新型冠状病毒信息简报

第 70 期（2020 年 8 月 29 日-9 月 4 日报）

上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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内容介绍

1. 2020 年 9 月 3 日疫情

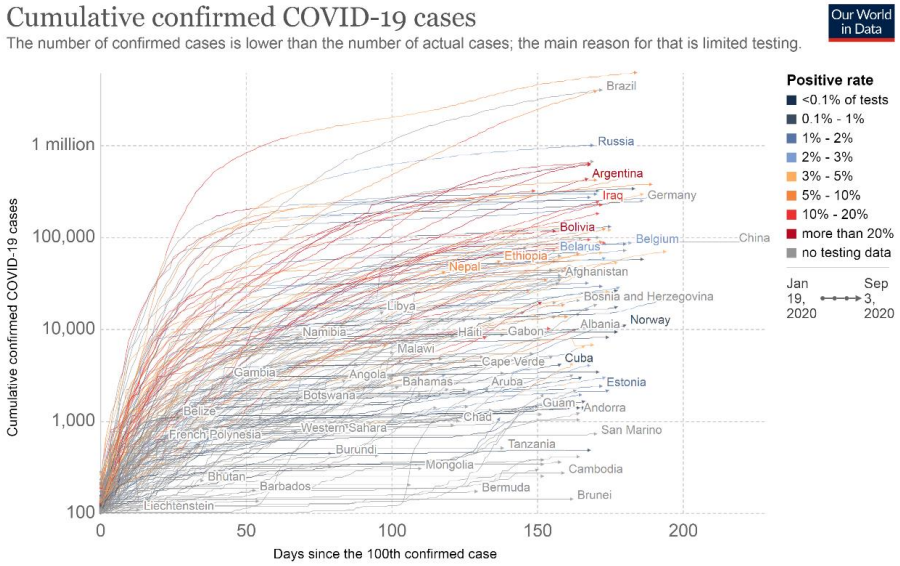
数据来源：WHO

发布时间：2020 年 9 月 3 日北京时间下午 4 点

链接：https://covid19.who.int/

根据 WHO 提供的数据，2020 年 9 月 3 日全球累计确诊新型冠状病毒病人 **25, 884, 895** 例，当日新增确诊 **279, 338** 例，累计死亡 **859, 130** 例，当日新增死亡 **6, 318**。

中国累计确诊 90, 442 例，累计死亡 4, 734 例，当日新增确诊 20 例，新增死亡 3 例。



Source: European CDC – Situation Update Worldwide – Last updated 3 September, 10:04 (London time), Official data collated by Our World in Data
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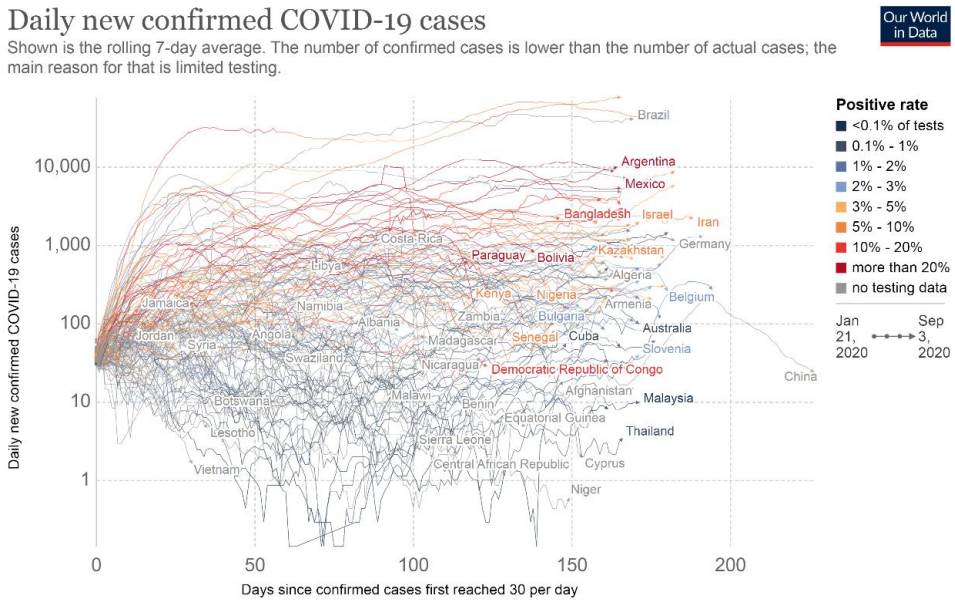
重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）

最上面的线为美国，巴西之下的线为印度。



Source: European CDC – Situation Update Worldwide – Last updated 3 September, 10:04 (London time), Official data collated by Our World in Data
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重点国家每日新增确诊数量曲线（https://ourworldindata.org/covid-

cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）

全国新型冠状病毒肺炎新增确诊病例分布图（9 月 3 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. FDA 允许 Sound Pharmaceuticals 测试 SPI-1005 作为 COVID-19 的新疗法

FDA allows Sound Pharmaceuticals to test SPI-1005 as a novel treatment for COVID-19

来源：PRNewswire

发布时间：2020-08-31

链接：https://www.prnewswire.com/news-releases/fda-allows-sound-pharmaceuticals-to-test-spi-1005-as-a-novel-treatment-for-covid-19-301120739.html

第一作者：Sound Pharmaceuticals

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编译者：张丽双

中文摘要：

中国上海科技大学免疫化学研究所蒋华良、饶子和、杨海涛课题组联合攻关，启动了一项结构辅助药物设计--虚拟药物筛选和高通量筛选相结合的计划，确定了 COVID-19 病毒主要蛋白酶 Mpro 的晶体结构，并从 10000 种化合物中筛选出 Mpro 的 6 种抑制剂，在六种抑制剂中，Ebselen 的 IC50 值低至 0.67 μM。研究成果近期发表在 Nature 杂志上。

FDA 已允许两项临床 2 期研究开始在 COVID-19 患者中测试 Ebselen（SPI-1005）。Sound Pharmaceuticals，Inc.（SPI）正在开发 SPI-1005，以 Ebselen 为主要成分。120 名中度或重度疾病成年人将参加两项随机，双绑定，安慰剂对照试验（RCT），并用口服药物治疗 7 或 14 天。SPI 将另外利用美国过敏和传染病研究所（NIAID）提供的非临床和临床前服务计划。这将包括在体外和体内扩大对 Ebselen 的测试，包括独特的 COVID-19 传播活体动物模型。

“我们很高兴地宣布，在 NIAID 的支持下，这些关键的 2 期 RCT 的启动以及非临床研究中依

布硒仑的持续测试，” Sound Pharmaceuticals 联合创始人兼首席执行官 Jonathan Kil 博士说。

Abstract:

SEATTLE, Aug. 31, 2020 /PRNewswire/ -- Sound Pharmaceuticals, Inc. (SPI) is pleased to announce that the FDA has allowed two Phase 2 studies to begin testing ebselen (SPI-1005) in COVID-19 patients. SPI is developing SPI-1005, a novel anti-inflammatory drug which was recently shown to inhibit nCoV2 activity and viral replication. 120 adults with moderate or severe disease will be enrolled in two randomized, double-bind, placebo-controlled trials (RCTs) and treated for 7 or 14 days with the oral drug. Separately, SPI will be utilizing the non-clinical and pre-clinical services program offered by the National Institute of Allergy and Infectious Diseases (NIAID). This will involve the expanded testing of ebselen both in vitro and in vivo, including a unique live animal model of COVID-19 transmission. "We are thrilled to announce the initiation of these critical Phase 2 RCTs and the continued testing of ebselen in non-clinical studies with the support of the NIAID," said Dr. Jonathan Kil, MD, Co-Founder and CEO of Sound Pharmaceuticals.

