Outlines of a probabilistic evaluation of possible SARS-CoV-2 origins

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ABSTRACT

A probabilistic treatment can be very useful when trying to discover the most probable causes that are consistent with the available information at the time. In particular in such a treatment all assumptions and all probability estimates are explicit and are open for investigation. Here we explore the relative probabilities of a lab-related accident against a non-lab-related zoonotic event being at the root of the current COVID-19 pandemic. In doing so we use estimates of the relevant probabilities published in the specialized literature, especially estimates of the risk of a lab-acquired infection (LAI) and of the subsequent community outbreak risk.

We show that, based on present knowledge, the relative probability of a lab-related accident against a non-lab related zoonotic event is not negligible across a wide range of defensible input probabilities. For instance, under a reference set of input probabilities, the relative probabilities are at least 55% for a lab-related event against 45% at most for a non-lab-related zoonotic event. Even under a particularly conservative set of assumptions the relative probability of the lab-related accident is still 6% (to 94% for the non-lab related zoonotic event).

Through a review of the Chinese specialized literature, we further show that our underlying estimate for the probability of lab-acquired infection is consistent with risk assessments from Chinese authorities and specialists. We then review a list of common probabilistic misunderstandings that are often associated with discussions about COVID-19 origins and conclude by discussing how such a probabilistic treatment can also offer a way to properly guide an investigation into the causes of the pandemic while being able to embrace different estimates of the underlying probabilities.

KEYWORDS

accident analysis, risk assessment, risk disclosure, laboratory escape, laboratory acquired infection, bayesian statistics, biosafety and biosecurity issues, COVID-19, SARS-CoV-2

INTRODUCTION

Despite considerable efforts, the exact origin of the current COVID-19 pandemic has to this date not been asserted. An initial theory of a zoonotic event at a wildlife market [1, 2] has been found wanting and is now considered unlikely [3, 94]. Various conspiracy theories have emerged in the meantime in the public debate [4], some heavily politicized [5], at times exactly mirroring earlier conspiracy theories involving SARS [6]. At the same time the scientific community is doing its best to explore the probable exact origins of the pandemic [7, 8, 9, 93] while focussing first on finding possible treatments and designing effective containment measures.

In that difficult context we believe that a probabilistic treatment of the possible origins of Covid-19 can help. Such a treatment is suited to a situation where different origins are probable. It does not require taking position for one specific probable origin but instead assigns a probability to each probable origin based on the available information at the time. In particular it allows for a constructive debate between parties who may estimate the input probabilities (the 'priors') differently. Such a probabilistic treatment offers thus a method to potentially bridge differences between expert opinions [10] and to keep updating these input probabilities as either more information or a consensus emerges.

We attempt here a probabilistic treatment of the main two probable origins of Covid-19: pure random zoonotic event and lab-related accident. While duly acknowledging that any such analysis must rely to a large extent on uncertain data and uncertain factors, we shall try to base our treatment on conservative values for the key input probabilities - conservative values which we believe provide a good basis to initiate a reasoned discussion of the resulting relative probabilities of the probable origins. We shall additionally consider alternative sets of values for these input probabilities so as to observe the variability of the results under such a range of plausible assumptions.

In the course of this analysis we do not get into any controversy about Gain-of-Function (GOF) and whether SARS-CoV-2 (the virus that causes Covid-19) is a virus that first came from nature or was man-made. That controversy is irrelevant to the scope of this paper. We shall instead simply suppose that SARS-CoV-2 is nature-made, from which point we can then consider whether the outbreak itself is nature-made or man-made.

Nor do we wish to get into any controversy about the so-called 'Wuhan P4 lab' (strictly meaning the National Biosafety Laboratory located in the Zhengdian Park of Wuhan Institute of Virology, which also hosts BSL-2 and BSL-3 labs [11]). So as to avoid any such controversy, this paper simply ignores the BSL-4 lab component of the Wuhan National Biosafety Laboratory in its risk estimates. Nor do we wish to get into any controversy about possible intentional release vs. possible accidental release. We fully trust that Ockham's razor has common enough applications to not have to suppose any malicious intent.

Last, in the hope that such a treatment may inform a larger audience, we shall intentionally keep the mathematical approach as simple as possible.

ESTIMATION OF THE ODDS

1. Hypotheses under consideration

When faced with a pandemic such as COVID-19 an essential question with huge implications for public policy is

> *'How probable is it for the initial COVID-19 outbreak in Wuhan to be linked to coronavirus lab activities in Wuhan against the alternative explanation of a purely natural zoonotic origin?'*

We will call the two hypotheses:

> ***Hacc:*** *The COVID-19 community outbreak that was first observed in Wuhan was caused by an accident linked to a Wuhan lab (be it collection, transport or lab accident, including leak)*
>
> ***Hrand:*** *The COVID-19 community outbreak that was first observed in Wuhan was caused by a random zoonotic event unrelated to a lab, somewhere in China*

2. Probabilities for each hypothesis

a. COVID-19 Random Zoonotic hypothesis (Hrand)

We need to estimate the probability of:

> ***Hrand***: *The COVID-19 community outbreak that was first observed in Wuhan was caused by a random zoonotic event unrelated to a lab, somewhere in China*

The underlying event behind Hrand is:

> ***Erand:*** *a random SARS-like zoonotic event somewhere in China leading to a first community outbreak in Wuhan*

The probability of that event is difficult to evaluate directly. As explained in Annex A, a more practical route is to consider a more general event:

> ***Grand:*** *a random SARS-like zoonotic event somewhere in China leading to a first community outbreak somewhere in China*

A SARS-like community outbreak is a real risk in China, especially in the context of changes in human population patterns and land use patterns [12, 13] close to natural reservoirs of animal carriers such as bats and other possible intermediate hosts. While the risk of the bat-host-human infection path is well understood, the practical risk of direct bat-human infection has so far eluded a precise answer [see Box 2]. Nevertheless the resulting risk of epidemic and then pandemic is clearly compounded by increasing movements of people around the country, particularly between countryside and cities [14]. Some major work and progress in understanding this risk has been done, often involving leading Chinese research institutions such as the WIV but also international organizations [15, 16, 17].

The last human coronavirus (HCoV) community outbreak that originated in China before COVID-19 was SARS in 2003. Between that SARS epidemic and the COVID-19 epidemic 16 years and a half have elapsed. Since we do not know yet if COVID-19 is an event unrelated to a lab or not, it means that - whatever the theoretical risk debates - we have observed at most 2 SARS-like community outbreaks in 16.5 years in China caused by a random zoonotic event.

It is very difficult to precisely estimate a probability from 2 data points (especially if the second one is tentative), but we shall start with an indicative probability of non-lab related community outbreak due to a SARS-CoV-like virus in China as being of 1 every 10 years and will later consider alternative values. The motivations for such an initial estimate and its intrinsic uncertainties are discussed in Annex A.

