21.7)
Chronic kidney disease	2067(1.5)	1471 (1.3)	150 (3.7)	0 (0)	2 (0.6)	7 (7)	286 (3.4)	1 (1.6)	0 (0)	300 (2.2)
Smoker	14727 (10.8)	12214 (10.7)	461 (11.4)	2 (5.6)	46 (14.4)	6 (6)	885 (10.5)	8 (13.1)	5 (12.8)	1561 (11.4)
Type of medical attention										
Ambulatory	109902 (80.3)	98060 (85.9)	2012 (49.8)	30 (83.3)	282 (88.4)	8 (8)	3187 (37.9)	48 (78.7)	19 (48.7)	8268 (60.2)
Hospitalization	26953 (19.7)	16083 (14.1)	2032 (50.2)	6 (16.7)	37 (11.6)	92 (92)	5227 (62.1)	13 (21.3)	20 (51.3)	5475 (39.8)
Severity of the disease										
Non-critical	129658 (94.7)	110009 (96.4)	3518 (87)	34 (94.4)	310 (97.2)	69 (69)	7126 (84.7)	58 (95.1)	34 (87.2)	12018 (87.4)
Critical	7197 (5.3)	4134 (3.6)	526 (13)	2 (5.6)	9 (2.8)	31 (31)	1288 (15.3)	3 (4.9)	5 (12.8)	1725 (12.6)
Time from symptom onset to medical attention	4.5 (3.8)	4.4 (3.8)	4.49 (3.9)	6.36 (4.6)	4.9 (3.6)	6.8 (4.1)	4.7 (3.7)	5.6 (4.2)	5.33 (4.7)	5.5 (3.8)
Baseline symptoms										
Fever	83120 (60.7)	66011 (57.8)	3332 (82.4)	25 (69.4)	198 (62.1)	81 (81)	6963 (82.8)	42 (68.9)	31 (79.5)	9769 (71.1)
Cough	96206 (70.3)	78367 (68.7)	3406 (84.2)	24 (66.7)	245 (76.8)	67 (67)	7055 (83.8)	42 (68.9)	35 (89.7)	10371 (75.5)
Sore throat	59040 (43.1)	48845 (42.8)	2014 (49.8)	12 (33.3)	159 (49.8)	31 (31)	3701 (44)	29 (47.5)	22 (56.4)	6241 (45.4)
Shortness of breath	42942 (31.4)	31061 (27.2)	2234 (55.2)	14 (38.9)	85 (26.6)	66 (66)	5170 (61.4)	22 (36.1)	23 (59)	6501 (47.3)
Irritability	24098 (17.6)	19460 (17)	1079 (26.7)	5 (13.9)	81(25.4)	7 (7)	1993 (23.7)	14 (23)	13 (33.3)	2525 (18.4)
Diarrhea	31649 (23.1)	25821 (22.6)	1152 (28.5)	11 (30.6)	96 (30.1)	19 (19)	2180 (25.9)	15 (24.6)	13 (33.3)	3494 (25.4)
Chest pain	36851 (26.9)	29524 (25.9)	1662 (41.1)	12 (33.3)	105 (32.9)	22 (22)	2979 (35.4)	25 (41)	15 (38.5)	4169 (30.3)
Chills	48282 (35.3)	39405 (34.5)	2138 (52.9)	16 (44.4)	158 (49.5)	34 (34)	3616 (43)	33 (54.1)	17 (43.6)	5003 (36.4)
Headache	95018 (69.4)	78893 (69.1)	3284 (81.2)	22 (61.1)	227 (71.2)	59 (59)	6348 (75.4)	40 (65.6)	29 (74.4)	9400 (68.4)
Myalgias	70666 (51.6)	57192 (50.1)	2633 (65.1)	27 (75)	201 (63.0)	60 (60)	5074 (60.3)	43 (70.5)	24 (61.5)	8045 (58.5)
Arthralgias	64381 (47)	51792 (45.4)	2377 (58.8)	22 (61.1)	179 (56.1)	48 (48)	4846 (57.6)	42(68.9)	23 (59)	7429 (54.1)
Abrupt deterioration	62460 (45.6)	48991 (42.9)	2704 (66.9)	20 (55.6)	180 (56.4	66 (66)	5367 (63.8)	34 (55.7)	20 (51.3)	7782 (56.6)
Rhinorrhea	38288 (28)	32135 (28.2)	1350 (33.4)	6 (16.7)	118 (37.0)	20 (20)	2283 (27.1)	27 (44.3)	11 (28.2)	3688 (26.8)
Polypnea	15868 (11.6)	11977 (10.5)	1081 (26.7)	3 (8.3)	46 (14.4)	13 (13)	1847 (22)	7 (11.5)	6 (15.4)	1969 (14.3)
Vomit	10123 (7.4)	8094 (7.1)	479 (11.8)	3 (8.3)	23 (7.2)	7 (79	870 (10.3)	8 (13.1)	2 (5.1)	1116 (8.1)
Abdominal pain	17338 (12.7)	14080 (12.3)	1025 (25.3)	3 (8.3)	60 (18.8)	8 (8)	1561 (18.6)	10 (16.4)	7 (17.9)	1609 (11.7)
Conjunctivitis	16941 (12.4)	14277 (12.5)	513 (12.7)	4 (11.1)	55 (17.2)	7 (7)	962 (11.4)	11 (18)	6 (15.4)	1619 (11.8)
Cyanosis	5917 (4.3)	4461 (3.9)	463 (11.4)	1 (2.8)	12 (3.8)	4 (4)	816 (9.7)	8 (13.1)	3 (7.7)	612 (4.5)
Sudden onset of symptoms	46723 (34.1)	37607 (32.9)	1574 (38.9)	10 (27.8)	96 (30.1)	48 (48)	3831 (45.5)	26 (42.6)	16 (41)	5089 (37)
Concomitant use of antibiotics	18840 (13.8)	172 (0.2)	-	29 (80.6)	151 (47.3)	77 (77)	4627 (55)	26 (42.6)	15 (38.5)	-