In a recent study published in the scientific journal Nature,1 Jin and colleagues detailed three major findings involving nCoV2, the virus responsible for COVID-19. First, they crystalized the main protease (Mpro) structure, a critical enzyme responsible for viral replication. Second, they identified several potential pharmacologic agents or drugs that inhibit Mpro activity, utilizing a structure-based virtual screening of >10,000 compounds including approved and investigational drugs, and other pharmacologically active compounds. Among the six compounds that showed significant inhibition of Mpro activity, ebselen demonstrated the lowest inhibitory concentration or IC50. Third, they screened the >10,000 compound library for viral load reduction in an in vitro cell-based assay, where ebselen demonstrated the lowest effective concentration or EC50. Mpro may be the first identified specific nCoV2 drug target that, when inhibited, could reduce viral load or virulence, and potentially mitigate the devastating course of COVID-19.

SPI-1005 is an investigational new drug that contains ebselen, a novel small molecule that mimics and induces the activity of Glutathione Peroxidase (GPx) in the inner ear, retina, brain, lung, and kidney. SPI-1005 represents a novel class of anti-inflammatory and is under clinical investigation in several neurotologic diseases where GPx activity is reduced including sensorineural hearing loss, tinnitus, ototoxicity, Meniere's disease, and in neuropsychiatric disease including bipolar mania and treatment-resistant depression. SPI-1005 is entering pivotal Phase 3 trials for the treatment of Meniere's Disease and is currently in a Phase 2b study involving Cystic Fibrosis patients with acute respiratory infections receiving IV antibiotics.

3. 到目前为止，非洲似乎没有受到 COVID-19 的影响，科学家们正在努力解释原因

The pandemic appears to have spared Africa so far. Scientists are struggling to

explain why
来源：Science
发布时间：2020-08-11
链接：https://www.sciencemag.org/news/2020/08/pandemic-appears-have-spared-africa-so-far-scientists-are-struggling-explain-why#
第一作者：Linda Nordling
编译者：王玮
中文摘要：
尽管非洲上周报告了其第一百万例官方 COVID-19 病例，但到目前为止，非洲似乎相对较好地抵御了这场大流行，每千人中只有不到一例确诊病例，到目前为止 23000 人死亡。然而，几项抗体调查显示，有更多的非洲人感染了冠状病毒，这一差异令非洲大陆的科学家感到困惑。“我们没有答案，”肯尼亚医学研究所- Wellcome Trust 研究计划的免疫学家 Sophie Uyoga 说。
在对 3000 多名献血者进行检测后，Uyoga 及其同事在上个月的一份预印本中估计，年龄在 15 至 64 岁之间的肯尼亚人中，每 20 人中就有 1 人（即 160 万人）具有 SARS-CoV-2 抗体，这是过去感染的迹象。这将使肯尼亚与 5 月中旬的西班牙平起平坐，当时该国正从冠状病毒峰值下降，官方公布的 COVID-19 死亡人数为 27000 人。研究结束时，肯尼亚官方公布的死亡人数为 100 人。肯尼亚的医院也没有报告有大量 COVID-19 症状的人。
非洲的其他抗体研究也得出了类似的发现。马拉维-利物浦 Wellcome Trust 临床研究项目的免疫学家 Kondwani Jambo 及其同事对马拉维布兰太尔的 500 名无症状医护人员进行了一项调查，得出的结论是，高达 12.3%的人接触过冠状病毒。根据这些发现和其他地方 COVID-19 的死亡率，他们估计当时布兰太尔报告的 17 岁死亡人数比预期低 8 倍。
科学家们在莫桑比克东北部城市楠普拉和彭巴对大约 1 万人进行了调查，发现 3%至 10%的被检测者具有 SARS-CoV-2 抗体，这取决于他们的职业；市场商贩的比率最高，其次是卫生工作者。然而，在人口约 75 万的楠普拉市，当时只有 300 人被确诊感染。莫桑比克只有 16 例确诊的 COVID-19 死亡病例。微生物学家和流行病学家 Yap Boum 说，他发现喀麦隆人身上也有很高的 SARS-CoV-2 抗体，这一结果尚未公布。
那么，如何解释抗体数据与官方病例和死亡人数之间的巨大差距呢？部分原因可能是非洲漏诊的病例比世界其他地区多，因为它的检测能力要少得多。肯尼亚每天每 10000 名居民中就有一人被检测到 SARS-CoV-2 感染，是西班牙或加拿大感染率的十分之一。尼日利亚是非洲大陆上人口最多的国家，每天每 5 万人中有一人接受测试。甚至许多死于 COVID-19 的人可能得不到正确的诊断。
内罗毕大学的病理学家 Anne Barasa 说，在这种情况下，你仍然会预期死亡率总体上会上升，但肯尼亚没有出现这种情况。领导西班牙抗体调查 Marina Pollán 说，非洲的年轻可能会保护它。西班牙的平均年龄是 45 岁；在肯尼亚和马拉维，分别是 20 岁和 18 岁。世界各地的年轻人患重病或死于病毒的可能性要小得多。
Jambo 正在探索一种假说，即非洲人接触其他冠状病毒的次数比人类感冒多，这可能对 COVID-19 有一定的防御作用。Boum 补充说，另一种可能是，经常接触疟疾或其他传染病可能会激发免疫系统对抗新的病原体，包括 SARS-CoV-2。另一方面，Barasa 怀疑基因因素可以保护肯尼亚人免受严重疾病的侵袭。
更多的抗体调查可能有助于了解情况。一项由法国资助的研究将在几内亚、塞内加尔、贝宁、加纳、喀麦隆和刚果民主共和国测试数千种抗体；预计结果将于 10 月公布。
南非国家传染病研究所的负责人 Lynn Morris 说，与此同时，南非计划在 COVID-19 热点地区和普通人群中进行一系列血清学研究。她指出，研究中发现的抗体流行率很可能低估了真

实感染率，因为病毒不会在某些人体内诱发抗体，而且抗体水平会随着时间的推移而下降。如果数千万非洲人已经被感染，这就提出了一个问题：非洲大陆是否应该在没有疫苗的情况下尝试“群体免疫”，Boum 说，一个有争议的想法是让病毒自行传播，让民众免疫，也许同时保护最脆弱的群体。这可能比控制措施更可取，因为从长远来看，这些措施会削弱经济，更可能损害公众健康。
但是南非医学研究委员会主席 Glenda Gray 说，将 COVID-19 政策建立在抗体调查的基础上可能是危险的。目前还不清楚抗体是否真的能产生免疫力，如果是，它能持续多久，格雷说，在这种情况下，她问道，“这些数字到底告诉我们什么？”

Abstract:
Although Africa reported its millionth official COVID-19 case last week, it seems to have weathered the pandemic relatively well so far, with fewer than one confirmed case for every thousand people and just 23,000 deaths so far. Yet several antibody surveys suggest far more Africans have been infected with the coronavirus—a discrepancy that is puzzling scientists around the continent. “We do not have an answer,” says immunologist Sophie Uyoga at the Kenya Medical Research Institute–Wellcome Trust Research Programme…