> *Probability of non-lab related SARS-like community outbreak in China ~ 1 every 10 years*

or to use some more standard notations:

$$P(Grand) \approx 0.1 \; per\ year$$

Additionally we know that the COVID-19 outbreak was first observed in Wuhan, with all the viral strains to date linking back to the Wuhan genomes published in the early days of the outbreak [18]. So the probability we need to estimate is the probability of *a random SARS-CoV-like zoonotic event leading to a first community outbreak in Wuhan (against any other place in China).*

In order to estimate this probability let's consider a few scenarios that should map all possibilities:

> ***Eloc:*** *A natural zoonotic event (possibly involving a host animal) of a SARS-CoV-like virus which happens in a given place in China can only lead to a first community outbreak in close proximity to that place.*

***Eprov**: A natural zoonotic event (possibly involving a host animal) of a SARS-CoV-like virus is most likely to happen and cause a first community outbreak in a province with known human SARS-CoV-like viruses.*

***Eany**: A natural zoonotic event (possibly involving a host animal) of a SARS-CoV-like virus which happens in a given place in China can lead to a first community outbreak anywhere in China with no preference for any particular place.*

Let's review each scenario and see what they imply for the probability of a random SARS-CoV-like zoonotic event leading to a first community outbreak in Wuhan (against any other place in China)

Scenario Eloc:

Supposing first that *Eloc* holds ($P(Eloc) = 1$), let's evaluate the probability of a first community outbreak in Wuhan due to a natural zoonotic event in close proximity to the city.

$$p1 = P(zoonotic\ outbreak\ in\ Wuhan \cap Grand \cap Eloc)$$

$$p1 = P(zoonotic\ outbreak\ in\ Wuhan \mid Grand \cap Eloc) \times P(Grand \cap Eloc)$$

and as in this scenario we are supposing $P(Eloc) = 1$

$$p1 = P_{Eloc}(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \times P(Grand)$$

$P_{Eloc}(zoonotic\ outbreak\ in\ Wuhan \mid Grand)$ is effectively our rescaling factor for $P(Grand)$, the larger distribution of human SARS-like random zoonotic events somewhere in China leading to an outbreak in the country.

We note that there are no known animal carriers reservoirs in the city of Wuhan (either bats or intermediate hosts) [19] and that a zoonotic event is thus more likely to happen in the countryside, close to bat cave reservoirs or in a farming environment involving possible intermediate hosts. Accordingly, under *Eloc* a Wuhan citizen is less at risk of being part of an initial SARS-like outbreak due to a zoonotic event than the 'average' Chinese citizen, since the overall Chinese population encompasses not only cities but also countryside.

The relative population of Wuhan compared to the whole of China is 0.79%, as 11 mln over 1,400 mln, which we shall round up as 1%. Hence based on the above:

$$P_{Eloc}(zoonotic\ outbreak\ in\ Wuhan \mid Grand) < 1\% \qquad [conservative]$$

and as $P(Grand) = 1\ in\ 10\ year$

$$p1 < 1\%\ of\ 1\ in\ 10\ year$$

Scenario Eprov:

Supposing first that *Eprov* holds ($P(Eprov) = 1$), let's evaluate the probability of a first community outbreak in Wuhan due to a natural zoonotic event in Hubei province.

$$p2 = P(zoonotic\ outbreak\ in\ Wuhan \mid Grand \cap Eprov) \times P(Grand \cap Eprov)$$

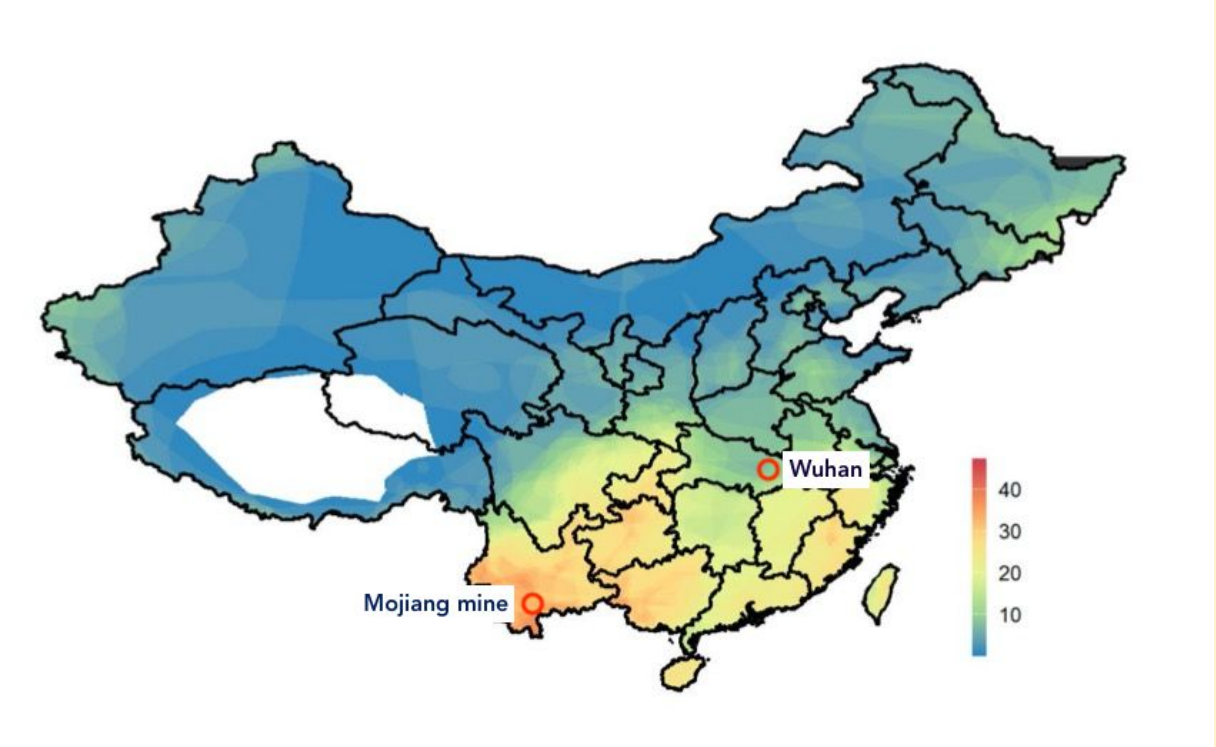
and as we are supposing $P(Eprov) = 1$

$$p2 = P_{Eprov}(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \times P(Grand)$$

$P_{Eprov}(outbreak\ in\ Wuhan \mid Grand)$ is effectively our rescaling factor for $P(Grand)$. Let's first consider a zoonotic event via an intermediate host and let's try to determine how likely a Hubei citizen is to be infected by an intermediate host compared to an 'average' Chinese citizen. Unfortunately at this stage little is known about possible animal hosts, but domestic animals,

chicken, pigs, ducks and pangolins seem to have been discounted while ferrets and bamboo rats (for instance) are still being considered [20, 21, 91]. Based on the limited knowledge available, at best what we can state is that the provinces with the strongest interfaces between bat populations and animal farming generally seem to be in the Southern province corridor (Yunnan, Guizhou, Guangxi, Guangdong, Fujian, up to Zhejiang), with Hubei sitting on the edge of that corridor [22, 92].

Box 1: Bat species richness in China:



Map extracted from Feijó et al [92], with overlays of the Mojiang and Wuhan locations.

If we consider a zoonotic event with a direct bat-human interface, the bat populations with known SARS-CoV-like virus seem to be in Yunnan, Guanxi, Zhejiang, but also with some incidences in Hubei itself and neighbouring Shanxi. However, the (limited) known bat populations with SARS-CoV-like viruses that make use of the human ACE2 receptor (essential for direct bat-human infection) are in Yunnan. All of this must nevertheless be taken carefully; for instance there could be a historical sampling bias for Guangdong and Yunnan with other provinces having been less systematically surveyed. Our present knowledge is still very patchy on these essential questions and at best what we can say at this stage is that Hubei seems less likely than Yunnan for such a direct bat-human zoonotic event, but also more likely than the average Chinese province [22]. This is also confirmed by the absence of any SARS-CoV2 related virus in any samples collected in Wuhan or Hubei to date. [94]

If we then try to translate the qualitative assessments (with and without intermediate host) into the resulting risks in terms of population, we further note that most of China's population is in the provinces along the East coast, with the South East coast being generally more at risk than Hubei, and the North East (including Beijing) at par or actually under Hubei. Hence a citizen of Hubei seems at most a bit more at risk under the *Eprov* scenario than the average Chinese citizen.