Data expressed as Frequency (%) or mean (SD)

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, HIV/AIDS: Human immunodeficiency virus/acquired immune deficiency syndrome.

Table 2. Adjusted multivariable Cox regression models for mortality risk in laboratory-confirmed COVID-19 patients receiving antivirals, antibiotics, both, or none in 688 accredited COVID-19 medical units in Mexico City.

	All patients[a]		Ambulatory[b]		Hospitalized[c]		Non-Critical[d]		Critical[e]	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Models for type of treatment										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Antiviral only	1.72 (1.61-1.84)	<.001	4.7 (3.94-5.62)	<.001	1.07 (0.99-1.15)	.07	2.03 (1.86-2.21)	<.001	1.09 (0.99-1.21)	.09
Antibiotic only	1.13 (1.08-1.19)	<.001	0.72 (0.58-0.89)	.003	0.81 (0.77-0.86)	<.001	1.05 (0.98-1.14)	.2	0.67 (0.63-0.72)	<.001
Antiviral + antibiotic	1.57 (1.47-1.67)	<.001	1.91 (1.47-2.49)	<.001	0.91 (0.86-0.97)	.004	1.63 (1.49-1.77)	<.0001	1.02 (0.93-1.11)	.7
Models for type of antiviral										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Acyclovir	1.37 (0.51-3.65)	.5	Not estimable		2.75 (1.03-7.33)	.04	1.19 (0.29-4.75)	.8	2.85 (0.71-11.4)	.1
Amantadine	0.73 0.44-1.21)	.2	0.08 0.24-2.36)	.6	0.88 (0.5-1.55)	.7	0.67 (0.33-1.34)	.3	1.05 (0.49-2.21)	.9
Lopinavir-Ritonavir	1.04 (0.69-1.55)	.9	4.28 (0.59-30.7)	.1	0.59 (0.4-0.89)	.01	0.69 (0.33-1.46)	.3	0.66 (0.41-1.04)	.08
Oseltamivir	1.66 (1.58-1.75)	<.001	3.52 (3.01-4.11)	<.001	0.98 (0.93-1.03)	.4	1.84 (1.72-1.96)	<.001	1.06 (0.99-1.14)	.1
Rimantadine	1.39 (0.66-2.92)	.4	2.54 (0.36-18.1)	.4	1.11 (0.49-2.46)	.8	1.48 (0.56-3.95)	.4	1.63 (0.52-5.09)	.4
Zanamivir	1.66 (0.83-3.32)	.2	2.49 (0.35-17.8)	.4	0.84 (0.39-1.76)	.6	1.43 (0.46-4.43)	.5	0.7 (0.29-1.69)	.4
Antibiotic only	1.14 (1.08-1.19)	<.001	0.72 (0.58-0.9)	.004	0.81 (0.77-0.86)	<.001	1.06 (0.98-1.14)	.2	0.68 (0.63-0.72)	<.001
Models for Acyclovir										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Acyclovir only	8.1 (1.14-57.6)	.04	Not estimable		8.98 (1.26-63.9)	.03	Not estimable		2.85 (0.39-20.3)	.3
Antibiotic only	1.11 (1.05-1.17)	<.001	0.71 (0.57-0.89)	.002	0.82 (0.77-0.86)	<.001	1.03 (0.96-1.11)	.4	0.67 (0.63-0.72)	<.001
Acyclovir + antibiotic	1.07 (0.35-3.33)	.9	Not estimable		2.28 (0.74-7.08)	.2	1.23 (0.31-4.92)	.8	3.11 (0.44-22.2)	.3
Models for Amantadine										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Amantadine only	1.78 (1.03-3.06)	.04	1.69 (0.42-6.79)	.5	1.62 (0.89-2.93)	.1	1.63 (0.78-3.42)	.2	1.39 (0.62-3.1)	.4
Antibiotic only	1.11 (1.05-1.17)	<.001	0.71 (0.57-0.89)	.002	0.82 (0.77-0.86)	<.001	1.03 (0.96-1.12)	.4	0.67 (0.63-0.72)	<0.001
Amantadine + antibiotic	0.15 (0.04-0.59)	.007	0.34 (0.05-2.39)	.3	0.15 (0.02-1.06)	.06	0.13 (0.02-0.9)	.04	0.44 (0.06-3.11)	.4
Models for Lopinavir-Ritonavir										