4. 在被 COVID-19 影响的护理机构人群中广泛存在 SARS-CoV-2 抗体：英国的一个回顾性队列研究

High prevalence of SARS-CoV-2 antibodies in care homes affected by COVID-19; a prospective cohort study in England
第一作者：Shamez N Ladhani
通讯作者：Shamez Ladhani
通讯作者单位：Public Health England, UK
DOI 或 PUBMED ID：Preprint
编译者：蒋立春
链接：
https://www.medrxiv.org/content/10.1101/2020.08.10.20171413v1
Abstract:
中文摘要：
作者们在 COVID-19 疫情爆发时对伦敦的 6 个护理机构进行了调研，发现其中护理人员和居住人员很高比例感染 SARS-CoV-2。在本研究中作者们报道了这些护理机构 5 周后的血清学分析结果。在主要的 COVID-19 爆发之时的研究之后的 5 周，采集护理机构护理人员和居住人员的血样进行 SARS-CoV-2 抗体水平和中和抗体的检测以及鼻咽拭子进行 RT-PCR 核酸检测。在原研究中的 518 位居住人员和护理人员中，有 208 位（占幸存总居住人员的 86.3%）幸存的居住人员以及 186 名护理人员（占幸存总护理人员的 73.2%）进行了血清学测试。几乎所有的 SARS-CoV-2 RT-PCR 阳性的居住人员和护理人员在 5 周后都是 SARS-CoV-2 抗体阳性。其中有症状的为 100%抗体阳性（居住人员 35/35，100%，护理人员 22/22，100%），无症状的抗体比例稍低（居住人员 32/33，97.0%，护理人员 21/22，95.1%）。有症状但是 SARS-CoV-2 RT-PCR 阴性的居住人员和护理人员也有很高的血清学阳性率(居住人员 23/27，85.2%；护理人员 18/21， 85.7%)。血清学阳性率在无症状 SARS-CoV-2 阴性的人群中也高（居住人员 62/92，67.3%；护理人员 95/143，66.4%)。中和抗体存在于 89.4%的血清学阳性个体中，和年龄或者是否有症状无关。还有 10 个居住人员仍然是 RT-PCR 阳性（10/108，9.3%），但

是 RT-PCR 的循环数下降。这 10 个人中做了血清学检测的所有 7 个人都是血清阳性。在 3 名居住人员以及护理人员中发现了新的感染。SARS-CoV-2 的 RT-PCR 检测显著低估了机构的疫情爆发程度。老年体弱的居住人员和更年轻的护理人员一样，也可以稳定产生对抗 SARS-CoV-2 的中和抗体（注：**80 岁以上的老人也可以产生中和抗体**）。不管鼻咽拭子 RT-PCR 是否阳性，是否有症状，这些护理机构超过 2/3 的人员可以检测到针对 SARS-CoV-2 的抗体。

FIGURE 4.

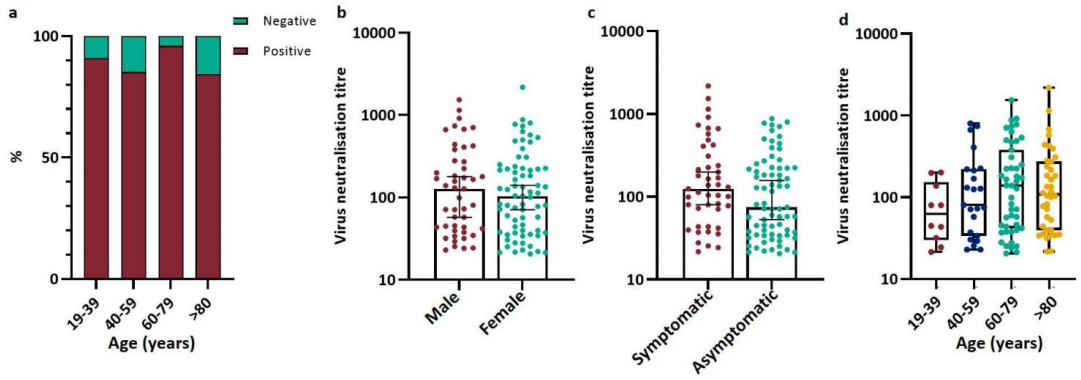

Figure 4. Virus neutralising antibody titre analysis. a) Virus neutralising positive and negative percentage by age group for whole cohort. N=132 b) Virus neutralisation titre by sex. Bars indicate median and 95% confidence interval. c) Virus neutralisation titre by symptom status during the initial testing period. Bars indicate median and 95% confidence interval. d) Virus neutralisation titre by age group. Box and whisker plot with bars indicating full range of results. N=118. Statistical analysis a) chi-square test, no significant difference; b and c) Mann-Whitney U Test; d) Kruskal Wallis with Dunn's multiple comparisons test adjustment, no significant difference

Background: We investigated six London care homes experiencing a COVID-19 outbreak and found very high rates of SARS-CoV-2 infection among residents and staff. Here we report follow-up serological analysis in these care homes five weeks later.

Methods: Residents and staff had a convalescent blood sample for SARS-CoV-2 antibody levels and neutralising antibodies by SARS-COV-2 RT-PCR five weeks after the primary COVID-19 outbreak investigation. Results: Of the 518 residents and staff in the initial investigation, 208/241 (86.3%) surviving residents and 186/254 (73.2%) staff underwent serological testing. Almost all SARS-CoV-2 RT-PCR positive residents and staff were antibody positive five weeks later, whether symptomatic (residents 35/35, 100%; staff, 22/22, 100%) or asymptomatic (residents 32/33, 97.0%; staff 21/22, 95.1%). Symptomatic but SARS-CoV-2 RT-PCR negative residents and staff also had high seropositivity rates (residents 23/27, 85.2%; staff 18/21, 85.7%), as did asymptomatic RT-PCR negative individuals (residents 62/92, 67.3%; staff 95/143, 66.4%). Neutralising antibody was present in 118/132 (89.4%) seropositive individuals and was not associated with age or symptoms. Ten residents (10/108, 9.3%) remained RT-PCR positive, but with lower RT-PCR cycle threshold values; all 7 tested were seropositive. New infections were detected in three residents and one staff member. Conclusions: RT-PCR

testing for SARS-CoV-2 significantly underestimates the true extent of an outbreak in institutional settings. Elderly frail residents and younger healthier staff were equally able to mount robust and neutralizing antibody responses to SARS-CoV-2. More than two-thirds of residents and staff members had detectable antibodies against SARS-CoV-2 irrespective of their nasal swab RT-PCR positivity or symptoms status.

5. 冰岛人群针对 SARS-CoV-2 的体液免疫反应

Humoral Immune Response to SARS-CoV-2 in Iceland

https://www.nejm.org/doi/full/10.1056/NEJMoa2026116?query=recirc_curatedRelated_article

来源：NEMJ

发表时间：2020-09-01

第一作者：Daniel F. Gudbjartsson

通讯作者： Kari Stefansson

通讯作者单位：deCODE Genetics, Amgen

DOI 或 PUBMED ID：10.1056/NEJMoa2026116

Amgen 公司位于冰岛的 deCODE Genetics 公司对冰岛人群进行了广泛（约人口 9%的人群）的血清学检测，发现，针对 SARS-CoV-2 的中和抗体在确诊感染后 4 个月内并未下降。研究者们估计因感染 SARS-CoV-2 而死亡的风险为 0.3%，冰岛感染者中有 44%未经过 qPCR 确诊。具体的翻译和评述可见于 NEMJ 的中文公众号。链接：链接:https://mp.weixin.qq.com/s/EnD1XHJ8T_PgBFBB4mcJGg

Abstract:

BACKGROUND

Little is known about the nature and durability of the humoral immune response to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

METHODS

We measured antibodies in serum samples from 30,576 persons in Iceland, using six assays (including two pan-immunoglobulin [pan-Ig] assays), and we determined that the appropriate measure of seropositivity was a positive result with both pan-Ig assays. We tested 2102 samples collected from 1237 persons up to 4 months after diagnosis by a quantitative polymerase-chain-reaction (qPCR) assay. We measured antibodies in 4222 quarantined persons who had been exposed to SARS-CoV-2 and in 23,452 persons not known to have been exposed.