However, we are not just considering the probability of an outbreak in Hubei but more specifically the probability of an outbreak in Wuhan. The continued absence of any detected initial case out of Wuhan nine months after the initial outbreak and the discarding of the early wet-market animal-host

theory both play against the scenario of a Hubei provincial zoonotic event leading to a first outbreak in Wuhan (with or without intermediate host). In the end we shall consider that the two factors (at most slightly higher risk for an average Hubei citizen compared to a population-adjusted average Chinese citizen, continued absence of any detected early case out of Wuhan) work to cancel each other, leading us to assume that the resulting probability is still in line with the previous population argument :

$$P_{Eprov}(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \approx 1\%$$

giving $p2 \approx 1\%\ of\ 1\ in\ 10\ year$.

Scenario Eany:

Supposing instead that *Eany* holds ($P(Eany) = 1$), let's evaluate the probability of a first community outbreak in Wuhan due to a natural zoonotic somewhere else in China.

$$p3 = P(zoonotic\ outbreak\ in\ Wuhan \mid Grand \cap Eany) \times P(Grand \cap Eany)$$

and as we are supposing $P(Eany) = 1$

$$p3 = P_{Eany}(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \times P(Grand)$$

$P(outbreak\ in\ Wuhan \mid Grand \cap Eany)$ is our rescaling factor for $P(Grand)$. Per *Eany*, Wuhan shall be treated exactly like any other place in China with 1% of the population. Hence:

$$P_{Eany}(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \approx 1\% \qquad [exact]$$

and $p3 \approx 1\%\ of\ 1\ in\ 10\ year$

For the sake of clarity, similarly to what we noted with *Eprov*, such an *Eany* scenario is rather unlikely due to the total absence of any detected early case out of Wuhan 9 months after the original outbreak. However, as shown below, this won't matter.

Retained probability:

The above analysis shows that, based on the information presently available, the probability of a zoonotic outbreak in Wuhan seems reasonably well approximated by a simple population argument under a range of scenarios that should map all possibilities. So without having to consider how to weight these scenarios, we can simply retain their common upper value:

$$P(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \approx 1\%$$

Given the uncertainties attached to the *Eprov* scenario, we will nevertheless later consider an alternative value of 2% for $P(zoonotic\ outbreak\ in\ Wuhan \mid Grand)$. For now we have:

$$P(zoonotic\ outbreak\ in\ Wuhan \mid Grand) \times P(Grand) \approx 1\%\ of\ 1\ in\ 10y$$

$$P(zoonotic\ outbreak\ in\ Wuhan) \approx 0.1\%\ per\ year$$

Or using the notation for the hypothesis:

$$P(Hrand) \approx 0.1\%\ per\ year$$

which can be also stated as a 'once in 1,000 years' event.

Box 2: A review of assessments of the direct spillover risk from natural bat reservoirs:

In the wake of SARS and given the role that an intermediate host animal is generally considered to have played, perceptions of the risk of direct transmission of a coronavirus from bats to humans were

initially rather low, the dominant assumption being that an intermediate host was required [23]. These perceptions changed with the discovery of a SARS-CoV-like virus that uses the ACE2 receptor in a Yunnan bat colony in Oct 2013 [24].

However, primacy should really go to the publication in May 2013 of the less well known but essential MS thesis on the Mojiang 'miners' severe pneumonia cases [25], following prolonged clearing out of bat guano in an abandoned hillside mine. That MS thesis, drawing on the diagnostic of the top SARS expert in China (Dt Zhong Nan Shan), notes in its conclusion:

> *'With the Kunming Institute of Zoology, we confirmed that the six patients were exposed to Chinese Rufous horseshoe bat, which caused the disease. However, a paper published in Science magazine in 2005 by Scientist Shi Zheng Li and Zhang Shu Yi from Wuhan Institute of Virology under the Chinese Academy of Science [see 23], concluded that the SARS-like-CoV carried by bats is not contagious to humans. This contradiction indicates the importance of these six cases: the severe pneumonia caused by the unknown virus and the bats in the cave merit further investigation and research.'*

Nevertheless, even today for many specialists the actual risk in normal circumstances still remains low. For instance in Feb 2010, Lin Fa Wang, a top specialist on bat coronavirus and a frequent collaborator of the WIV rated the risk a low:

> *Still, very few bat viruses are ready to transmit directly to humans, said Wang, who has been studying bat origins of human viruses for decades and works with a group of researchers sometimes dubbed 'The Bat Pack.' "I always say that if they could do that, then the human population would have been wiped out a long time ago because bats have been in existence for 80-to-100 million years -- much older than humans" [26]*

Not that long ago (Dec 2017), the WIV scientists who regularly do bat samplings in the wild voiced a similar opinion:

> *'These SARS-like viruses usually stay quietly among wild animals in nature. They have never attacked humans. The problem always first comes from humans. So the method is very simple. If you don't touch or disturb wild animals such as bats and civet cats, the virus will naturally not spread to humans.'[27]*

In contrast to these low risk estimates, a pandemic scenario by USAID-PREDICT [28] published around 2014 may be seen as a high point in the risk evaluation of a possible direct bat-to-human coronavirus infection. This was done in the context of bat guano collection, a possibility highlighted in a study by PREDICT a bit earlier in 2013 [29]. That pandemic scenario insisted on the risk of direct infection while collecting bat guano from caves and further gave an indicative estimate of the probability of a subsequent pandemic of 96%. These alarmist estimates seem high; first as far as the risk of infection is involved some of the bat guano collectors in the case studied had been doing so for 40 years without any issue [30], and - secondly - as far as the risk of subsequent pandemic is involved, that scenario came out around a year after the Mojiang 'miners' accident with its suspected CoV infections while clearing up bat guano (albeit after long exposure times of 4 to 14 days) which did not actually lead to any community transmission from any of the 6 cases [31]. Additionally, some of the people involved in that USAID-PREDICT study stated in subsequent papers (including one published in Nov. 2019) that a coronavirus spillover in communities living close to bat colonies is nevertheless a 'rare event', with mostly 'subclinical or [...] only mild symptoms' [19, 88].

All things considered it is quite possible that the actual risk of direct bat-to-human transmission is still rather low as long as bat colonies are not under environmental stress, including human encroaching and land change use [12, 13]. In contrast, what has most definitely changed over the recent past, has added substantially to the risk and is unlikely to change, is the increased possibility of a local outbreak turning in an epidemic and then into a pandemic, due to the important developments in national and international travelling patterns [32]. That in itself should certainly not invite complacency.

b. COVID-19 Lab-related accident hypothesis (Hacc)

We need to estimate the probability of:

> ***Hacc:*** *The COVID-19 community outbreak that was first observed in Wuhan was caused by an accident linked to a Wuhan lab (be it collection, transport or lab accident, including leak)*

In order to estimate Hacc, let's start by considering the underlying event:

> ***Eacc:*** *An accident involving a SARS-like coronavirus linked to a Wuhan lab (be it collection, transport or lab accident, including leak)*

Let's then decompose this accident probability between collection, transport and lab accidents:

Accident during collection of a virus:

Thousands of SARS-like coronaviruses have been found in bats populations in particular in South China caves. In less than 10 years the research teams at the WIV have collected 15,000 bat samples mostly from China (a lesser part being from Africa and other countries), which have delivered so far around 1,500 types of virus strains and more than 60,000 individual virus strains (individual occurrence of a virus strain type in a sample) [33, 34]. While these numbers are already impressive, potentially there could be even more viruses waiting to be identified in these samples as it is not clear if all the samples have been fully tested as the tools to do so are still being tested and refined [35].

