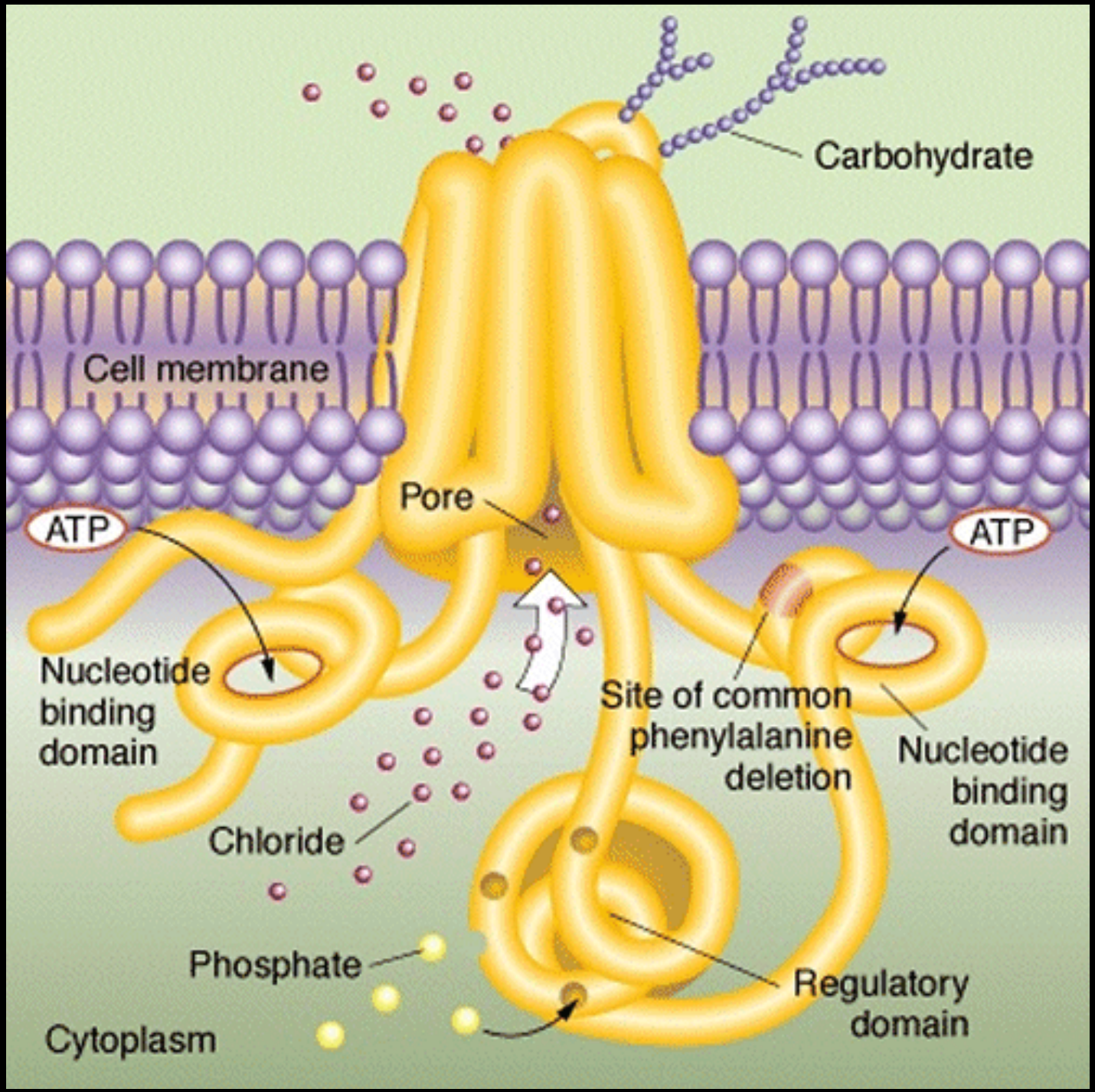
An example of a resident ER protein

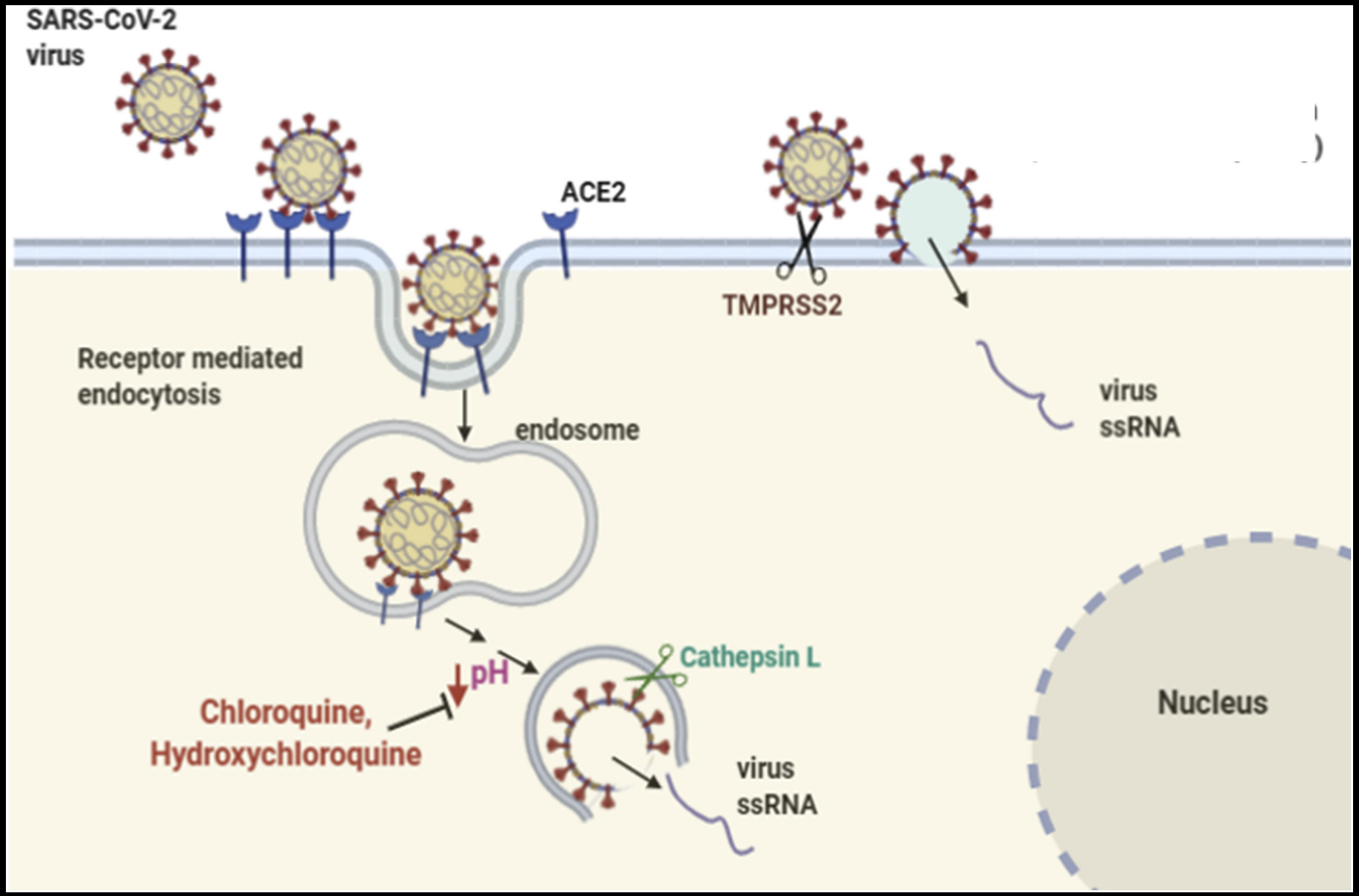
MFGTLLLYCFFLATVPALAETGGERQLSPEKSEIWGPGLKADVV
LPARYFYIQAVDTSGNKFTSSPGEKVFQVKVSAPEEQFTRVGVQ
VLDRKDGSFIVRYRMYASYKNLKVEVKFQGQHVAKSPYILKGPV
YHENCDCPLQDSAAWLREMNCPETIAQIQRDLAHFPAVDPEKIA
VEIPKRFGQRQSLCHYTLKDNKVYIKTHGEHVGFRIFMDAILLS
LTRKVKMPDVELFVNLGDWPLEKKKSNSNIHPIFSWCGSTDSKD
IVMPTYDLTDSVLETMGRVSLDMMSVQANTGPPWESKNSTAVWR
GRDSRKERLELVKLSRKHPELIDAAFTNFFFFKHDENLYGPIVK
HISFFDFFKHKYQINIDGTVAAYRLPYLLVGDSVVLKQDSIYYE
HFYNELQPWKHYIPVKSNLSDLLEKLKWAKDHDEEAKKIAKAGQ
EFARNNLMGDDIFCYYFKLFQEYANLQVSEPQIREGMKRVEPQT
EDDLFPCTCHRKKT**KDEL**