RESULTS

Of the 1797 persons who had recovered from SARS-CoV-2 infection, 1107 of the 1215 who were tested (91.1%) were seropositive; antiviral antibody titers assayed by two pan-Ig assays increased during 2 months after diagnosis by qPCR and remained on a plateau for the remainder of the study. Of quarantined persons, 2.3% were seropositive; of those with unknown exposure, 0.3% were positive. We estimate that 0.9% of Icelanders were infected with SARS-CoV-2 and that the infection was fatal in 0.3%. We also estimate that 56% of all SARS-CoV-2 infections in Iceland had been diagnosed with qPCR, 14% had occurred in quarantined persons who had not been tested with qPCR (or who had not received

a positive result, if tested), and 30% had occurred in persons outside quarantine and not tested with qPCR.
CONCLUSIONS
Our results indicate that antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis. We estimate that the risk of death from infection was 0.3% and that 44% of persons infected with SARS-CoV-2 in Iceland were not diagnosed by qPCR.

6. 对错误的 SARS-CoV-2 抗原的反应进行检测？

Testing for responses to the wrong SARS-CoV-2 antigen?
来源：The Lancet
发布时间：2020-08-28
链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31830-4/fulltext
第一作者：Carolina Rosadas
通讯作者：Richard S Tedder
通讯作者单位：Department of Infectious Disease, Imperial College London, London, UK
DOI 或 PUBMED ID：https://doi.org/10.1016/S0140-6736(20)31830-4
编译者：宋张悦
中文摘要：
两种商用抗体检测（雅培 SARS-CoV-2 IgG，美国；和罗氏 Elecsys Anti-SARS-CoV-2，瑞士），都针对核蛋白抗体(抗-NP)，构成了英国政府应对 COVID-19 大流行的基石。该检测由雅培公司生产，在欧洲和美国广泛使用，声称在症状开始后 14 天或更长时间的特异性和敏感性大于 99%，并已得到英国公共卫生局的验证。
研究人员共收集到了 2204 份来自工作人员和患者的血清样本，这些患者之前在雅培平台上筛查过抗-NP，这是英国国家卫生服务的常规诊断服务的一部分。主要选择雅培结合比率（Abbott binding ratio）在 0.25-2.5 范围内的样本，并使用内部双结合抗原 ELISA（Imperial Hybrid DABA; Imperial College London, London, UK）进一步检测，它检测对严重急性呼吸综合征冠状病毒 2 (SARS-CoV-2)受体结合域(RBD)的总抗体。检测 cov-19 大流行前的 825 份血清样本，该检测方法的特异性为 100% (95% CI 99.6-100)，在评估 RT-PCR 确诊的 SARS-CoV-2 感染个体的 276 份血清样本时，其敏感性为 98.9%(96.8-99.8)。
在 511 个雅培结合比率为 0.25-1.4 的样本中，294 个(58%)检测到抗 RBD 抗体（范围：结合比 0.25-0.5 为 34%，结合比 1.25-1.4 为 94%）。按 Imperial Hybrid DABA 结合率将样本分为 5 组。从每组随机抽取 8 份血清样本，通过第二步内部测定法，即 S1 G 和 M 捕获 ELISA 来验证抗 RBD 结果。32 份样本中有 28 份(88%)检测到抗 S1 抗体，这些样品对抗 RBD 有反应，但对抗 NP 不反应。未被 S1 捕获 ELISA 确认的四份血清样本在 Imperial Hybrid DABA 中结合率较低，与 Imperial Hybrid DABA 相比，S1 的非反应性与捕获测定的较低灵敏度相符。在雅培试验中，从 76 份有反应的血清中随机抽取 8 份样本，对 S1 抗体无反应。
这些发现有两种可能的解释：雅培测定结果存在假阳性反应；或这些患者没有对 S1 产生可检测到的体液反应，如无症状或轻度感染。
英国政府促进使用雅培的测定法的决定是轻率的。抗-NP 在该领域不敏感：为什么这种不敏感没有被那些在英国验证其使用的人所认识到？而且，雅培的测定法不能准确地表明恢复期个体中存在中和性和潜在保护性抗体。那些仍然打算将此检测作为过去感染的唯一标志物的

人，明智的做法是考虑验证性算法，以便更好地告知被调查抗-NP 的个体。

Abstract
Two commercial antibody tests (Abbott SARS-CoV-2 IgG, Abbott Diagnostics, Abbott Park, IL, USA; and Roche Elecsys Anti-SARS-CoV-2, Roche Diagnostics, Basel, Switzerland), both targeting antibodies to nucleoprotein (anti-NP), constitute the cornerstone of the UK Government's response to the COVID-19 pandemic. The test manufactured by Abbott, which is widely used in Europe and the USA, claims a specificity and sensitivity of greater than 99% at 14 days or more after symptoms started and has been validated by Public Health England.
The UK Government's decision to facilitate use of Abbott' assay was intemperate. Anti-NP is insensitive in the field: why was this insensitivity not recognised by those who validated its use in the UK? Moreover, Abbott's assay does not indicate accurately the presence of neutralising and potentially protective antibodies in the convalescent individual. Those who might still deign to use this assay as the sole marker of past infection would be wise to consider confirmatory algorithms to better inform individuals investigated for anti-NP.

7. 康希诺生物新冠疫苗进入 III 期临床

根据微信公众号药物简讯的报道，康希诺生物新冠疫苗 9 月 2 日进入 III 期临床。首批三期临床将在俄罗斯进行。

链接：https://mp.weixin.qq.com/s/a9DrtKB5L9XA-50Ppox5YA

编者注：上期简报小编根据三期临床注册情况认为康希诺新冠疫苗已经进入 III 期临床，**属错误报道。**

8. 皮质类固醇在 COVID-19 引起的急性呼吸窘迫综合征中的作用

Corticosteroids in COVID-19 ARDS

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中文摘要：

皮质类固醇，例如氢化可的松和地塞米松，具有抗炎、抗纤维化和血管收缩作用，重症治疗主治医师们数十年来一直在尝试利用这些激素来改善急性呼吸窘迫综合征（ARDS）和败血性休克患者的预后。在 COVID-19 大流行开始时，有关糖皮质激素的指导意见不一。本期 JAMA 包括了 3 个评估 COVID-19 重症患者糖皮质激素治疗的多中心 RCT，以及 WHO 支持的前瞻性

Meta 分析。REMAP-CAP 试验是一项针对肺炎的多中心多国适应性平台试验，将 403 例重症 COVID-19 患者（在重症监护病房[ICU]中接受呼吸或心血管辅助）随机分配到 3 个开放标签组中：固定的小剂量氢化可的松，休克依赖性氢化可的松，或不加氢化可的松。CoDEX 试验将巴西的 41 名重症监护病房中的 299 名患有中度或重度 ARDS 和 COVID-19 的患者随机分配给高剂量地塞米松（20 毫克/天，连续 5 天，然后 10 毫克/天，连续 5 天）与常规护理。CAPE COVID 是这 3 项研究的唯一的遮盲安慰剂对照试验，在法国 9 个 ICU 中将 149 例 COVID-19 严重呼吸系统疾病患者给小剂量氢化可的松（200 mg / d 输注，根据方案逐渐减少），与安慰剂进行了随机对照。世卫组织 COVID-19 疗法快速证据评估（REACT）工作组的前瞻性 Meta 分析汇总了 7 项试验（RECOVERY，REMAP-CAP，CoDEX，CAPE COVID 和 3 项其他试验）的数据，共 1703 例患者（678 例随机接受皮质类固醇激素治疗，1025 接受常规护理或安慰剂治疗），其中 59％来自 RECOVERY 试验。这 3 项皮质类固醇随机试验的发表以及本期 JAMA 的前瞻性 Meta 分析代表了 COVID-19 患者治疗方面的重要一步。这些试验和 Meta 分析增强了信心，进一步确定了获益，并将 COVID-19 相关 ARDS 的常规治疗转向了糖皮质激素。