No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Lopinavir-Ritonavir only	0.68 (0.26-1.82)	.4	56.9 (7.87-412)	<.001	0.39 (0.15-1.05)	.06	0.47 (0.07-3.37)	.5	0.41 (0.15-1.08)	.07
Antibiotic only	1.11 (1.05-1.17)	<.001	0.71 (0.57-0.89)	.002	0.82 (0.77-0.86)	<.001	1.04 (0.96-1.12)	.4	0.67 (0.63-0.72)	<.001
Lopinavir-Ritonavir + antibiotic	1.1 (0.71-1.7)	.7	Not estimable		0.67 (0.43-1.05)	.08	0.69 (0.31-1.53)	.4	0.79 (0.47-1.34)	.4
Models for Oseltamivir										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Oseltamivir only	1.72 (1.61-1.84)	<.001	4.79 (4.01-5.75)	<.001	1.07 (0.99-1.15)	.06	2.05 (1.88-2.23)	<.001	1.11 (1.0-1.23)	.05
Antibiotic only	1.13 (1.08-1.19)	<.001	0.72 (0.58-0.89)	.003	0.81 (0.77-0.86)	<.001	1.06 (0.98-1.14)	.2	0.67 (0.63-0.72)	<.001
Oseltamivir + antibiotic	1.61 (1.51-1.71)	<.001	2.1 (1.65-2.8)	<.001	0.92 (0.87-0.98)	.01	1.68 (1.55-1.83)	<.001	1.02 (0.94-1.12)	.6
Models for Rimantadine										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Rimantadine only	1.88 (0.85-4.21)	.1	4.9 (0.69-34.9)	.1	1.21 (0.5-2.91)	.7	1.81 (0.58-5.62)	.3	1.69 (0.54-5.27)	.4
Antibiotic only	1.11 (1.05-1.17)	<.001	0.71 (0.57-0.89)	<.001	0.82 (0.77-0.86)	<.001	1.03 (0.96-1.12)	.4	0.67 (0.63-0.72)	<.001
Rimantadine + antibiotic	0.51 0.07-3.6)	.5	Not estimable		0.77 (0.11-5.45)	.8	0.88 (0.12-6.23)	.9	-	-
Models for Zanamivir										
No antiviral / antibiotic	Reference		Reference		Reference		Reference		Reference	
Zanamivir only	1.9 (0.85-4.25)	.12	3.99 (0.55-28.9)	.2	0.9 (0.37-2.17)	.8	1.2 (0.17-8.49)	.9	0.72 (0.29-1.74)	.7
Antibiotic only	1.11 (1.05-1.17)	<.001	0.71 (0.57-0.89)	<.001	0.82 (0.77-0.86)	<.001	1.03 (0.96-1.12)	.4	0.67 (0.63-0.72)	<.001
Zanamivir + antibiotic	1.14 (0.28-4.55)	.9	Not estimable		0.74 (0.18-2.94)	0.7	1.57 (0.39-6.29)	.5	-	-

HR: Hazard ratio, 95%CI: 95% confidence intervals

a: Model adjusted by : Sex (men), Age, Indigenous self-identification, Diabetes, Chronic obstructive pulmonary disease, Immunosuppression, Hypertension, Human immunodeficiency virus/acquired immune deficiency syndrome, Cardiovascular disease, Obesity, Chronic kidney disease, Unemployed, Time from symptom onset to medical attention, Fever, Cough, Shortness of breath, Irritability, Chest pain, Chills, Myalgias, Arthralgias, Abrupt deterioration, Polypnea, Abdominal pain, Cyanosis.

b: Model adjusted by: Sex (men), Age, Indigenous self-identification, Diabetes, Chronic obstructive pulmonary disease, Immunosuppression, Hypertension, Cardiovascular disease, Obesity, Chronic kidney disease, Unemployed, Time from symptom onset to medical attention, Fever, Cough, Shortness of breath, Irritability, Chest pain, Chills, Myalgias, Arthralgias, Abrupt deterioration, Polypnea, Vomit, Abdominal pain, Cyanosis.