Human CFTR protein sequence

MQRSPLEKASVVSKLFFSWTRPILRKGYRQRLELSDIYQIPSVDSADNLSEKLEREWDRELASKK
NPKLINALRRCFFWRFMFYGIFLYLGEVTKAVQPLLLGRIIASYDPDNKEERSIAIYLGIGLCLL
FIVRTLLLHPAIFGLHHIGMQMRIAMFSLIYKKTLKLSSRVLDKISIGQLVSLLSNNLNKFDEGL
ALAHFVWIAPLQVALLMGLIWELLQASAFCGLGFLIVLALFQAGLGRMMMKYRDQRAGKISERLV
ITSEMIENIQSVKAYCWEEAMEKMIENLRQTELKLTRKAAYVRYFNSSAFFFSGFFVVFLSVLPY
ALIKGIILRKIFTTISFCIVLRMAVTRQFPWAVQTWYDSLGAINKIQDFLQKQEYKTLEYNLTTT
EVVMENVTAFWEEGFGELFEKAKQNNNNRKTSNGDDSLFFSNFSLLGTPVLKDINFKIERGQLLA
VAGSTGAGKTSLLMVIMGELEPSEGKIKHSGRISFCSQFSWIMPGTIKENII**F**GVSYDEYRYRSV
IKACQLEEDISKFAEKDNIVLGEGGITLSGGQRARISLARAVYKDADLYLLDSPFGYLDVLTEKE
IFESCVCKLMANKTRILVTSKMEHLKKADKILILHEGSSYFYGTFSELQNLQPDFSSKLMGCDSF
DQFSAERRNSILTETLHRFSLEGDAPVSWTETKKQSFKQTGEFGEKRKNSILNPINSIRKFSIVQ
KTPLQMNGIEEDSDEPLERRLSLVPDSEQGEAILPRISVISTGPTLQARRRQSVLNLMTHSVNQG
QNIHRKTTASTRKVSLAPQANLTELDIYSRRLSQETGLEISEEINEEDLKECFFDDMESIPAVTT
WNTYLRYITVHKSLIFVLIWCLVIFLAEVAASLVVLWLLGNTPLQDKGNSTHSRNNSYAVIITST
SSYYVFYIYVGVADTLLAMGFFRGLPLVHTLITVSKILHHKMLHSVLQAPMSTLNTLKAGGILNR
FSKDIAILDDLLPLTIFDFIQLLLIVIGAIAVVAVLQPYIFVATVPVIVAFIMLRAYFLQTSQQL
KQLESEGRSPIFTHLVTSLKGLWTLRAFGRQPYFETLFHKALNLHTANWFLYLSTLRWFQMRIEM
IFVIFFIAVTFISILTTGEGEGRVGIILTLAMNIMSTLQWAVNSSIDVDSLMRSVSRVFKFIDMP
TEGKPTKSTKPYKNGQLSKVMIIENSHVKKDDIWPSGGQMTVKDLTAKYTEGGNAILENISFSIS
PGQRVGLLGRTGSGKSTLLSAFLRLLNTEGEIQIDGVSWDSITLQQWRKAFGVIPQKVFIFSGTF
RKNLDPYEQWSDQEIWKVADEVGLRSVIEQFPGKLDFVLVDGGCVLSHGHKQLMCLARSVLSKAK
ILLLDEPSAHLDPVTYQIIRRTLKQAFADCTVILCEHRIEAMLECQQFLVIEENKVRQYDSIQKL
LNERSLFRQAISPSDRVKLFPHRNSSKCKSKPQIAALKEETEEEVQDTRL