Abstract

Corticosteroids, such as hydrocortisone and dexamethasone, have anti-inflammatory, antifibrotic, and vasoconstrictive effects, which intensivists have been trying to leverage for decades to improve outcomes in patients with acute respiratory distress syndrome (ARDS) and septic shock.At the onset of the coronavirus disease 2019 (COVID-19) pandemic, guidance regarding corticosteroids was mixed. This issue of JAMA includes 3 multicenter RCTs that assessed corticosteroid therapy in critically ill patients with COVID-19, as well as the WHO-sponsored prospective meta-analysis. The REMAP-CAP trial, an existing multicenter, multinational adaptive platform trial for pneumonia, randomized 403 patients with severe COVID-19 (in the intensive care unit [ICU] and receiving respiratory or cardiovascular organ support) to 1 of 3 open-label groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone. The CoDEX trial randomized 299 patients in 41 ICUs in Brazil with moderate or severe ARDS and COVID-19 to open-label high-dose dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) vs usual care alone. In the only blinded, placebo-controlled trial of the 3, CAPE COVID randomized 149 patients in 9 ICUs in France with severe respiratory disease from COVID-19 to low-dose hydrocortisone (200 mg/d infusion, tapered per protocol) vs placebo. The prospective meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials) totaling 1703 patients (678 had been randomized to corticosteroids and 1025 to usual care or placebo), of which 59% were from the RECOVERY trial. The publication of these 3 randomized trials of corticosteroids and the prospective meta-analysis in this issue of JAMA represents an important step forward in the treatment of patients with COVID-19. These trials and the meta-analysis have strengthened confidence, further defined the benefit, and shifted usual care of COVID-19–related ARDS to include corticosteroids.

9. 地塞米松对中重度急性呼吸窘迫综合征和 COVID-19 患者存活天数和无呼吸机天数的影响

Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients WithModerate or Severe Acute Respiratory Distress Syndrome and COVID-19

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中文摘要：

重要性：由 2019 年冠状病毒病（COVID-19）引起的急性呼吸窘迫综合征（ARDS）与大量死亡率和卫生保健资源的使用有关。使用地塞米松可以减轻这些患者的肺损伤。

目的：确定静脉注射地塞米松是否增加了 COVID-19 相关 ARDS 患者的无呼吸机天数。

设计、设置和参与者：在巴西 41 家重症监护病房（ICU）进行的多中心、随机、开放标签临床试验。根据柏林定义，COVID-19 和中重度 ARDS 患者于 2020 年 4 月 17 日至 6 月 23 日登记。最终随访于 2020 年 7 月 21 日完成。在达到 350 名患者的计划样本量之前，试验在相关研究发表后提前停止。

干预措施：每天静脉注射 20 mg 地塞米松，持续 5 天，每天 10 mg 地塞米松，持续 5 天或直到 ICU 出院，外加标准护理（n = 151）或单独的标准护理（n = 148）。

主要结果和措施：主要结果是在最初的 28 天内无呼吸机天数，定义为存活和无机械通气。次要结果是 28 天的全因死亡率，使用 6 点序量表的第 15 天患者临床状况（范围为 1，未住院至 6，死亡），前 28 天无 ICU 天数，机械通气 28 天的持续时间，以及 48 小时，72 小时和 7 天的顺序器官衰竭评估（SOFA）得分（范围 0-24，得分越高表示器官功能障碍越严重）。

结果 共有 299 名患者（平均[标准差]岁，61 岁；37%的女性）被纳入并完成随访。随机分入地塞米松组的患者在前 28 天内平均无呼吸机天数为 6.6 天（95%CI，5.0-8.2），而在标准护理组中，平均无呼吸机天数为 4.0（95%CI，2.9-5.4）（差异），2.26； 95%CI，0.2-4.38；P = 0.04）。在第 7 天，地塞米松组患者的平均 SOFA 评分为 6.1（95%CI，5.5-6.7），而标准护理组为 7.5（95%CI，6.9-8.1）（差异，-1.16； 95%CI ，-1.94 至-0.38； P = 0.004）。在第 28 天全因死亡率，前 28 天无 ICU 天数，第 28 天的机械通气持续时间或第 15 天的 6 分序数评分等方面的预先确定的次要结果中，全因死亡率没有显着差异。地塞米松组 33 例（21.9%）出现继发感染，标准护理组 43 例（29.1%）出现继发感染，47 例（31.1%）对 42 例（28.3%）需要胰岛素控制血糖，5 例（3.3%）对 9 例（6.1%）发生其他严重不良事件。

结论和相关性：在 COVID-19 中度或重度 ARDS 患者中，静脉注射地塞米松加标准护理与单独使用标准护理相比，28 天内无呼吸机天数（存活天数和无机械通气天数）显著增加。

Abstract:

Importance Acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) is associated with substantial mortality and use of health care resources. Dexamethasone use might attenuate lung injury in these patients.

Objective To determine whether intravenous dexamethasone increases the number of ventilator-free days among patients with COVID-19–associated ARDS.

Design, Setting, and Participants Multicenter, randomized, open-label, clinical trial conducted in 41 intensive care units (ICUs) in Brazil. Patients with COVID-19 and moderate to severe ARDS, according to the Berlin definition, were enrolled from April 17 to June 23, 2020. Final follow-up was completed on July 21, 2020. The trial was stopped early following publication of a related study before reaching the planned sample size of 350 patients.

Interventions Twenty mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n =151) or standard care alone (n = 148).

Main Outcomes and Measures The primary outcome was ventilator-free days during the first 28 days, defined as being alive and free from mechanical ventilation. Secondary outcomes were all-cause mortality at 28 days, clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death), ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, and Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days.

Results A total of 299 patients (mean [SD] age, 61 years; 37% women) were enrolled and all completed follow-up. Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; P =0 .04). At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, -1.16; 95% CI, -1.94 to -0.38; P=0.004). There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days. Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections, 47 (31.1%) vs 42 (28.3%) needed insulin for glucose control, and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events.

Conclusions and Relevance Among patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.