c: Model adjusted by: Sex (men), Age, Diabetes, Chronic obstructive pulmonary disease, Immunosuppression, Hypertension, Cardiovascular disease, Chronic kidney disease, Smoker, Unemployed, Cough, Shortness of breath, Chest pain, Chills, Myalgias, Arthralgias, Abrupt deterioration, Polypnea, Cyanosis.

d: Model adjusted by: Sex (men), Age, Indigenous self-identification, Diabetes, Chronic obstructive pulmonary disease, Immunosuppression, Hypertension, Hypertension, Human immunodeficiency virus/acquired immune deficiency syndrome, Cardiovascular disease, Obesity, Chronic kidney disease, Unemployed, Time from symptom onset to medical attention, Fever, Cough, Shortness of breath, Irritability, Chest pain, Myalgias, Arthralgias, Polypnea, Vomit, Abdominal pain, Cyanosis.

e: Model adjusted by: Sex (men), Age, Diabetes, Chronic obstructive pulmonary disease, Immunosuppression, Hypertension, Cardiovascular disease, Chronic kidney disease, Unemployed, Time from symptom onset to medical attention, Cough, Sore throat, Shortness of breath, Chest pain, Headache, Myalgias, Arthralgias, Rhinorrhea, Polypnea, Abdominal pain, Cyanosis.

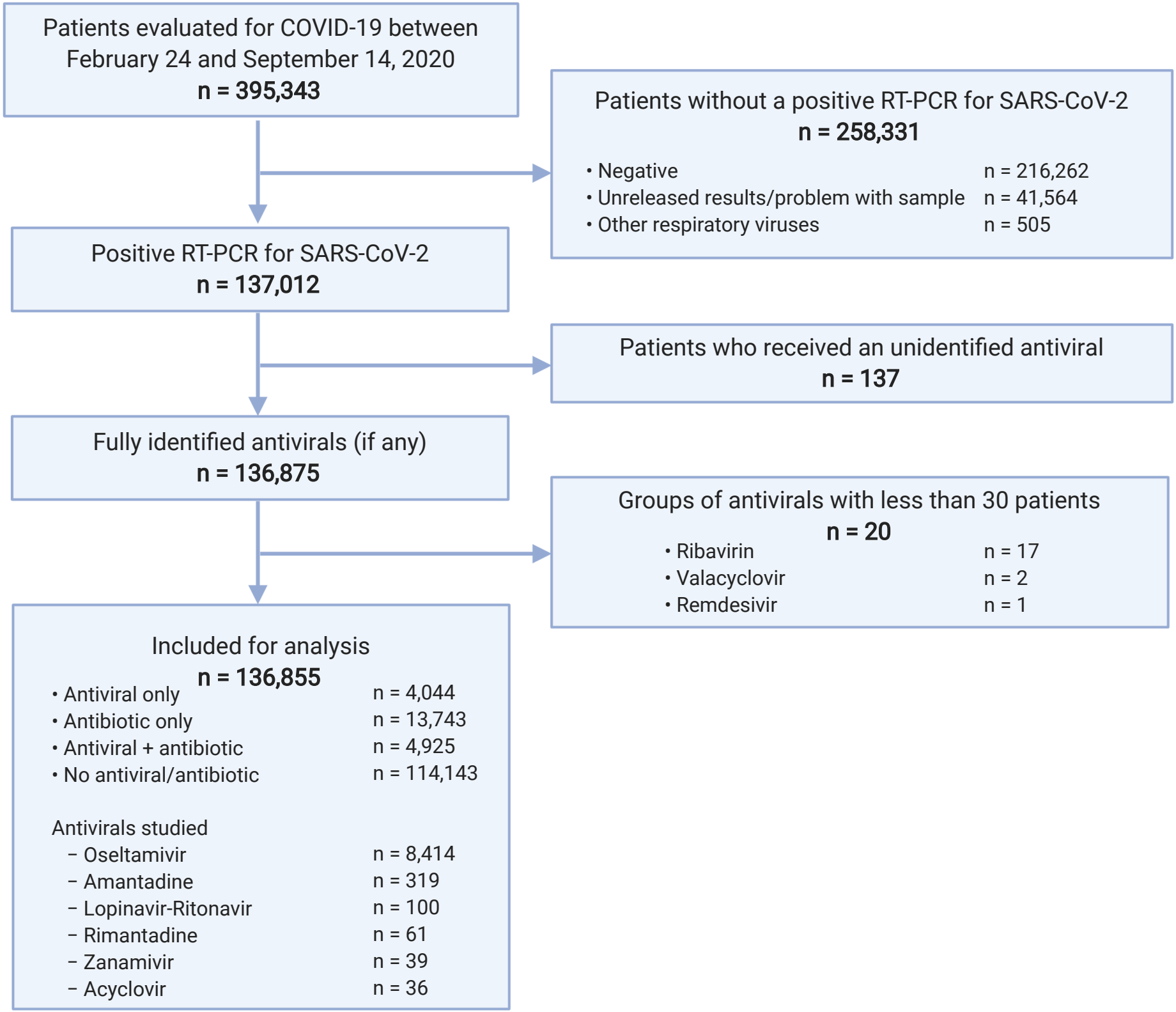
Figure 1. Flow diagram of patients assessed for eligibility.