CFTR


Carbohydrate
Cell membrane
Pore
ATP
ATP
Nucleotide binding domain
Site of common phenylalanine deletion
Nucleotide binding domain
Chloride
Phosphate
Regulatory domain
Cytoplasm


SARS-CoV-2
virus
ACE2
TMPRSS2
Receptor mediated
endocytosis
endosome
virus
ssRNA
pH
Cathepsin L
Chloroquine,
Hydroxychloroquine
virus
ssRNA
Nucleus

Article

Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates

https://doi.org/10.1038/s41586-020-2558-4

Received: 30 April 2020

Accepted: 10 July 2020

Published online: 22 July 2020

Check for updates

Pauline Maisonnasse[1,11], Jérémie Guedj[2,11], Vanessa Contreras[1,11], Sylvie Behillil[3,4,11], Caroline Solas[5,11], Romain Marlin[1,11], Thibaut Naninck[1], Andres Pizzorno[6], Julien Lemaitre[1], Antonio Gonçalves[2], Nidhal Kahlaoui[1], Olivier Terrier[6], Raphael Ho Tsong Fang[1], Vincent Enouf[3,4,7], Nathalie Dereuddre-Bosquet[1], Angela Brisebarre[3,4], Franck Touret[8], Catherine Chapon[1], Bruno Hoen[9], Bruno Lina[6,10], Manuel Rosa Calatrava[6], Sylvie van der Werf[3,4], Xavier de Lamballerie[8] & Roger Le Grand[1] ✉

Coronavirus disease 2019 (COVID-19) has rapidly become a global pandemic and no antiviral drug or vaccine is yet available for the treatment of this disease[1–3]. Several clinical studies are ongoing to evaluate the efficacy of repurposed drugs that have demonstrated antiviral efficacy in vitro. Among these candidates, hydroxychloroquine (HCQ) has been given to thousands of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus that causes COVID-19—worldwide but there is no definitive evidence that HCQ is effective for treating COVID-19[4–7]. Here we evaluated the antiviral activity of HCQ both in vitro and in SARS-CoV-2-infected macaques. HCQ showed antiviral activity in African green monkey kidney cells (Vero E6) but not in a model of reconstituted human airway epithelium. In macaques, we tested different treatment strategies in comparison to a placebo treatment, before and after peak viral load, alone or in combination with azithromycin (AZTH). Neither HCQ nor the combination of HCQ and AZTH showed a significant effect on viral load in any of the analysed tissues. When the drug was used as a pre-exposure prophylaxis treatment, HCQ did not confer protection against infection with SARS-CoV-2. Our findings do not support the use of HCQ, either alone or in combination with AZTH, as an antiviral drug for the treatment of COVID-19 in humans.

Infection with SARS-CoV-2 is characterized by initial mild disease associated with respiratory symptoms at the peak of viral replication[1,8]. In some patients, a late severe immunological syndrome occurs 6–14 days after the onset of symptoms that may require intensive care and is responsible for most of the fatalities[1–3].