10. 氢化可的松对重度新冠肺炎病患者死亡率和器官支持的影响——一项新冠肺炎皮质类固醇领域随机临床试验

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

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DOI： 10.1001/jama.2020.17022
编译者：孔娟
中文摘要：
重要性：关于 2019 新冠肺炎使用皮质类固醇的证据有限。
目的：确定氢化可的松是否能改善患者的预后。
设计、设置和参与者：这是一项正在进行的适应性平台试验，其中包括多个治疗领域内的多种干预措施，例如抗病毒药物、皮质类固醇或免疫球蛋白。研究中共纳入来自 8 个国家的 121 个地方的 614 名疑似或确诊为新冠肺炎病的成年患者。其中，403 例被随机分配到皮质类固醇组，并随机分为 7 天固定疗程的静脉注射氢化可的松(每 6 小时 50 毫克或 100 毫克)(n = 143)、休克依赖性疗程(当休克临床明显时每 6 小时 50 毫克)(n = 152)或不注射氢化可的松(n = 108)。
主要结果和测量：主要终点为 21 天内无器官支持的天数(存活天数和无重症监护室呼吸或心血管支持的天数)，死亡患者被指定为 1 天。主要根据贝叶斯逻辑模型进行分析，根据年龄、性别、部位、地区、时间、其他领域内的干预分配以及领域和干预资格进行调整。优势被定义为优势比大于 1 的后验概率(优势试验结论的阈值> 99%)。
结果：排除 19 名撤回同意的参与者后，共有 384 名患者(平均年龄 60 岁；29%女性)随机分为固定剂量组(n = 137)、休克依赖组(n = 146)和无氢化可的松组(n = 101)；379 人(99%)完成了研究并被纳入分析。3 组的平均年龄在 59.5-60.4 岁之间；大多数患者为男性(范围，70.6%-71.5%)；平均体重指数在 29.7 和 30.9 之间；接受机械通气的患者在 50.0%和 63.5%之间。对于固定剂量组、休克依赖组和无氢化可的松组，平均无器官支持天数分别为 0(IQR，－1 至 15)、0(IQR，－1 至 13)和 0(－1 至 11)天(死亡率分别为 30%、26%和 33%，幸存者平均无器官支持天数分别为 11.5、9.5 和 6 天)。与无氢化可的松相比，固定剂量氢化可的松的中位数调整优势比和贝叶斯优势概率分别为 1.43(95%可信区间，0.91-2.27)和 93%，休克依赖性氢化可的松的中位数调整优势比和贝叶斯优势概率分别为 1.22 (95%可信区间，0.76-1.94)和 80%。在固定剂量组、休克依赖组和无氢化可的松组中，分别有 4 例(3%)、5 例(3%)和 1 例(1%)患者报告了严重不良事件。
结论和相关性：在重度新冠肺炎病患者中，与不使用氢化可的松相比，使用氢化可的松的 7 天固定剂量疗程或氢化可的松的休克依赖性给药治疗，在 21 天内器官支持改善的几率方面，产生了 93%和 80%的优势概率。然而，试验被提前停止，没有治疗策略符合统计学优势的预先指定标准，最终无法定论。
Abstract
IMPORTANCE: Evidence regarding corticosteroid use for severe coronavirus disease 2019 (COVID-19) is limited.
OBJECTIVE To determine whether hydrocortisone improves outcome for patients

with severe COVID-19.
DESIGN, SETTING, AND PARTICIPANTS An ongoing adaptive platform trial testing multiple interventions within multiple therapeutic domains, for example, antiviral agents, corticosteroids, or immunoglobulin. Between March 9 and June 17, 2020, 614 adult patients with suspected or confirmed COVID-19 were enrolled and randomized within at least 1 domain following admission to an intensive care unit (ICU) for respiratory or cardiovascular organ support at 121 sites in 8 countries. Of these, 403 were randomized to open-label interventions within the corticosteroid domain. The domain was halted after results from another trial were released. Follow-up ended August 12, 2020.
INTERVENTIONS The corticosteroid domain randomized participants to a fixed 7-day course of intravenous hydrocortisone (50mg or 100mg every 6 hours) (n = 143), a shock-dependent course (50mg every 6 hours when shock was clinically evident) (n = 152), or no hydrocortisone (n = 108).
MAIN OUTCOMES AND MEASURES The primary end point was organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who died were assigned −1 day. The primary analysis was a bayesian cumulative logistic model that included all patients enrolled with severe COVID-19, adjusting for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility. Superiority was defined as the posterior probability of an odds ratio greater than 1 (threshold for trial conclusion of superiority >99%).
RESULTS After excluding 19 participants who withdrew consent, there were 384 patients (mean age, 60years;29% female) randomized to the fixed-dose (n = 137), shock-dependent (n = 146), and no (n = 101) hydrocortisone groups; 379 (99%) completed the study and were included in the analysis. The mean age for the 3 groups ranged between 59.5 and 60.4 years; most patients were male (range, 70.6%-71.5%); mean body mass index ranged between 29.7 and 30.9; and patients receiving mechanical ventilation ranged between 50.0%and 63.5%. For the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively, the median organ support–free dayswere0(IQR, −1 to 15),0(IQR, −1 to 13), and0(−1 to 11) days (composed of 30%, 26%, and 33%mortality rates and 11.5, 9.5, and 6 median organ support–free days among survivors). The median adjusted odds ratio and bayesian probability of superioritywere 1.43 (95%credible interval,0.91-2.27) and 93%for fixed-dose hydrocortisone, respectively,and were 1.22 (95% credible interval,0.76-1.94) and80%for shock-dependent hydrocortisone compared with no hydrocortisone. Serious adverse eventswere reported in 4 (3%), 5 (3%), and 1 (1%) patients in the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively.
CONCLUSIONS AND RELEVANCE: Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93%and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early and no

treatment strategymet prespecified criteria for statistical superiority, precluding definitive conclusions.

11. 氢化可的松对 COVID-19 重症患者 21 天死亡率或呼吸支持的影响

Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19

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中文摘要：

探讨氢化可的松对 SARS-CoV-2 感染和急性呼吸衰竭患者第 21 天治疗失败的影响。患者随机接受低剂量氢化可的松(n=76)或安慰剂(n=73)。这项研究有 149 名患者参与(平均年龄 62.2 岁;30.2%的女性;81.2%采用机械通气)。148 名患者(99.3%)完成了这项研究，有 69 个治疗失败事件，其中氢化可的松组 11 人死亡，安慰剂组 20 人死亡。主要结果是第 21 天治疗失败，氢化可的松组 76 例患者中有 32 例(42.1%)出现，安慰剂组 73 例患者中有 37 例(50.7%)出现(比例差异，-8.6% [95.48% CI,-24.9% - 7.7%];P = 29)。在 4 个预先指定的次要结果中，没有一个显示有显著差异。没有与研究治疗相关的严重不良事件。在这项研究中，与安慰剂相比，低剂量氢化可的松在第 21 天没有显著降低治疗失败(定义为死亡或持续呼吸支持)。然而，这项研究在早期就停止了，并且很可能无法在主要结果上找到统计学和临床意义上的重要差异。

Abstract

To determine the effect of hydrocortisone on treatment failure on day 21 in critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and acute respiratory failure. Patients were randomized to receive low-dose hydrocortisone (n = 76) or placebo (n=73).The study was stopped after 149 patients (mean age, 62.2 years; 30.2% women;81.2% mechanically ventilated) were enrolled. One hundred forty-eight patients (99.3%)completed the study, and there were 69 treatment failure events, including 11 deaths in the hydrocortisone group and 20 deaths in the placebo group. The primary outcome, treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, -8.6% [95.48% CI, -24.9% to 7.7%]; P = .29). Of the 4 prespecified secondary outcomes, none showed a significant difference. No serious adverse events were related to the study treatment.In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose

hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21.However, the study was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome.