Figure 2. Survival of patients (general population, ambulatory, and hospitalized) treated with antivirals and/or antibiotics.

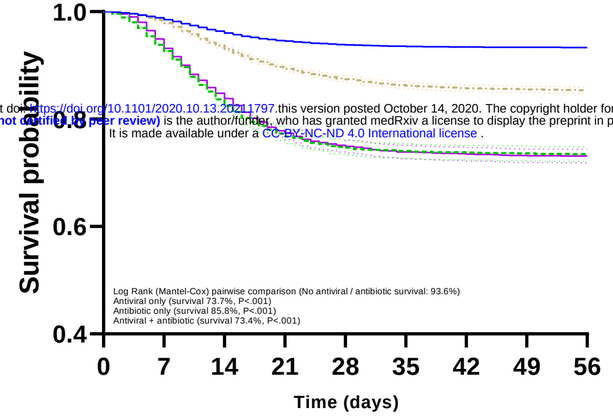
Survival curves are shown according to treatment modality in the general population (a), ambulatory (b), and hospitalized (c) patients. Survival in patients receiving specific antivirals, antibiotics, both, or none in the general population (d), ambulatory (e), and hospitalization (f) settings.

Figure 3. Survival of patients (non-critical and critical) treated with antivirals and/or antibiotics.

Survival curves are shown according to treatment modality in non-critical (a) and critical (b) patients. Survival in patients receiving specific antivirals, antibiotics, both, or none in critical (c) and non-critical (d) patient

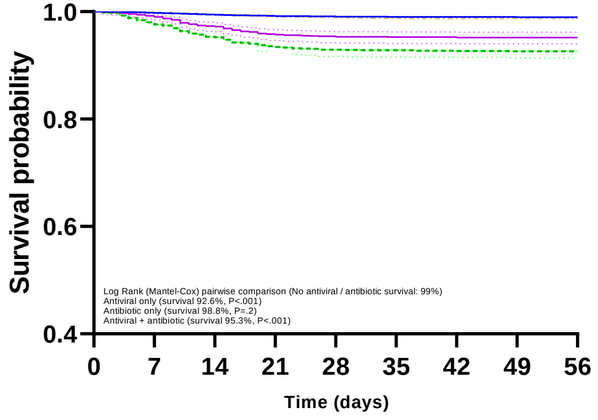

Patients evaluated for COVID-19 between February 24 and September 14, 2020
n = 395,343
Patients without a positive RT-PCR for SARS-CoV-2
n = 258,331
• Negative n = 216,262
• Unreleased results/problem with sample n = 41,564
• Other respiratory viruses n = 505
Positive RT-PCR for SARS-CoV-2
n = 137,012
Patients who received an unidentified antiviral
n = 137
Fully identified antivirals (if any)
n = 136,875
Groups of antivirals with less than 30 patients
n = 20
• Ribavirin n = 17
• Valacyclovir n = 2
• Remdesivir n = 1
Included for analysis
n = 136,855
• Antiviral only n = 4,044
• Antibiotic only n = 13,743
• Antiviral + antibiotic n = 4,925
• No antiviral/antibiotic n = 114,143
Antivirals studied
– Oseltamivir n = 8,414
– Amantadine n = 319
– Lopinavir-Ritonavir n = 100
– Rimantadine n = 61
– Zanamivir n = 39
– Acyclovir n = 36

a



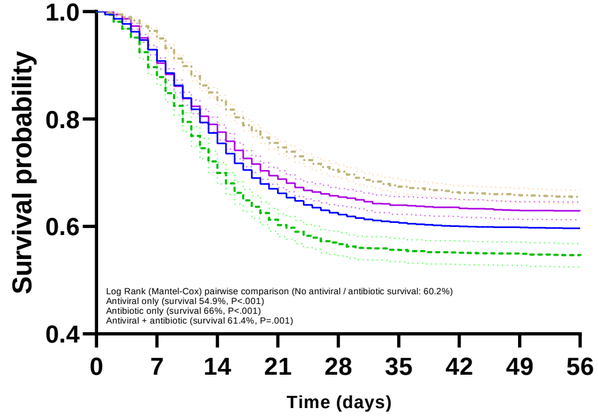
No antiviral / antibiotic	114143	112401	109591	107940	107247	106991	106885	106843	106824
Antiviral only	4044	3745	3336	3107	3027	3004	2993	2988	2983
Antibiotic only	13743	13449	12788	12298	12051	11902	11845	11824	11806
Antiviral + antibiotic	4925	4586	4127	3815	3700	3652	3634	3623	3620