The risk of infection of a worker through these collections is not negligible, especially considering some of the collection conditions that have been reported [36] while the real risk of direct infection of a SARS-like coronavirus from bats to humans has been recognized since 2013 [24, 16, 37] even if the actual likelihood of such an event under normal circumstances is still heavily debated [see Box 2].

Yet we do not have a precise estimate for such a risk. At best we can show that even with a very small risk per virus strain contained in a sample, we shall still end up with a non-negligible risk of Collection-Acquired Infection over the unprecedented sheer quantity of virus strains being handled - effectively at no other time in history have so many bat viruses been handled, amongst which some are likely to have a potential for a human jump. For instance if we suppose an a-priori low 0.0001% (one in a million) risk of infection per virus strain thus detected, counting around 50,000 identified virus strains collected in China itself (out of the 60,000), this still sums up to a 5% risk of a Collection-Acquired Infection over the full collection over the years.

Additionally we do not know how many strains and samples were collected in the few months prior to the start of the outbreak (which is really what matters here). There is unfortunately no open record on this.

While from the above we can reasonably conjecture that the cumulative probability of a Collection-Acquired Infection being the cause of the outbreak is not exactly null and may not even be negligible, we must concede that it is very difficult to estimate that number even approximately and we shall not attempt it here - leaving it instead as a possible refinement of our probability estimates. Instead we shall simply conservatively ignore the risk of an accident during collection leading to some worker getting infected:

$$P(Collection\text{–}Acquired\ Infection) \approx 0\%\ per\ year \qquad [conservative]$$

Accident during transport a virus:

Next there is the probability of an infection during transport of virus samples to Wuhan. We know little about these transport conditions, and equally little about the number of strains and samples that were collected in the few months preceding the outbreak.

So we shall simply assume that the virus samples are safely transported according to best practices and that the risk of infection during transport is quasi null. We will again invite a proper assessment as a possible refinement of our probability estimates, knowing that this anyway puts us on the conservative side:

$$P(Transport\text{–}Acquired\ Infection) \approx 0\%\ per\ year \qquad [conservative]$$

Accident directly involving a lab:

Last we need to consider two possible accident scenarios directly involving a lab:

- Lab-Acquired Infection (LAI): a lab worker gets infected in the lab and passes on that infection to the community.
- Lab Leakage: the virus escapes the lab without first infecting a lab worker, for instance due to an issue with the treatment of solid, liquid or gaseous wastes [90].

The two scenarios can be both described as 'Lab Escapes'. However it is much easier to find records of Lab-Acquired Infections than of Lab Leakages. LAIs are actually not that uncommon and are typically recorded by international organizations [38], while Lab Leakages are not necessarily even detected [39], especially since not all Lab Leakages would necessarily result in an infection in the community. Additionally such accidents may simply not be reported to authorities even if detected by the laboratory itself [40].

For the reason just given we shall simply ignore the contribution of Lab Leakages to the probability of a Lab Escape. The probability of a Lab Escape via a Lab-Acquired Infection can then be estimated through official records and then checked against a few reference points.

In doing so we shall only consider those labs in Wuhan that we know were actively working on SARS-like coronaviruses. Work on SARS and SARS-like coronaviruses started in China just after the 2002 epidemic [92], with many samples being collected, tested and sequenced, and key papers being published - especially after the discovery of large natural reservoirs of coronaviruses in South China bat colonies in 2005 [23], and again following the discovery of the potential of some bat coronavirus to infect humans without any intermediate hosts in 2013 [24, 25]. From 2003 to 2017 all that work was without any doubt done at BSL-3 or lower (some at BSL-2 [41, 94]) since the BSL-4 suite at the WIV (Zhendian site) would only open in 2017.

In any case the revised guidelines specifically aimed at SARS-CoV-2 [42] that were published in January 2020 stipulate that BSL-3 is the suitable level for work on the live virus ([A]BSL-3 for animal experiments) while BSL-2 is the suitable level for work on uncultured SARS-CoV-2 infectious materials, which is fully consistent with the standard biosafety levels for this type of pathogen [Annex D]. Hence to this day most of the work involving live coronaviruses culture in Wuhan is still being done at [A]BSL-3, often by the same teams in the same labs [Annex E].

With this in mind we shall conservatively ignore the BSL-4 suite at the Wuhan Institute of Virology (VIW) and the various Wuhan BSL-2 labs involved (which should only handle uncultured coronaviruses), focusing purely on BSL-3 labs where the cultured strains were normally handled.

It is important to note that there is no easy consensus on an estimate of LAIs for BSL-3 labs [Annex B]. First such estimates depend on many variables (level of activity of the lab, level of expertise of lab personnel, physical characteristics of the lab, characteristics of the virus being handled, type of work on these viruses, etc), which we are already difficult to obtain for known LAIs in US BSL-3 labs, and even more difficult if not impossible to obtain for the Chinese BSL-3 labs of interest.

Secondly, even knowing these variables many differences in assumptions and methodology behind these estimates may remain.

In the end, the inherent limitations of trying to rigorously evaluate the risk of LAIs may be best illustrated by the case of the planned National Bio- and Agro-Defense Facility in Manhattan, Kansas, for which the Department of Homeland Security released a first assessment of LAI escape risk at 2.4% per year and a final risk assessment of around 0.002% per year, immediately criticized by the National Research Council.

With all these limitations in mind, we shall follow the analysis of Klotz [43-46] who derives an estimate of the risk of a Lab Escape via an Lab-Acquired Infection in a BSL-3 lab-complex of 0.2% per year, based on a US CDC report [47]. Further estimates will be considered in section 4 below.

As is shown in Annex E, 3 Wuhan lab-complexes with either BSL-3 or ABSL-3 labs are most definitely actively involved in the study of SARS-like coronaviruses. So considering 3 BSL-3 lab-complexes that were very active working on coronaviruses over the last few years, we get:

$$P(Wuhan\ Lab\ Escape \mid 3\ BSL\text{–}3) \;=\; 1 \;-\; (1-0.2\%)^3 \quad per\ year$$

which in first order (thereafter systematically used) becomes:

$$P(Wuhan\ Lab\ Escape \mid 3\ BSL\text{–}3) \;\approx\; 3 \times 0.2\%\ per\ year$$

$$P(Wuhan\ Lab\ Escape \mid 3\ BSL\text{–}3) \;\approx\; 0.6\%\ per\ year$$

Summing over the 3 types of possible accidents (collection, transport and lab), we get:

$$P(Wuhan\ Lab\ Related\ Accident \mid 3\ BSL\text{–}3) \;\approx 0.6\%\ per\ year$$

Probability of a community outbreak following a Lab-Related SARS-like Infection:

As further explained in Annex C and illustrated in Annex D, an isolated infection - or even a few concurrent cases of infections due to a Lab Escape - will not necessarily lead to a community outbreak. Here we shall refer to Klotz [48] (building on Lipsitch *et al* [49] and Merler *et al* [39]) who uses an intermediate estimate of 25% for the probability of an outbreak given a Lab-Acquired Infection. Merler *et al* shows that the 25% outbreak probability is consistent with an infectious disease with an R_0 of around 1.75, under a specific scenario of urban lab escape followed by closure of the laboratory closure and quarantine of the households of laboratory workers. We further note that such an R_0 is on the lower side of available estimates of the R_0 for COVID-19 which are generally between 2 and 2.5 [50]. If we were instead to use a common estimate of 2.2 for COVID-19 R_0, the probability of an outbreak estimated by Merler *et al* would become around 50%.