12. 全身性皮质类固醇给药与新冠肺炎病危重患者的死亡率之间的关系—— 一项 Meta 分析

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

来源：JAMA

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DOI：10.1001/jama.2020.17023

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中文摘要：

重要性：针对 2019 年新冠肺炎的治疗临床试验数据表明，低剂量地塞米松可降低需要呼吸支持的新冠肺炎病住院患者的死亡率。

目的：评估与常规护理或安慰剂相比，皮质类固醇给药与 28 天全因死亡率之间的关系。

设计、设置和参与者：这是一项前瞻性分析，包括 7 项随机临床试验的数据，评估了皮质类固醇在 1703 名新冠肺炎病危重患者中的疗效。汇集的数据是从单个试验、整体和预先定义的亚组中汇总。使用 Cochrane 风险评估工具评估偏倚风险。使用 I2 统计评估试验结果之间的不一致性。主要分析是总死亡率的反向方差加权固定效应荟萃分析，干预和死亡率之间的关联用优势比(ORs)量化。还进行了随机效应荟萃分析和使用风险比的反向方差加权固定效应分析。患者被随机分配接受全身地塞米松治疗，氢化可的松、或甲基强的松龙(678 名患者)或接受常规护理或安慰剂(1025 名患者)。

主要结果和测量主要终点：主要结果和测量主要终点是随机化后 28 天全因死亡率。次要结果是研究者定义的严重不良事件。结果共有 1703 名患者(中位年龄，60 岁[四分位数范围，52-68 岁]；488 名[29%]妇女)被纳入分析。在 7 项死亡率结果中，有 6 项的偏倚风险被评估为“低”，在 1 项试验中，由于随机化方法，被评估为“一些问题”。五项试验报告了 28 天的死亡率，一项试验报告了 21 天的死亡率，一项试验报告了 30 天的死亡率。678 名随机接受皮质类固醇治疗的患者中有 222 人死亡，1025 名随机接受常规护理或安慰剂治疗的患者中有 425 人死亡。试验结果之间几乎没有不一致(I2 = 15.6%；异质性 P = 0.31)，总 OR 为 0.70(95%置信区间，0.48-1.01；P = .053)。死亡率相关的固定效应汇总 OR 为 0.64(95%置信区间，0.50-0.82；地塞米松与常规护理或安慰剂相比(3 项试验，1282 名患者，527 例死亡)，OR 为 0.69(95%置信区间，0.43-1.12；对于氢化可的松(3 项试验，

374 名患者，和 94 例死亡)，OR 为 0.91(95%置信区间，0.29-2.87；P = 0.87) (1 项试验，47 名患者，26 例死亡)。在报告严重不良事件的 6 项试验中，354 名随机接受皮质类固醇治疗的患者发生了 64 起事件，342 名随机接受常规护理或安慰剂治疗的患者发生了 80 起事件。

结论和相关性:在这项对新冠肺炎危重患者临床试验的前瞻性荟萃分析中，与常规护理或安慰剂相比，全身性皮质类固醇的给药与较低的 28 天全因死亡率相关。

Abstract

IMPORTANCE Effective therapies for patients with coronavirus disease 2019 (COVID-19) are needed, and clinical trial data have demonstrated that low-dose dexamethasone reduced mortality in hospitalized patients with COVID-19 who required respiratory support.

OBJECTIVE To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality.

DESIGN, SETTING, AND PARTICIPANTS Prospective meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The trials were conducted in 12 countries from February 26, 2020, to June 9, 2020, and the date of final follow-up was July 6, 2020. Pooled data were aggregated from the individual trials, overall, and in predefined subgroups. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool. Inconsistency among trial results was assessed using the I2 statistic. The primary analysis was an inverse variance–weighted fixed-effect meta-analysis of overall mortality, with the association between the intervention and mortality quantified using odds ratios (ORs). Random-effects meta-analyses also were conducted (with the Paule-Mandel estimate of heterogeneity and the Hartung-Knapp adjustment) and an inverse variance–weighted fixed-effect analysis using risk ratios.

EXPOSURES Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients).

MAIN OUTCOMES AND MEASURES The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events.

RESULTS A total of 1703 patients (median age, 60 years [interquartile range, 52-68 years]; 488 [29%] women) were included in the analysis. Risk of bias was assessed as “low” for 6 of the 7 mortality results and as “some concerns” in 1 trial because of the randomization method. Five trials reported mortality at 28 days, 1 trial at 21 days, and 1 trial at 30 days. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95%CI, 0.53-0.82]; P <0.001 based on a fixed-effect meta-analysis). There was little inconsistency between the trial results (I2 = 15.6%; P = .31 for heterogeneity) and the summary OR was 0.70 (95%CI, 0.48-1.01; P = 0.053) based on the random-effects meta-analysis. The fixed-effect summary OR for the association with mortality was 0.64 (95%CI, 0.50-0.82; P < 0.001) for dexamethasone compared with

usual care or placebo (3 trials, 1282 patients, and 527 deaths), the OR was 0.69 (95%CI, 0.43-1.12; P = 0.13) for hydrocortisone (3 trials, 374 patients, and 94 deaths), and the OR was 0.91 (95%CI, 0.29-2.87; P = 0.87) for methylprednisolone (1 trial, 47 patients, and 26 deaths). Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.

CONCLUSIONS AND RELEVANCE In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

13. 卡介苗接种预防老年人感染的随机临床试验

ACTIVATE: RANDOMIZED CLINICAL TRIAL OF BCG VACCINATION AGAINST INFECTION IN THE ELDERLY

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DOI 或 PUBMED ID：https://doi.org/10.1016/j.cell.2020.08.051

编译者：刘焕珍

中文摘要：

儿童接种卡介苗可预防异源感染和提高生存率。III 期激活试验评估了卡介苗在老年人中是否有类似的作用。在这项双盲、随机试验中，老年患者（n=198）在出院时接种卡介苗或安慰剂疫苗，并进行了 12 个月的随访。在中期分析中，卡介苗接种显著增加了首次感染的时间（中位数为 16 周，而安慰剂接种后为 11 周）。安慰剂接种后新感染的发生率为 42.3%（95%可信区间为 31.9-53.4%），卡介苗接种后为 25.0%（95%可信区间为 16.4-36.16%）；大多数预防措施是针对可能的病毒性呼吸道感染（危险比 0.21，p:0.013）。没有发现不良反应发生频率的差异。数据表明，卡介苗接种是安全的，可以保护老年人免受感染。需要更大的研究来评估针对呼吸道感染（包括 COVID-19）的防护。

Abstract:

BCG vaccination in children protects against heterologous infections and improves survival independently of tuberculosis prevention. The phase III ACTIVATE trial assessed whether BCG has similar effects in the elderly. In this double-blind, randomized trial, elderly patients (n=198) received BCG or placebo vaccine at hospital discharge, and were followed for 12 months for new infections. At interim analysis, BCG vaccination significantly increased the time to first infection (median 16 weeks compared to 11 weeks after placebo). The incidence of new infections was 42.3% (95% CIs 31.9-53.4%) after placebo vaccination and 25.0% (95% CIs 16.4- 36.16%) after BCG vaccination; most of the protection was against respiratory tract infections of probable viral origin (hazard ratio 0.21, p: 0.013). No difference in the frequency of adverse effects was found. Data show

that BCG vaccination is safe and can protect the elderly against infections. Larger studies are needed to assess protection against respiratory infections, including COVID-19.

14. Covid-19 和老年群体的免疫，一个新的研究议题

Covid-19 and Immunity in Aging Populations — A New Research Agenda

作者：Wayne C. Koff, Ph.D., and Michelle A. Williams, Sc.D.

