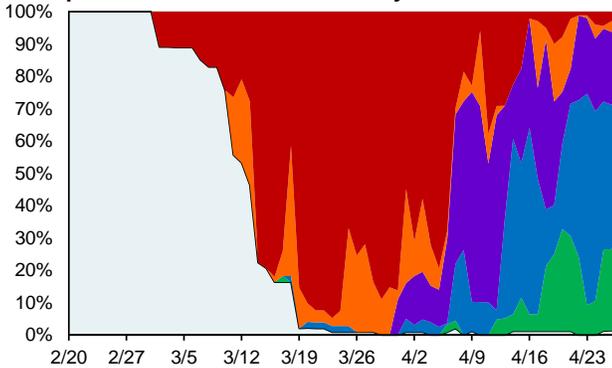




Topics: Lockdown relaxation and economic reawakening...are we there yet? The questionable logic underlying the BCG vaccine thesis; Latest serology results; Vaccine timetables

In Europe and Asia, yes; elsewhere, not yet. The charts below show infection trends for different regions with a GDP lens. For example, in late March countries comprising almost all of European GDP were experiencing rising infections. That figure has fallen below 10%, with large portions of the region’s GDP seeing sharp infection declines since peak levels. In Asia, outbreaks were never sustained at high levels. US infection trends are rising again, but this increase is in many places the by-product of increased testing (orange segment). Infections are also picking up in South America and the Mid East. Since our trend calculation is calibrated to high frequency data, categories can change a lot on a day to basis. We will be updating these monitors daily on our web portal along with the rest of the tracking charts.

Europe COVID infection monitor by GDP

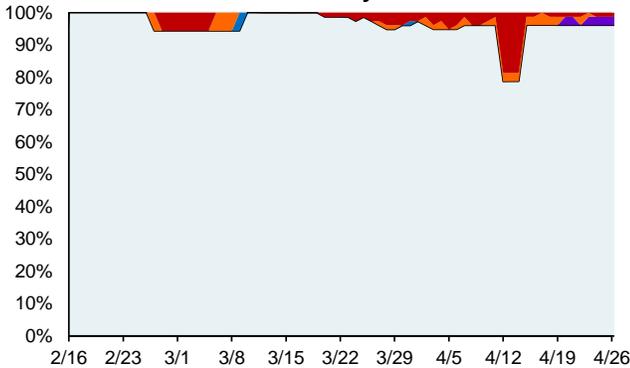


Source: Johns Hopkins University. IMF. JPMAM. April 26, 2020

Legend

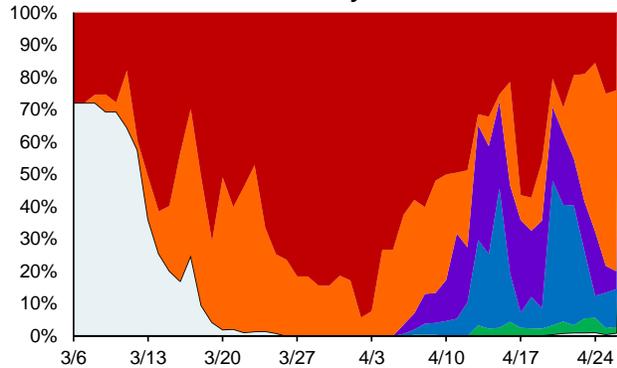
- Infections rising faster than tests
- Infections rising slower than tests
- Infections falling, 100% - 85% of peak
- Infections falling, 85% - 50% of peak
- Infections falling, 50% - 25% of peak
- Infections falling, below 25% of peak
- No infections, or < 5 cases per mm