With this in mind, in order to remain conservative we shall retain a value of 20% as reference value, slightly less than the 25% used by Klotz.

$$P(lab\text{–}related\ outbreak \mid infection\ due\ to\ a\ Wuhan\ lab\text{–}related\ accident) \;\approx\; 20\%$$

Strictly speaking this is the probability of a community outbreak due to a Wuhan Lab Escape, but that outbreak itself could happen in Wuhan or elsewhere. Nevertheless such a Wuhan Lab Escape would most likely cause the outbreak to happen locally in Wuhan, and much less likely cause a distant first outbreak away from the escaped lab. So at most a slight curtailment of the 20% may be needed to allow for that unlikely alternative of a distant first outbreak. This won't change the

probabilities significantly and since we are already sitting on the conservative side overall, we shall simply take:

$$P(\textit{lab–related outbreak in Wuhan} \mid \textit{infection due to a Wuhan lab–related accident}) \approx 20\%$$

Hacc - SARS-like community outbreak due to a Wuhan lab-related accident:

Putting the above probabilities together we get:

$$P(\textit{lab–related outbreak in Wuhan} \mid \textit{Eacc with } 3\ BSL\text{–}3) \approx 0.20 \times 0.6\%\ \textit{per year}$$

$$P(\textit{lab–related outbreak in Wuhan} \mid \textit{Eacc with } 3\ BSL\text{–}3) \approx 0.12\%\ \textit{per year}$$

Or using the notation for the hypothesis:

$$P(Hacc \mid 3\ BSL\text{–}3) \approx 0.12\%\ \textit{per year}$$

This can be also stated as a ‘once in 833 years’ event.

3. Resulting Odds

Now let’s calculate the odds or relative probabilities.

We found that:

$$P(Hrand) \simeq 0.10\%\ \textit{per year}$$

$$P(Hacc \mid 3\ BSL\text{–}3) \simeq 0.12\%\ \textit{per year}$$

and since the random zoonotic hypothesis is in no way linked to any lab:

$$P(Hrand) = P(Hrand \mid 3\ BSL\text{–}3)$$

Hence we have:

$$P(Hacc \mid 3\ BSL\text{–}3) \simeq 1.2 \times P(Hrand \mid 3\ BSL\text{–}3)$$

Since we are only considering the two hypotheses Hacc and Hrand:

$$P(Hacc \mid 3\ BSL\text{–}3) + P(Hrand \mid 3\ BSL\text{–}3) = 1$$

hence:

$$P(Hacc \mid 3\ BSL\text{–}3) \simeq 54.5\%$$

$$P(Hrand \mid 3\ BSL\text{–}3) \simeq 45.5\%$$

Said otherwise *under conservative assumptions,* the probability that the COVID-19 community outbreak first observed in Wuhan is linked to some Wuhan lab activity is at least 54.5% (given by 0.12/(0.12+0.10)) and the probability of the alternate purely natural origin is at most 45.5%.

In odds terms one would formulate that as saying that, under conservative assumptions, the odds of a lab-induced origin to a purely natural origin - given a first observed community outbreak in Wuhan - are at least 6 to 5 on.

$$Odds(Hacc\ vs.\ Hrand \mid 3\ BSL\text{–}3) \simeq 1.2 = 6\ \textit{to}\ 5\ \textit{on}$$

How conservative are these odds of a lab-induced origin?

A number of conservative assumptions were made during the derivation of the odds:

- We did not take into account the collection and transport risks
- We only considered 3 Wuhan [A]BSL-3 lab-complexes which we can ascertain were actively working on coronaviruses. We ignored 2 other BSL-3 lab-complexes that were also known to be working to some degree on SARS-like coronaviruses .
- We totally ignored the many BSL-2s (including the one at the Wuhan CDC) and one BSL-4 lab in Wuhan that were either storing or actively working on SARS-like coronaviruses [51, 41].
- The reference Lab Escape probability of 0.2% only considers a Lab-Acquired Infection (LAI), meaning a lab worker being infected and spreading the virus to the community. It does not include the very possible risk of Lab Escape without LAI (for instance via a waste treatment problem) which is more difficult to tabulate [52].
- The Lab-Acquired Infection probability of 0.2% per year per BSL-3 lab-complex is conservative. As shown in Annex B, the Department of Homeland Security used instead a reference probability of 2.4% per year in its first assessment of the risk for the planned National Bio and Agro-Defense Facility (NBAF, to be opened in 2022).
- That 0.2% is calibrated on US data, when it could be argued the safety of Chinese BSL-3 labs is on average (and not in all cases) still lagging behind the US ones (see point 3 of the Discussion below).
- The 20% probability of outbreak given a Lab Escape was arrived at for an infectious disease with R_0 of around 1.75 in a scenario of active countermeasures (including closure of the urban lab and quarantine of the lab workers' households) [39]. COVID-19 had an initial R_0 closer to 2.2 [50] and a Lab Escape may not necessarily be met with countermeasures, especially if undetected for a while.
- The 6 recorded SARS Lab-Acquired Infections (including 4 in China, some with community transmission), in only 2 years following the 2002 SARS outbreak [53], show that the risk of an LAI when working with highly dangerous coronavirus is likely higher than this 0.2% per year baseline.
- We had to assume that COVID-19 is a non-lab related accident to estimate the mean time interval between purely zoonotic SARS-like community outbreaks in China. From this we actually find a non-negligible probability that COVID-19 is a lab-related accident. So our estimate of that mean interval is favouring a non-lab origin, which means that the odds should be even more in favour of the lab-related accident.

4. Variations on Estimate Input Probabilities

The main issue when trying to come up with reasonable estimates for the key input probabilities is that there is not much data to work with. For instance there has been a limited number of human-coronaviruses community outbreaks in China over the last 20 years, making it difficult to estimate the arrival process (a Poisson process) - in this case the data is available but not dense. Or we do not have available data where it should theoretically be possible to have some (such as the precise numbers of live coronavirus worked on in Wuhan BSL-3 labs, type of activity involving them, the total durations and types of exposures, lab conditions, biosafety training of employees, even general statistics about LAIs in Chinese labs, etc).

So while we started with some specific choices for the key input probabilities (our *Reference* scenario), it must be clear that these priors are just educated estimates, based on available information at the time and our understanding. Any such estimate is partly arbitrary and complex mathematical models - while they may be able to deliver structural insights [54] - cannot solve this fundamental lack-of-data issue. Still a redeeming grace of such probabilistic outline is that we do not

need exact estimates to engage in a constructive discussion about probable origins, since using conservative estimates may be enough to assess whether the possibility of a lab-Induced community outbreak is negligible or not.

With this in mind we shall explore alternative sets of input probabilities beyond our Reference scenario. We will consider a Base scenario which uses 'raw' values for these probabilities, and a De Minimis where values in favour of the purely zoonotic event hypothesis (Hrand) are systematically used. These scenarios are presented in Box 3 and the resulting relative probabilities in Table 1 below.

We note that even under the very conservative De Minimis scenario, the relative probability of a lab induced accident being the origin of the COVID-19 community outbreak is not negligible, at 6%.