链接：https://www.nejm.org/doi/full/10.1056/NEJMp2006761

摘要：

作者从讨论老年人受到 COVID-19 影响、其可能机制、老年人对疫苗的反应差异扩展到讨论老龄化带来的全球健康挑战。最后作者们提出：鉴于 COVID-19 的高度可传染性，以及特别是老年人群中的高致死率，目前成为了一个全球疫情，短期当务之急是快速开发出救命的疫苗和治疗方案。长期来讲，我们需要从主要研究特定疾病转换为同时投资足够的资源来研究人的免疫系统，特别是世界上最脆弱的人群。这样的努力将加速新疫苗的开发、疾病诊断和治疗,不仅仅针对 COVID-19,也会为将来出现的新发病原物以及其他非传染性的但是已经成为全球主要杀手的老年性疾病。我们需要尽快坚定地行动起来帮忙人类活得更长更健康。

Abstract:

The race is on throughout the world to develop Covid-19 vaccines and therapeutics and end a pandemic that threatens to infect a substantial portion of the planet's population and perhaps kill millions of people, especially older adults. As billions of dollars flow into research and development efforts aimed at controlling the virus, the pandemic response remains hamstrung by our limited understanding of how to generate effective immunity, particularly in the elderly. As we age, health conditions associated with aging, particularly noncommunicable diseases such as heart disease, cancers, and metabolic and autoimmune diseases, combined with treatments for these diseases and with immune senescence, substantially affect responses to vaccines and infectious diseases.1 Angiotensin-converting enzyme 2 (ACE2) has been identified as the receptor for SARS-CoV-2, the virus that causes Covid-19, and it has been suggested that differential levels of ACE2 in the cardiac and pulmonary tissues of younger versus older adults may be at least partially responsible for the spectrum of disease virulence observed among patients with Covid-19. These findings have led to debate regarding the potential use of ACE inhibitors in the context of the pandemic.2 This idea highlights the need for longitudinal studies in aging populations — such as the Rotterdam Study (a prospective cohort study focused on cardiovascular, neurologic, ophthalmologic, and endocrine diseases) — to examine the impact of coexisting conditions and therapies on the effects of vaccines and infectious diseases.

Even as the brunt of severe illness from Covid-19 is being borne by aging adults, we are navigating partially blind in efforts to develop vaccines and therapies to stop this and future pandemics, since we lack knowledge of the mechanisms of immunity to protect this population. If we can delineate principles of effective immunity in the elderly, we might also be able to develop new strategies for broader disease prevention and control in older populations.

Covid-19 has highlighted the vulnerability of aging populations to emerging diseases. This susceptibility to disease and death is also a major challenge for the development of vaccines and immunotherapeutic agents. Numerous studies have shown that vaccine efficacy decreases significantly with age, a reduction that is thought to be driven by the progressive age-related decline of innate and adaptive immune responses.3 Yet we know that some older people are protected by generally poorly performing vaccines, and some vaccines work very well in elderly populations: the Shingrix vaccine for shingles, for example, is 90% effective in people over 70. What accounts for the variability in immune responses from one elderly person to another? How can we use our understanding of this variability in developing new and improved vaccines and therapies?

Far from being mere academic exercises, the answers to these questions are critical to the future of global health. The Covid-19 experience in aging populations offers a window into the profound, long-term, global demographic challenges the world is facing. According to the United Nations, projections indicate that by 2050 there will be more than twice as many people over 65 as there are children under 5, and the number of people 65 years of age or older globally will surpass the number of people 15 to 24 years of age.4

This global aging will create widespread public health challenges, dramatically increasing the burden of noncommunicable diseases and exposing our vulnerability to infectious diseases. The number of deaths related to antimicrobial resistance is projected to reach 10 million per year by 2050, exceeding mortality from cancer. Climate change could put an additional 1 billion people at risk from tropical vector borne diseases, and potentially pandemic diseases are emerging with greater frequency. Protecting aging populations will be a central, if not the primary, question in maintaining global health and biosecurity.

Recent technological advances in biomedical and computer sciences provide an unprecedented opportunity to decode the human immune system. Innovations in systems biology applied in clinical immunology studies now allow immensely detailed measurements of human transcriptomic, proteomic, immune, and metabolic responses. Such studies have already led to improved understanding of the extent to which human responses within a population vary on several parameters, and of the influence of the microbiome in host immunity, leading to considerations for novel vaccination and immune-therapeutic strategies.5 For example, many baseline “omic” signatures predictive of vaccine-induced immunity have been associated with innate immune parameters, which suggests that specific and novel immunomodulators may enhance future vaccines and immunotherapies.

Moreover, advances in bioinformatics, causal inference, and artificial intelligence (AI) — building on AI advances from other fields, such as biomedical imaging — enable analyses of large-scale data sets that can help in determining the key elements and principles of effective human immunity. These tools offer the potential for elucidating the mechanisms that differentiate people who have a response to vaccines from those who do not, and for clarifying why some people develop effective immune responses to disease. These answers should provide the

basis for accelerating the discovery and development of new vaccines, diagnostics, and therapies for major diseases. Generating systems-biology data on an unprecedented scale should also enable computational scientists to begin to develop AI models of human immunity, which, if successful, could transform product development, enabling computer-generated simulation trials to facilitate faster and cheaper development, with a much greater probability of success.

Innovative new studies are needed to investigate questions of why some people have stronger responses to vaccines or diseases than others so that we can better prevent and treat disease. This undertaking will require a global approach and a radically new vision — one that spans diseases and sectors of society, bringing together academia, industry, government, and philanthropic organizations. Covid-19 is already catalyzing collaboration among these sectors, and this work must continue beyond the pandemic.

Thus, the tools are now available to decipher the principles of effective immunity in aging populations. If investigators study cohorts of elderly people longitudinally and globally and probe their immune systems with licensed vaccines to distinguish people with effective responses from those without, and apply cutting-edge tools from systems biology and AI, it should be feasible to identify biomarkers for effective immunity in this population, which could then be applied to other vulnerable populations, such as those living in low- and middle-income countries. Over the long term, the research agenda will need to include cultivation of a new generation of multidisciplinary scientists trained in biomedical, informatics, and computer sciences in order to fully prepare for the next wave of emerging diseases.

Covid-19 is highly transmissible, causes relatively high mortality, particularly in aging populations, and has emerged globally in our highly interconnected world. Short-term efforts to quickly develop lifesaving vaccines and therapeutics are of the utmost importance.

In the long term, however, we will have to shift from investing primarily in disease-specific research to simultaneously targeting sufficient resources toward decoding the human immune system, particularly for the world’s most vulnerable populations.

Such an effort could accelerate the development of new vaccines, diagnostics, and treatments — not just for Covid-19, but also for future emerging pathogens as well as the noncommunicable diseases of aging that are our major global killers. We need bold action as soon as possible to help all of humanity live longer and healthier lives.

15.美国国家科学、工程与医学院联合发布公平分配 COVID-19 疫苗的讨论框架草案

National Academies of Sciences, Engineering, and Medicine released Discussion Draft of the Preliminary Framework for Equitable Allocation of COVID-19 Vaccine (2020)

美国国家科学、工程与医学院联合发布公平分配疫苗草案并征询大众意见(9 月 1 日至 4 日)。该 115 页的草案，讨论了疫苗公平分配的历史经验、疫苗公平分配里面怎么设定优先标准以

及草拟了公平分配的方案。

链接：https://www.nap.edu/download/25914

作者：National Academies of Sciences, Engineering, and Medicine， USA

Highlights

What criteria should be used in setting priorities for equitable allocation of vaccine?

• How should the criteria be applied in determining the first tier of vaccine recipients?

As more vaccine becomes available, what populations should be added successively to the priority list of recipients? How do we take into account factors such as:

o Health disparities and other health access issues

o Individuals at higher risk (e.g., elderly, underlying health conditions)

o Occupations at higher risk (e.g., health care workers, essential industries, meat

packing plants, military)

o Populations at higher risk (e.g., racial and ethnic groups, incarcerated individuals, residents of nursing homes, individuals who are homeless)

o Geographic distribution of active virus spread

o Countries/populations involved in clinical trials

• How will the framework apply in various scenarios (e.g., different characteristics of vaccines and differing available doses)?

• If multiple vaccine candidates are available, how should we ensure equity?

• How can countries ensure equity in allocation of COVID-19 vaccines?

• For the United States, how can communities of color be assured access to vaccination?

• How can we communicate to the American public about vaccine allocation to minimize perceptions of lack of equity?

• What steps should be taken to mitigate vaccine hesitancy, especially among high priority populations?