Asia COVID infection monitor by GDP



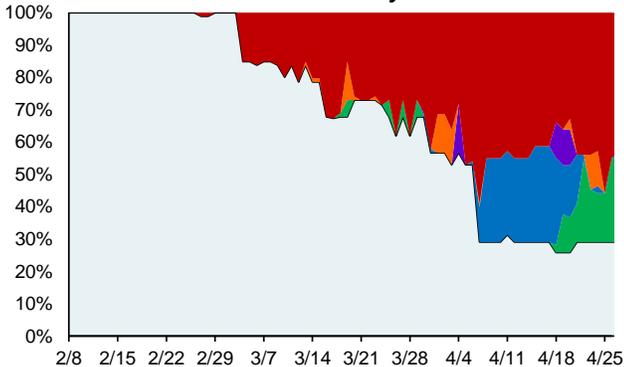
Source: Johns Hopkins University. IMF. JPMAM. April 26, 2020

US COVID infection monitor by state GDP



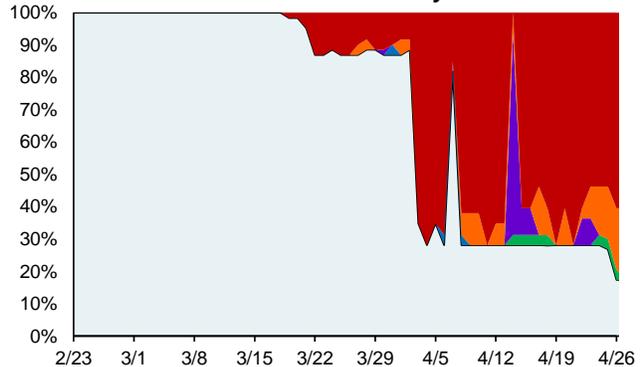
Source: Johns Hopkins University. IMF. JPMAM. April 26, 2020

M East COVID infection monitor by GDP



Source: Johns Hopkins University. IMF. JPMAM. April 26, 2020

S America COVID infection monitor by GDP



Source: Johns Hopkins University. IMF. JPMAM. April 26, 2020



Latest serology results (tests for COVID-19 antibodies), to be interpreted with a grain of salt

Let’s discuss caveats first (we discuss all of this in detail in Section 5 on the web portal):

- As many as one third of recovered patients in a 175-person cohort in China did not possess high levels of COVID-19 antibodies normally associated with disease recovery. Whether low-antibody patients are still susceptible to the disease remains to be determined
- Serology manufacturers’ kits differ on “specificity” (false anti-body positive) and “sensitivity” (false anti-body negative), in which case antibody presence could be misestimated¹. A study from UCSF and UC Berkeley analyzed 12 different tests and provides insight into these questions. The authors found “good to excellent sensitivity for all evaluated tests in hospitalized patients three or more weeks into their disease course”, and that their data “demonstrate specificity > 95% for the majority of tests evaluated, and > 99% for three of them”
- There are not enough high quality serology kits yet, the FDA does not exercise quality control over them, and study sizes are very small relative to the populations they are extrapolated against
- Some studies make adjustments for age/gender/race to the extent that the serology group differs from the broader population, which further muddies the results

Even so, these serology markers are informative as to the progression of the virus and are better measures of infection and mortality rates than reported alternatives. Warts and all, here are the latest results.

Serology test results to date

	Time from outbreak to day of serology test	Reported case to population ratio	Est. population with antibodies	Reported case fatality rate	Case fatality rate based on serology estimate	Study size
Scotland	21	0.1%	1.2%	0.4%	0.04%	1,000
Denmark	35	0.1%	2.7%	2.2%	0.1%	1,000
Netherlands	49	1.6%	3.0%	1.5%	0.8%	7,000
NY State	52	1.4%	13.9%	7.4%	0.7%	3,000
Geneva Swi	52	0.5%	5.5%	8.8%	0.8%	760
Santa Clara	64	0.1%	3.3%	3.4%	0.1%	3,330
Gangelt Ger	73	2.4%	14.0%	2.3%	0.4%	500
Los Angeles	76	0.1%	4.2%	2.9%	0.1%	863

Source: JPMAM, JHU. 2020. See page 7 for serology data sources.

¹ On serology tests: please do not send me emails stating that you believe that false positives outnumber actual positives unless (a) you have made an estimate of disease prevalence and can explain how that affects your results; (b) you estimate the number of actual (correct) negatives relative to false positives and are prepared to discuss the public policy implications of this comparison; and (c) you cite false positive and false negative accuracy of PCR virus testing kits, since that’s the most likely alternative/complement to serology-based reopening strategies.