Box 3: Base, Reference and De minimis scenarios:

P(Grand): probability of occurrence of a purely zoonotic human outbreak in China of a SARS-like coronavirus, per year		
Base: we retain the MLE (Maximum Likelihood Estimate) for the mean of the Poisson process associated with the occurrence of the event of interest. Specifically SARS and COVID-19 occurred at an interval of 16.5 years, which gives one additional event every 16.5 years, so around 6.06% per year (with the initial SARS event starting the clock).	**Reference:** we use 1 additional event in 10 years as an estimate of the mean of the Poisson process associated with the occurrence of an event of interest. We can show that there is around a 45% probability that we should observe one or no additional event in 16.5 years (on top of the initial SARS event) if that estimate is indeed the true mean.	**De minimis**: we use 2.2 additional events in 10 years as an estimate of the mean of the Poisson process associated with the occurrence of an event of interest. We can show that there is only around a 10% probability that we should observe one or no additional event in 16.5 years (on top of the initial SARS event) if that estimate is indeed the true mean.
P(Wuhan | China): rescaling factor applied to P(Grand) to get the probability of occurrence of a purely zoonotic community outbreak in Wuhan of a SARS-like coronavirus, per year		
Base: we use the population proportion as described in 2.a. Wuhan has around 11mln inhabitants and China as a whole around 1,400mln. 11/1,400 gives us 0.79%.	**Reference:** we round up the base value to 1% which will favour the non-lab induced zoonotic event hypothesis.	**De minimis**: in order to account for uncertainties around bat populations carrying SARS-CoV-like viruses, especially those with the ability to directly infect humans, we use twice the Reference value.
P(Active-Lab Acquired Infection | 1 BSL–3): probability of a Lab-Acquired Infection with a human SARS-like coronavirus for one BSL-3 lab complex actively working on these (cell cultures or animal experiments).		
Base: Based on the structural issues with some Chinese labs reported in point 3 of the Discussion, we increased the 0.2% per BSSL-3 complex (that was calibrated on US labs) to 0.25% - which likely still does not properly reflect the relative risk level.	**Reference:** We use the estimate of 0.2% per BSL-3 complex per year discussed in Annex B.	**De minimis**: We use a low estimate of 0.1% per BSL-3 complex per year which would mean that either our base estimate is much too high compared to the actual safety of US BSL-3 labs, or that the average Wuhan lab of interest is much safer than the average US lab.

P(community outbreak | escape due to a Wuhan lab–related accident)		
Base: we use the 25% discussed in Annex C.	**Reference:** we use an intermediate 20%.	**De minimis:** we use a lower 10% to reflect the difficulty of generalizing from a specific simulation with its specific assumptions.

Inputs	Notation	Base	Reference	De minimis
probability of a purely zoonotic human SARS-like virus community outbreak in China, per year	P(Grand)	6.06%	10.00%	22.00%
rescaling of above probability based on population	P(zoonotic outbreak in Wuhan | Grand)	0.79%	1.00%	2.00%
Resulting probability of pure zoonotic human SARS-like virus community outbreak starting in Wuhan, per year	P(Hrand)	0.05%	0.10%	0.44%
probability of LAI during collection in the wild of a human SARS-like virus, per year	P(Collection–Acquired Infection)	0.00%	0.00%	0.00%
probability of LAI during transport of a human SARS-like virus collected in the wild, per year	P(Transport–Acquired Infection)	0.00%	0.00%	0.00%
probability of a human SARS-like virus escape from one BSL-3 complex actively working on such virus (cell culture or animal experimentation), per year	P(Active-Lab Acquired Infection | 1 BSL–3)	0.25%	0.20%	0.10%
probability of a human SARS-like virus escape from one BSL-3 complex actively working on such virus (cell culture or animal experimentation), per year	P(Active-Lab Escape | 1 BSL–3)	0.25%	0.20%	0.10%
number of Wuhan BSL-3 complexes actively working on such virus (cell culture or animal experimentation)	n	3	3	3
probability of community outbreak given a Wuhan lab-related escape of a human SARS like virus (R0 around 2.2 amongst other factors)	P(community outbreak | escape due to a Wuhan lab–related accident)	25%	20%	10%
Resulting probability of a Wuhan lab-induced human SARS-like community outbreak in Wuhan, per year (1st order)	P(Hacc | n BSL–3)	0.19%	0.12%	0.03%
Relative probability of purely zoonotic event given human SARS-like community outbreak in Wuhan - upper bound	P(Hrand)/(P(Hrand)+P(Hacc))	20.3%	45.5%	93.6%
Relative probability of lab-escape event given human SARS-like community outbreak in Wuhan - lower bound	P(Hacc)/(P(Hrand)+P(Hacc))	79.7%	54.5%	6.4%

Table 1: Relative probabilities for the two hypotheses

DISCUSSION

1. Understanding the odds: A simple analogy

A simple analogy may provide a good summary of our key findings about the odds.

Let's suppose that the risk of an epidemic starting due to a SARS-like coronavirus escaping a lab is a lottery. Let's also suppose that the risk of an epidemic starting due to a SARS-like purely random zoonotic event is another lottery.

We showed that while the risk of a lab-related epidemic is less than the risk of a pure zoonotic event epidemic *when considering the whole of China* (as is often correctly mentioned in the SARS-CoV-2 origins debate), *for the city of Wuhan itself* the balance of risks is actually very different.

Based on the fact that Wuhan has some the most active labs in China working on these SARS-like coronaviruses but has only 1% of the population of China, following the lottery analogy we observed that Wuhan has bought a large chunk of the lab-related epidemic lottery tickets but less than 1% of the purely zoonotic epidemic lottery tickets.

It then followed that - based on rather conservative assumptions - Wuhan should be expected to win the purely-zoonotic epidemic lottery every 1,000 years and to win the lab-related epidemic lottery every 833 years (on average). Said otherwise, a lab-related epidemic is more likely to first break out in Wuhan than a purely zoonotic-based epidemic.

From there, knowing that Wuhan is today in possession of a winning lottery ticket, we considered the question: 'Which lottery did Wuhan likely win?'. Our answer to that question is based purely on what we know of the two lotteries, but it is clear: using conservative assumptions, there is at least a 54% chance of Wuhan having won the lab-related epidemic lottery and at most a 46% chance of Wuhan having won the purely zoonotic event lottery.

2. A rebuttal of common misunderstandings

Misunderstanding #1:

> *'Since we know that a SARS-like epidemic in China is much more likely to be triggered by a natural encounter with some animal rather than by any lab accident, saying that the recent epidemic may have been caused by a lab accident is simply unscientific and not worth discussing.'*

This misunderstanding is often repeated in the current debate [55, 56]. It is true that *for China as a whole* the risk of a SARS-like community outbreak triggered by a purely random zoonotic event is likely higher than a lab-induced one, using the 0.2% per year baseline. With the probabilities used for the Reference odds and supposing another 6 BSL-3 lab-complexes actively working on SARS-like coronaviruses beyond Wuhan (for a total of 9 lab-complexes doing such work in China), we indeed get:

$$P(\textit{community outbreak in China} \mid \textit{Grand}) = 10\%\ \textit{per year}$$

and

$$P(\textit{community outbreak in China} \mid \textit{Eacc with } 9\ \textit{BSL}\text{–}3) = 9 \times 0.20 \times 0.2\%\ \textit{per year}$$

$$P(\textit{community outbreak in China} \mid \textit{Eacc with } 9\ \textit{BSL}\text{–}3) = 0.36\%\ \textit{per year}$$

so that:

$$Odds(Hrand\ vs.\ Hacc \mid 9\ BSL\text{–}3) \ \approx\ 28\ to\ 1\ on$$

which effectively is a huge weighting of the odds towards the random zoonotic event when considering the whole of China, in full opposition to the Wuhan odds that we previously calculated:

$$Odds(Hacc\ vs.\ Hrand \mid 3\ BSL\text{–}3) \ >\ 6\ to\ 5\ on$$

or $$Odds(Hrand\ vs.\ Hacc \mid 3\ BSL\text{–}3) \ <\ 5\ to\ 6\ on$$

Said otherwise, the odds totally pivot in favour of the lab-induced accident once we know that the outbreak started in Wuhan. Using again the lottery analogy, Wuhan bought a large portion of the lab-induced 'SARS-like community outbreak' lottery tickets (as per above 3 out of every 9 tickets, so a third of the tickets), but it purchased less than 1% of the random zoonotic community outbreak tickets.