b



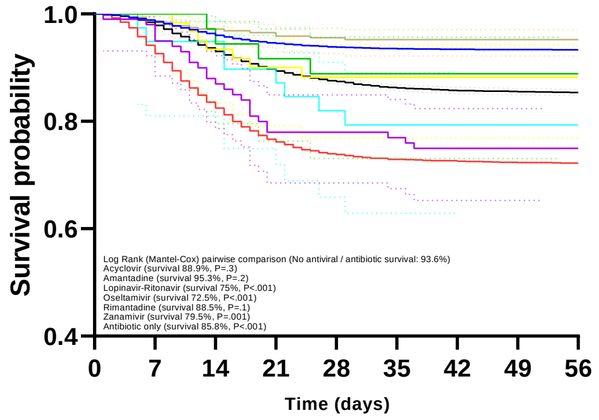
No antiviral / antibiotic	98060	97831	97475	97278	97184	97144	97128	97114	97111
Antiviral only	2012	1964	1916	1881	1871	1869	1867	1866	1864
Antibiotic only	8668	8648	8618	8597	8584	8576	8573	8573	8572
Antiviral + antibiotic	1562	1547	1519	1496	1490	1489	1488	1488	1488

c



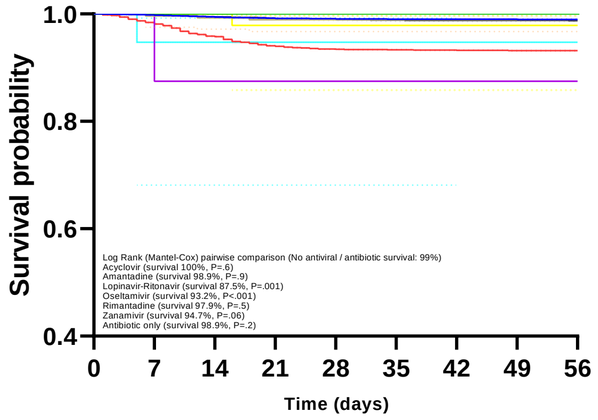
No antiviral / antibiotic	16083	14570	12116	10662	10063	9838	9748	9720	9704
Antiviral only	2032	1781	1420	1226	1156	1135	1126	1122	1117
Antibiotic only	5475	5201	4570	4101	3867	3726	3672	3651	3634
Antiviral + antibiotic	3363	3039	2608	2319	2210	2163	2146	2135	2132

d



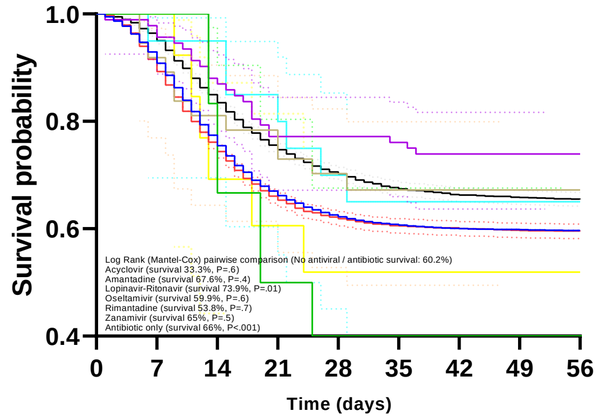
No antiviral / antibiotic	114143	112401	109591	107940	107247	106982	106876	106834	106815
Acyclovir	36	36	34	33	32	32	32	32	32
Amantadine	319	315	310	306	305	304	304	304	304
Lopinavir-Ritonavir	100	95	87	78	77	77	75	75	75
Oseltamivir	8414	7787	6938	6416	6226	6158	6131	6115	6107
Rimantadine	61	61	57	55	54	54	54	54	54
Zanamivir	39	37	37	34	32	31	31	31	31
Antibiotic only	13743	13449	12788	12298	12051	11902	11845	11794	11776