The most ambitious vaccine timetables I have seen so far

Most of the news on anti-virals has been a letdown recently, particularly the Gilead/Remdesivir mess in which a paper was posted online by accident, the fact that the study was reportedly terminated due to lack of patients and the fact that more people apparently died in the Remdesivir group than in the control group. However, on the vaccine front, two large companies have announced ambitious timetables that are faster than the base case that I and many others have been assuming. I take this as a positive given their extensive experience in vaccine development, but we will have to see how the trials go. See Section 4 on the web portal for more on anti-virals and vaccines.

- **Oxford** University announced a very aggressive timetable for development of a vaccine based on a chimpanzee virus that is altered to be harmless to humans, and which includes genetic components coding for the SARS-CoV-2 spike proteins. As with other vaccine ideas, the spike proteins of the coronavirus are expected to provoke the body's immune system into generating the necessary antibodies. Oxford's Jenner Institute hopes to produce one million doses by the fall of 2020 if current clinical trials are successful (1,100 volunteers have been recruited into a randomized trial)
 - The Serum Institute of India, one of the world's largest vaccine companies, actually announced that they will produce 40 million of Oxford's vaccines now, even before trials are completed
- **J&J** announced a very ambitious timetable for a COVID-19 vaccine that uses the same technology platform as their Ebola vaccine (which took 5 years to complete). This platform is also used by J&J for its Zika, RSV, and HIV vaccine candidates which are currently in Phase 2 or Phase 3 trials. J&J aims to begin Phase I trials in September 2020 with production as early as spring 2021. They have reportedly identified a lead vaccine candidate (with two backups)
- **Other longer term vaccine initiatives** discussed on our web portal include candidates from Sanofi/GlaxoSmithKline, CanSino, BioNTech/Pfizer, Sinovac/Dynavax, Moderna and Inovio
- Keep in mind that some of these vaccine candidates are based on RNA/DNA or viral vector technologies that have never been approved for use before in vaccines used for communicable diseases



The questionable premise that the BCG vaccine is a driver of COVID severity

Some healthcare professionals have advanced the premise that the BCG vaccine (a tuberculosis vaccine given to children) somehow explains regional differences in COVID severity. In epidemiology, mathematical biology and medical communities, there's a LOT of BCG skepticism:

- The WHO has stated that there is no medical evidence to support the BCG thesis²
- The BCG vaccine is used more widely in less developed, younger countries. As severity of COVID-19 is strongly linked to age, population distributions (or vaccines other than BCG) may be much better ways to explain cross-country differences³. It's also an odd time to draw conclusions about cross-country BCG impacts since the virus is now rising more sharply in parts of the developing world that use it
- Chinese healthcare professionals said they did not see any variation in COVID infection or mortality rates based on BCG vaccination histories⁴
- Tuberculosis is a bacteria while SARS-CoV-2 is a virus, raising questions as to why a BCG vaccine would work in the first place
- Some studies supporting the BCG concept didn't incorporate population heterogeneity, actual vaccination rates or differences in response rates among individuals⁵
- The key flaw: many BCG studies are derived from quick and dirty cross-country comparisons, and are prone to biases that "confuse the public"⁶. They compare groups rather than individuals, and are much less helpful in identifying what may cause or prevent disease. Cross-country comparisons are simple and don't require a lot analysis, but are prone to "ecological fallacy" (just because you observe a correlation between average exposure and outcomes does not mean that individuals with greater exposures have a higher/lower risk of disease). We already have in hydroxychloroquine a "stunning example of policy decisions made on the basis of weak evidence"

If that's not enough for you, see the chart on the next page.

² "Bacille Calmette-Guérin (BCG) vaccination and COVID-19", WHO Science Brief, April 12, 2020

³ The Imperial College of London has made it clear in their research that % of symptomatic cases requiring hospitalization, % of hospitalized cases requiring critical care and case fatality rates closely track age distributions.