As a result Wuhan is more likely to be holding a 'winning ticket' from the lab lottery than from the natural encounter lottery. From this we can see that the relative probabilities (natural vs. lab induced) for a community outbreak in China *as a whole* do not extend to a community outbreak that actually started in Wuhan - quite the contrary. Hence it is unfortunately misleading to generalize the China odds to the Wuhan odds.

Additionally there is good circumstantial evidence to believe that the 0.2% baseline is very conservative when applied to a highly transmissible coronavirus and to variable lab safety conditions. Indeed it is impossible to explain otherwise how 6 SARS LAIs could have happened in only 2 years (2003-04), with 4 incidents in Chinese labs, if these LAIs were universally governed by such a low baseline probability.

Misunderstanding #2:

> *'The virus could have emerged naturally somewhere else in China and before causing the Wuhan community outbreak - hence the odds are wrong because they do not consider the possible emergence out of Wuhan'.*

The possibility of natural emergence out of Wuhan with a first detected community outbreak in Wuhan is already in the odds as we explicitly reviewed that possibility and included it in our estimate of $P(community\ outbreak\ in\ Wuhan \mid Grand)$. See the discussion on *Eloc*, *Eprov* and *Eany*.

Misunderstanding #3:

> *'Considering that the risk of a purely zoonotic event is linked to the population size of a city or region makes no sense because all you need is just one infected person to start an infection'.*

While it is correct that only one initial carrier (the 'patient zero') is needed to start an outbreak of a contagious disease, this does in no way invalidate the population size argument. The chance of that initial carrier being present in a certain population is still linked to that population size as well as to the proximity of that population to natural reservoirs of the responsible pathogen. These two aspects were covered in our estimate of $P(community\ outbreak\ in\ Wuhan \mid Grand)$.

Misunderstanding #4:

> *'If you suppose that a community outbreak happens in China, then by definition it must happen somewhere. So there is no point saying that there was a 1% chance that it*

> *happened in a particular place after the fact. It had to happen somewhere and it just happened in Wuhan by chance.'*

An easy way to see why this is incorrect is to notice that for the Wuhan community outbreak to be a purely neutral after-the-fact random observation, then the rest of China must look like Wuhan. Hence given that we are considering 3 BSL-3 lab-complexes in Wuhan actively working on coronaviruses and given that Wuhan has 1% of China's population, this means that the argument would be correct if China had at least 300 BSL-3 lab-complexes actively working on coronaviruses.

With 300 BSL-3 working on these SARS-like coronaviruses:

$$P(lab\text{–}related\ outbreak\ in\ China \mid Eacc\ with\ 300\ BSL\text{–}3) \simeq 300 \times 0.2\% \times 20\%\ per\ year$$

$$P(lab\text{–}related\ outbreak\ in\ China \mid Eacc\ with\ 300\ BSL\text{–}3) \simeq 0.12\ per\ year$$

This 0.12 per year is to be compared with the 0.10 per year for the pure zoonotic event epidemic expectation over China. Hence under the conditions necessary for the logic behind this misunderstanding to be correct, we are effectively back to the same '6 to 5 on' odds, this time over the whole of China.

Interestingly, if told that 300 lab-complexes were actively working on SARS-like coronaviruses in China, most people at this stage would not intuitively consider the odds of a lab-related origin for a SARS-like community outbreak somewhere in China to be negligible (compared to a purely random zoonotic event) without even needing a more detailed inspection of individual probabilities. But crucially this is exactly the same odds as when considering the probability of an observed first community outbreak in Wuhan with 3 active BSL-3 lab-complexes against a purely random zoonotic community outbreak there.

Misunderstanding #5:

> *'There is still nothing proving that the COVID-19 community outbreak was caused by a lab-related accident, whatever the probabilities. So it makes no sense to talk about a possible lab accident.'*

This misunderstanding seems to be surprisingly common in the debate about COVID-19. It is easy to see why it is wrong: *there is simply nothing proving that the outbreak is actually a purely random zoonotic event either.*

The too-often accompanying assertion that, when considering China as whole, a natural origin SARS-like community outbreak is anyway much more likely than a lab-induced SARS-like community outbreak - so that the probabilities are actually as good as a proof - offers no support at all here since it is based on another misunderstanding (see Misunderstanding #1).

When faced with this kind of situation where there is no definite proof for any of the possible causes, or even no dominating probability for any of the probable causes, all we can do is to try to evaluate the relative probabilities as we did here, to use these probabilities to inform the debate and a reasoned investigation, and then to keep updating these probabilities as more insights are collected [57].

Misunderstanding #6:

> *'You suppose a 1 in 10y probability for a random SARS-like community outbreak in China but we know that coronaviruses outbreaks are more common (MERS, SARS pig, etc) across the world. We also know that populations living close to bat colonies in China carry*

> *antibodies for SARS-like coronaviruses, so this is only the tip of the iceberg and outbreaks involving SARS-like coronaviruses are much more common than that'.*

This misunderstanding is based on three possible confusions. There is first a confusion on the probability of interest, which is the probability of a non-lab related (1) community outbreak of a (2) human (3) SARS-like coronavirus (4) in Wuhan. As discussed in Annex A, the only one of these 4 attributes that we can reasonably relax to get more events and still be able to carefully rescale to the probability of interest is (4) 'in Wuhan'.

If we consider the attribute 'community outbreak' for instance, there is no point considering a probability based on local *non-outbreaks* because there is no meaningful way to translate that denser probability distribution into the probability of a proper SARS-like outbreak. These local non-outbreaks are fundamentally different: they are effectively only detected through some antibodies in a small fraction of rural populations living close to bat colonies [94] (2.7% in the study reported in Ning Wang *et al* [19], 0.7% in the study reported by Hongying Li *et al* [88]) - antibodies which are not only conspicuously absent in the Wuhan population but also suggest that 'infections were subclinical or caused only mild symptoms' [19].

The second confusion is a logical one. Local non-outbreaks in these populations living close to bat colonies, as inferred by antibodies, are by definition local. So one would have to contrive an exclusively directed scenario where someone in such a community got infected with SARS-CoV2 (or a an early strain of it), for some reason remained asymptomatic, did not create a local outbreak but somehow led to an outbreak in Wuhan and nowhere else along the way, and particularly not back home if home that was. This would have to involve some very directed travelling from such a local community to Wuhan. Interestingly the people who do such directed travelling between these communities and Wuhan are quite likely often involved with bat coronavirus studies.