HCQ has well-documented in vitro activity against various viruses[4] and has emerged as an active compound against SARS-CoV-2 in different screening programmes, including a library of 1,520 Food and Drug Administration (FDA)-approved compounds[5]. In Vero E6 cells, HCQ has a 50% maximal effective concentration (EC_{50})[5,9,10] that varies between 0.7 and 4 μM. It may inhibit viral transport in endosomes by alkalinizing the intra-organelle compartment[10,11] and affect glycosylation, as reported for other viruses[12]. The drug may also act as an immunomodulatory agent[13,14]. In patients with lupus, HCQ decreases the level of inflammatory cytokines[11,15,16], which may be relevant for the treatment of COVID-19[2]. Furthermore, it has been proposed that AZTH, which displays in vitro antiviral activity against SARS-COV-2[5,17], could potentiate the efficacy of HCQ[6]. On the basis of these properties, HCQ has been considered for the treatment of COVID-19, alone or in combination with AZTH[6,7].

We and others have set up non-human primate (NHP) models of SARS-CoV-2 infection[18–20]. Here we used cynomolgus macaques (*Macaca fascicularis*) to test different treatment strategies with HCQ, alone or in combination with AZTH, before or after the peak of viral replication. We also tested HCQ administration as pre-exposure prophylaxis treatment against SARS-CoV-2 infection.

In vitro efficacy of HCQ against SARS-CoV-2 infection

We first evaluated the in vitro antiviral activity of HCQ against a SARS-CoV-2 strain isolated from one of the first patients with COVID-19 in France. Post-infection treatment of Vero E6 cells with HCQ resulted in a dose-dependent antiviral effect, with 50% inhibitory concentration

Hydroxychloroquine versus placebo in the treatment of non-hospitalised patients with COVID-19 (COPE – Coalition V): A double-blind, multicentre, randomised, controlled trial

Álvaro Avezum,[a] Gustavo B F Oliveira,[a] Haliton Oliveira,[a] Rosa C Lucchetta,[a] Valéria F A Pereira,[b] André L Dabarian,[b] Ricardo DO Vieira,[c] Daniel V Silva,[c] Adrian P M Kormann,[d] Alexandre P Tognon,[e] Ricardo De Gasperi,[f] Mauro E Hernandes,[g] Audes D M Feitosa,[h] Agnaldo Piscopo,[i] André S Souza,[j] Carlos H Miguel,[k] Vinicius O Nogueira,[l] César Minelli,[m] Carlos C Magalhães,[n] Karen M L Morejon,[o] Letícia S Bicudo,[p] Germano E C Souza,[q] Marco A M Gomes,[r] José J F Raposo Fo,[s] Alexandre V Schwarzbold,[t] Alexandre Zilli,[u] Roberto B Amazonas,[v] Frederico R Moreira,[a] Lucas B O Alves,[a] Silvia R L Assis,[ac] Precil D M M Neves,[a] Jessica Y Matuoka,[a] Icaro Boszczowski,[a] Daniela G M Catarino,[a] Viviane C Veiga,[w] Luciano C P Azevedo,[x] Regis G Rosa,[y] Renato D Lopes,[z,aa] Alexandre B Cavalcanti,[ab] and Otavio Berwanger[ac], on behalf of the COPE - COALITION COVID-19 Brazil V Investigators [1]*

[a]International Research Center, Hospital Alemão Oswaldo Cruz, Rua Treze de Maio, 1815; Bloco A, 1o SS, São Paulo, SP 01327-001, Brazil
[b]ALPHACOR Cardiologia Clínica e Diagnóstica, Barueri, SP, Brazil
[c]Hospital e Clínica São Roque, Ipiaú, BA, Brazil
[d]AngioCor, Blumenau, SC, Brazil
[e]Hospital São Vicente de Paulo, Passo Fundo, RS, Brazil
[f]Hospital Tacchini, Bento Goncalves, RS, Brazil

Hydroxychloroqu
of non-hospitalis
Coalition V): A do
controlled trial

Álvaro Avezum,[a] Gustavo B F Oliveira,[a]
Ricardo DO Vieira,[c] Daniel V Silva,[c] Adria
Audes D M Feitosa,[h] Agnaldo Piscopo,[i] A
Carlos C Magalhães,[n] Karen M L Morejor
Alexandre V Schwarzbold,[t] Alexandre Zil
Precil D M M Neves,[a] Jessica Y Matuoka,[
Regis G Rosa,[y] Renato D Lopes,[z,aa] Alexa
COVID-19 Brazil V Investigators [1]*