e



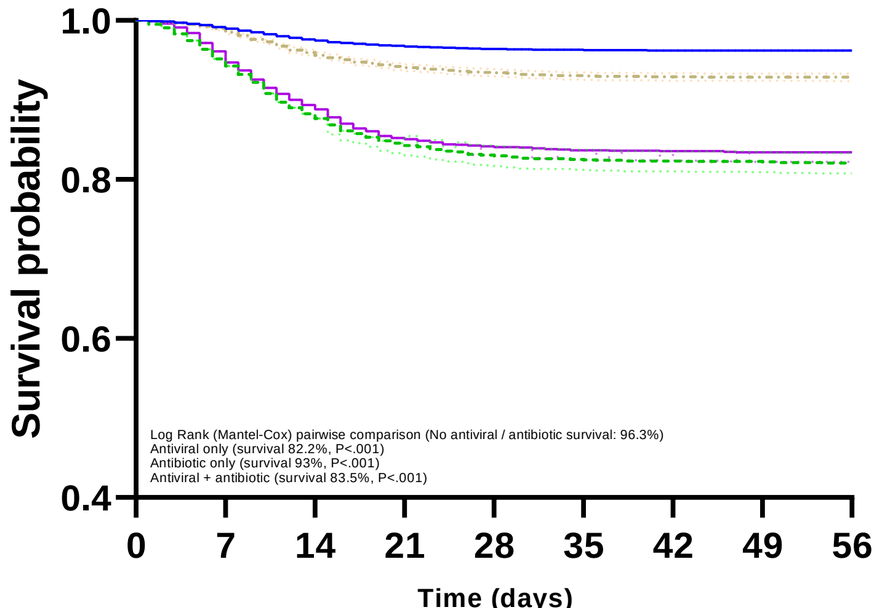
No antiviral / antibiotic	98060	97831	97475	97278	97184	97144	97128	97114	97111
Acyclovir	30	30	30	30	30	30	30	30	30
Amantadine	282	281	280	279	279	279	279	279	279
Lopinavir-Ritonavir	8	7	7	7	7	7	7	7	7
Oseltamivir	3187	3127	3052	2996	2980	2977	2974	2973	2973
Rimantadine	48	48	47	47	47	47	47	47	47
Zanamivir	19	18	18	18	18	18	18	18	18
Antibiotic only	8268	8248	8218	8197	8184	8176	8173	8173	8172

f



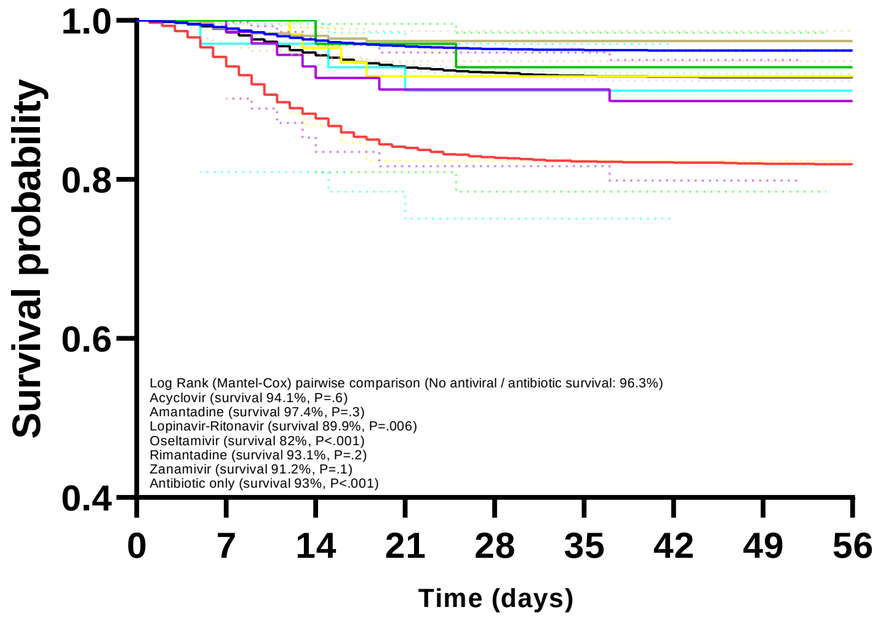
No antiviral / antibiotic	16083	14570	12116	10662	10063	9838	9748	9720	9704
Acyclovir	6	6	4	3	2	2	2	2	2
Amantadine	37	34	30	27	26	25	25	25	25
Lopinavir-Ritonavir	92	88	80	71	71	70	68	68	68
Oseltamivir	5227	4660	3886	3420	3246	3181	3157	3142	3134
Rimantadine	13	13	9	8	7	7	7	7	7
Zanamivir	20	19	19	16	14	13	13	13	13
Antibiotic only	5475	5201	4570	4101	3867	3726	3672	3651	3634