⁴ Epidemiologist Salim Karim, Columbia University Mailman School of Public Health, Adjunct Professor of Medicine at Weill Medical College of Cornell University

⁵ "Coronavirus and the tuberculosis vaccine", Dr. M. Noon, University of Goettingen, April 21, 2020

⁶ "A Skeptic's Guide To Ecologic Studies During A Pandemic", Madhukar Pai, Canada Research Chair in Translational Epidemiology & Global Health, McGill University, April 22, 2020



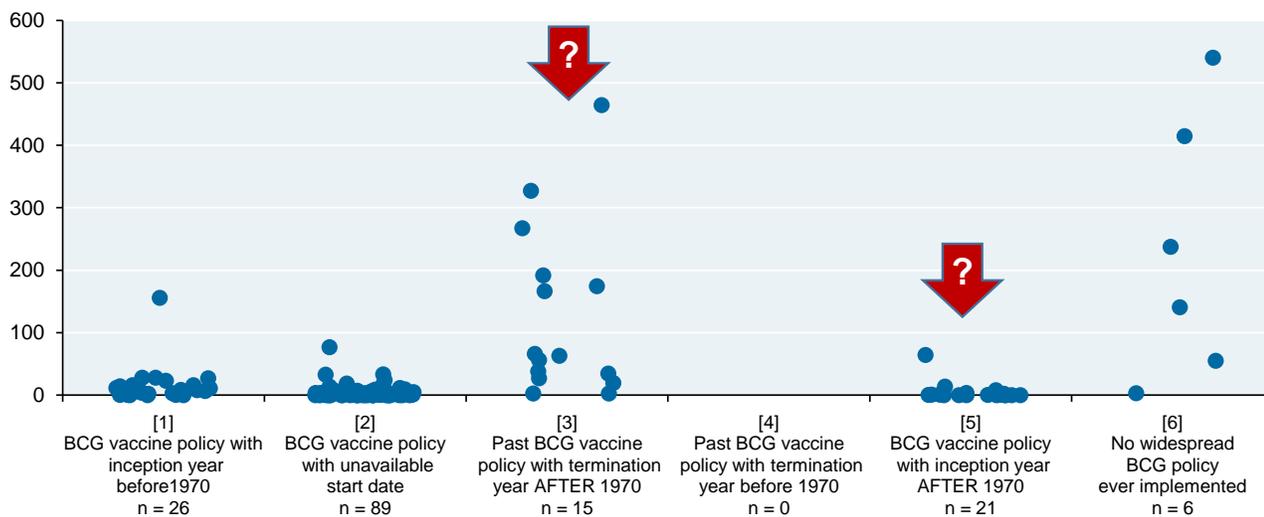
Let’s make it even simpler. Consider reported COVID deaths per million people as a function of BCG vaccine policy (assuming that reported deaths in developing economies are accurate, which is a big “if”). Yes, as shown in the chart, there’s a cluster of low death rates in countries with long-standing BCG vaccine policies [group 1]. But analytically, **the entire BCG thesis falls apart in my view for the following three very simple reasons:**

- The number of countries that “never had a widespread BCG vaccine policy” [group 6] is extremely small, and its dispersion is very wide
- There are a lot of countries that no longer use the BCG vaccine but only terminated it **after** 1970 [group 3]. In other words, **anyone over the age of 50 in these countries had the BCG vaccine, and many of these countries have high COVID death rates anyway (e.g., France, Spain). Why?**
- There’s also a cluster of countries that only instituted BCG vaccine policies **after** 1970, and their COVID death rates are low as well [group 5]. **If that’s the case, how were their older people protected if they didn’t get the vaccine???**

Given the unknowable complexity of the body’s immune system, it’s impossible to predict if the BCG vaccine will or won’t work against COVID-19, and any clinical trials conducted will be interesting to watch. I sure hope it works, like every other idea proposed. But to me, the BCG thesis so far is very sloppy science.

COVID-19 deaths per million people as a function of BCG vaccine policy

Each dot represents one of 157 countries with BCG vaccine history



Source: Johns Hopkins University, BCG World Atlas. April 23, 2020.



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