[a]International Research Center, Hospita
01327-001, Brazil
[b]ALPHACOR Cardiologia Clínica e Diagn
[c]Hospital e Clínica São Roque, Ipiaú, BA, Brazil
[d]AngioCor, Blumenau, SC, Brazil
[e]Hospital São Vicente de Paulo, Passo Fundo, RS, Brazil
[f]Hospital Tacchini, Bento Gonçalves, RS, Brazil

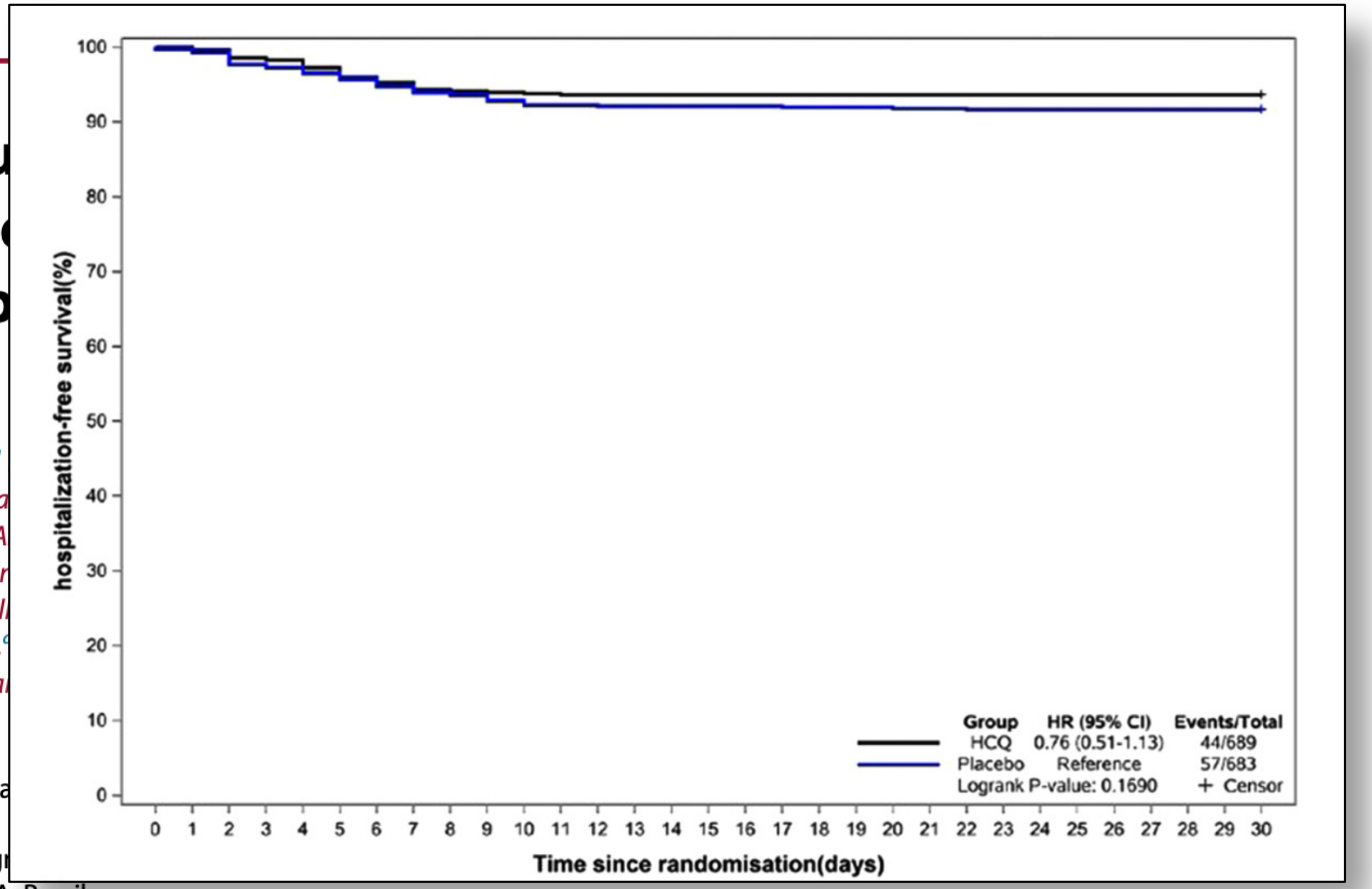
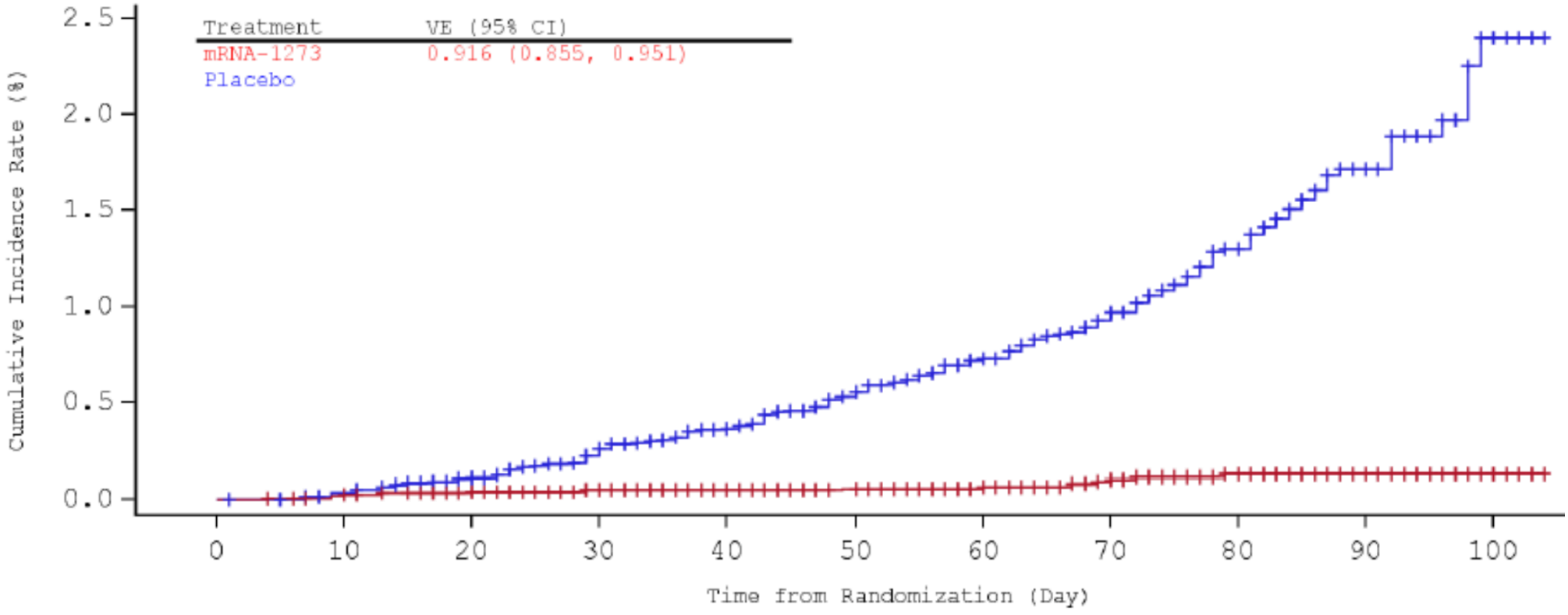
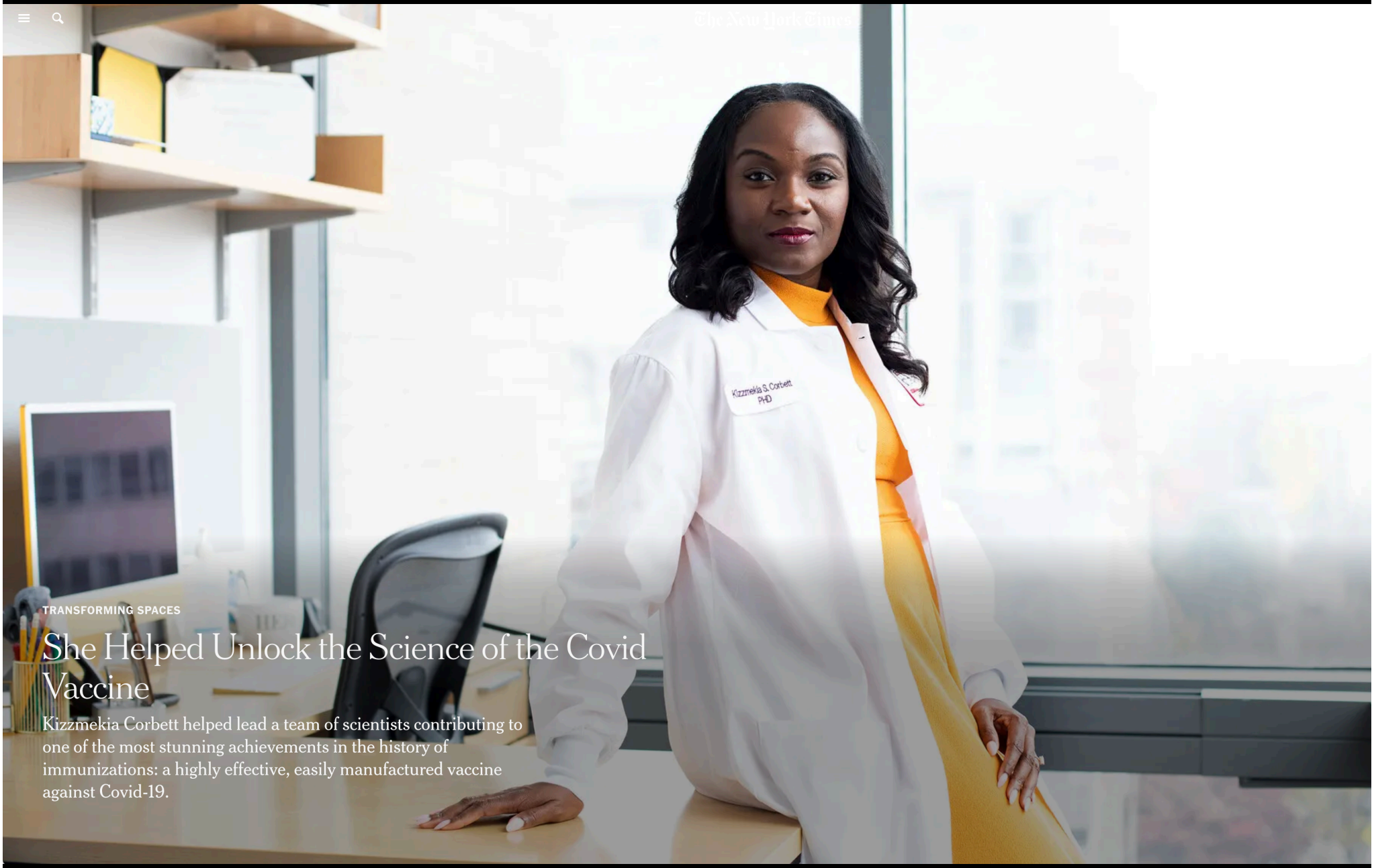


Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set





TRANSFORMING SPACES

She Helped Unlock the Science of the Covid Vaccine

Kizzmekia Corbett helped lead a team of scientists contributing to one of the most stunning achievements in the history of immunizations: a highly effective, easily manufactured vaccine against Covid-19.