a



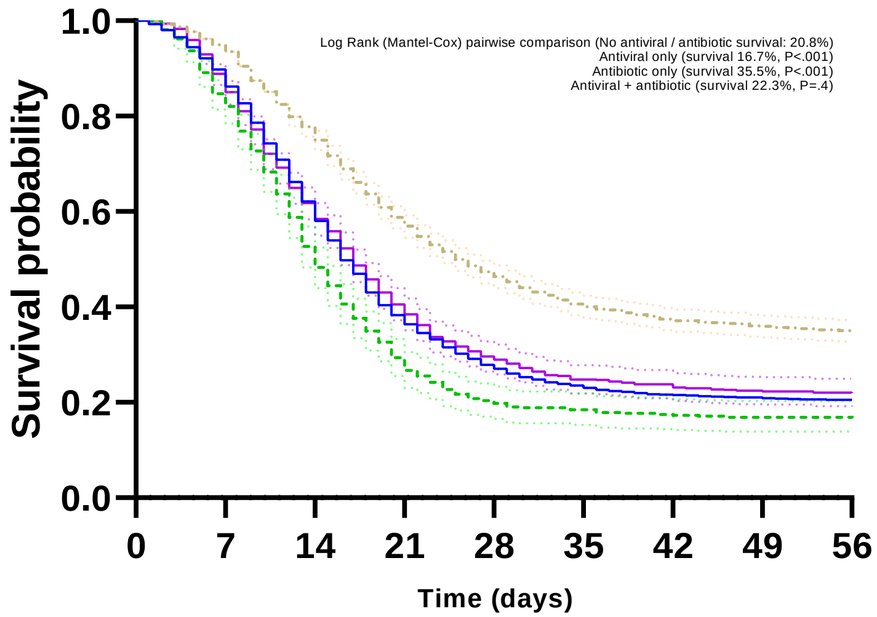
No antiviral / antibiotic	110009	108852	107202	106438	106125	106018	105972	105953	105947
Antiviral only	3518	3315	3083	2967	2923	2907	2902	2899	2895
Antibiotic only	12018	11835	11494	11310	11239	11194	11184	11182	11180
Antiviral + antibiotic	2824	2607	2364	2213	2174	2173	2168	2163	2163

b

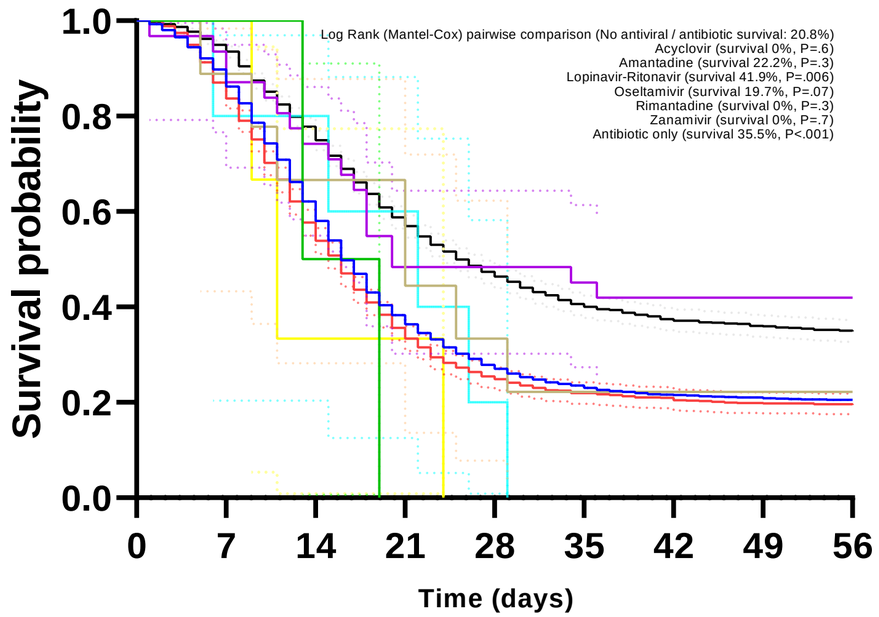


No antiviral / antibiotic	110009	108852	107202	106438	106125	106018	105972	105953	105947
Acyclovir	34	34	33	33	32	32	32	32	32
Amantadine	223	220	217	215	215	215	215	215	215
Lopinavir-Ritonavir	69	68	64	63	63	63	62	62	62
Oseltamivir	7126	6711	6246	5986	5904	5873	5864	5856	5852
Rimantadine	58	58	56	54	54	54	54	54	54
Zanamivir	34	33	33	31	31	31	31	31	31
Antibiotic only	12018	11835	11494	11310	10599	10554	10544	10542	10540

c



No antiviral / antibiotic	4134	3549	2389	1502	1122	964	904	881	868
Antiviral only	526	430	253	140	104	97	91	89	88
Antibiotic only	1725	1614	1294	988	812	708	661	642	626
Antiviral + antibiotic	812	690	474	313	237	204	191	185	182



No antiviral / antibiotic	4134	3549	2389	1502	1122	964	904	881	868
Acyclovir	2	2	1	0	0	0	0	0	0
Amantadine	9	8	6	4	3	2	2	2	2
Lopinavir-Ritonavir	31	27	23	15	15	14	13	13	13
Oseltamivir	1288	1076	692	430	322	285	267	259	255
Rimantadine	3	3	1	1	0	0	0	0	0
Zanamivir	5	4	4	3	1	0	0	0	0
Antibiotic only	1725	1614	1294	988	812	708	661	642	626