The third confusion is a cognitive confusion between risk awareness and the actual level of risk. Specifically, the knowledge that bat-colonies are natural reservoirs of SARS-like coronaviruses and that some people living close to bat colonies often have antibodies for SARS-like coronaviruses has certainly dramatically increased our awareness of the possible mechanisms of a SARS-CoV-like spillover, but it has not in itself proportionally increased the risk level itself [see Box 2]. In the same way (taking a much more extreme example) that our tracking of asteroids over the last 30 years has not increased the risk of the earth being hit by one. What may have much more impact on the actual risk level are the trends governing the intensity of the possible contacts between populations and bats (possibly through an intermediate animal host), land use and the development of transport links.

Most importantly, whatever the theoretical debates, in the end we have only at most two non-lab related occurrences of human SARS-like community outbreaks in China over 16.5 years. Based on the above discussion we consider that these 2 events provide the best available signature of the actual outbreak distribution applicable to Wuhan via a rescaling argument. We further investigate the estimation issues caused by such a small sample in Annex A.

Misunderstanding #7:

> *'You start by estimating the risk of a Wuhan lab-induced community outbreak of a human SARS-like coronavirus to 1 in 833 years, and your conclusion is that most likely the outbreak in Wuhan is due to a lab escape. But such a chance is so remote, as a 1 in 833 years event, that it just makes no sense. The whole argument is suspect.'*

Let's first notice that the probability of a community outbreak starting in Wuhan due to a pure random zoonotic origin is actually even smaller at less than 1 every 1,000 years. So the question

being really asked is how one can intuitively reconcile the Wuhan community outbreak to such small probabilities (‘1 in 1000 years’ and ‘1 in 833 years). Given that the outbreak must be explained by either one of the two hypotheses - dismissing any conspiracy theory [5, 6] - most likely one or maybe both probabilities are too low.

Let’s then note that even supposing that a SARS-like community outbreak could happen every single year in China (instead of every 10 years), we still get a probability of less than 1 in 100 years for an outbreak in Wuhan. Said otherwise using this clearly excessive probability of 1 per year for a pure random SARS-like zoonotic community outbreak in China, we are still left with a very small and intuitively unsatisfactory probability of that community outbreak happening in Wuhan against any other place in China.

The only alternative to try to intuitively reconcile the Wuhan community outbreak to the small probabilities we used is that the ‘1 in 833 years’ lab-induced community outbreak probability is underestimated. We already noticed that that probability is conservative and we listed some of the reasons. But actually the best insight into why this probability is likely seriously underestimated may be provided by some Chinese assessments of the actual risk as detailed in the following section.

3. Evaluation of the Lab Escape risk by the Chinese authorities

A review of Chinese scientific papers and government-aligned publications shows that the relevant Chinese supervising authorities and the Chinese government itself have consistently evaluated the Lab Escape risk as all too real. Their declarations and writings are therefore consistent with the scale of the Lab Escape risk highlighted in this paper. Here is a quick review of such evaluations:

Yang Zhanqiu’s evaluation of the risk in Chinese BSL labs (16th Feb 2020):

Yang Zhanqiu, a deputy director of the pathogen biology department at Wuhan University, was recently quoted by the Global Times, a Chinese newspaper considered as strongly aligned with the government [52]. The article shows a clear understanding of the risks:

> *‘The Ministry of Science and Technology issued new rules [--] that experts said could fix chronic inadequate management issues [--]. The release of the guideline deals with chronic loopholes at laboratories [--]*
>
> *“Laboratories in China have paid insufficient attention to biological disposal”, Yang said.*
>
> *Lab trash can contain man-made viruses, bacteria or microbes with a potentially deadly impact on human beings, animals or plants.*
>
> *“Some researchers discharge laboratory materials into the sewer after experiments without a specific biological disposal mechanism”, Yang explained.*
>
> *Medical staff and experts have long been asking for better regulation and supervision of biological research institutes in China, but with mixed results.‘*

‘Notice on Strengthening the Biosafety Management of Pathogenic Microorganism Laboratories’ (9th Feb 2020)

On the 9th Feb 2020, 6 government offices (of the Ministry of Agriculture and Rural Affairs, Ministry of Education, Ministry of Science and Technology, the National Health Commission, the Customs Administration, the National Forestry and Grassland Administration) and the Chinese Academy of Sciences together issued a notice detailing new rules to strengthen the security of Chinese bio-labs [58].

That notice starts by mentioning that in recent years the safety of bio-labs has 'significantly improved' but that some 'problems and risks' still remain. It then calls for

- cooperation in the review of new, developed or expanded BSL-3 and BSL-4 labs
- increased sharing of information relative to BSL-3 and BSL-4 labs across departments
- improved regulation of the attributions of authorisations for experimental activities
- suspension of any lab activity if the lab cannot meet the approval or review criteria

It further calls for a strict supervision and enforcement of the laws and regulations, especially with regards to labs activities which have not received the relevant authorisations and stipulates that any scientific results from such irregular activities shall not be recognized (which may tentatively be interpreted as meaning that the need to publish is a common factor behind such activities).

It also reminds that only specialized institutions and laboratories designated by the Ministry of Agriculture and Rural Affairs are allowed to keep stocks of bacteria and viruses, either isolated strains or samples. It further asks for the supervising administrations to either destroy offendings stocks and samples according to the relevant regulations or to send them to a specialized institution.

If then calls for the bio-laboratories to properly implement relevant safety guidelines, covering transport, reception and use of the pathogens, putting particular emphasis on the transport and shipment of these.

The collection of pathogens is also addressed, stressing that this must be done according to relevant regulations and that the exact sources, collection samples and methods should be properly documented.

It then asks laboratories to improve the process for disposal of wastes from experimental activities (in particular as to proper sterilization), to reinforce their organization and management, to implement information and record management and develop better training and biosafety awareness.

Last, it explicitly asks all [A]BSL-3 and BSL-4 labs to proactively engage with relevant public offices and to fully accept their supervision and guidance - which may seem to suggest that a few BSL-3s may not always have been exactly cooperative in this regard.

Yuan Zhiming's evaluation of the risk in Chinese BSL-2 and BSL-3 labs (Oct 2019):

A good introduction to the very real risk of a lab related accident is provided by Yuan Zhiming - the director of the WIV (the Wuhan P4 lab) and a top CCP representative there. In October 2019, the Journal of Biosecurity and Biosafety published an article by Y. Zhiming [59] that highlighted major structural issues with Chinese labs, including lack of funding, lack of training, lack of standard operating procedures:

> *'[...] due to different investment sources, affiliations, and management systems, the implementation of these laboratories faces difficulties converging objectives and cooperation workflows. This scenario puts laboratory biosafety at risk since the implementation efficiency and timely operations are relatively compromised.*
>
> *[...] several high-level BSLs have insufficient operational funds for routine yet vital processes. Due to the limited resources, some BSL-3 laboratories run on extremely minimal operational costs or in some cases none at all.*
>
> *Currently, most laboratories lack specialized biosafety managers and engineers. In such facilities, some of the skilled staff is composed by part-time researchers. This makes it*

difficult to identify and mitigate potential safety hazards in facility and equipment operation early enough.'

Yuan Zhiming & al evaluation of the risk in Chinese BSL labs (2016):

This 2019 assessment above essentially repeats the one offered in a 2016 paper [60] co-authored by Yuan Zhiming (with an additional insight on issues at the BSL-4), thus showing perduring chronic issues:

[translation from the original document]

'China has certain problems in the construction and management of high-level biosafety laboratory systems.

At present, only one BSL-4 laboratory has been built in the country, and the management and maintenance of its key equipment and the personnel's mastery of the standardized operating procedures (SOP) of Level 4 laboratories are not mature enough.

Among the BSL-3 laboratories that have been built, the distribution of laboratories across the country is uneven, and many laboratories have low utilization rates due to insufficient construction, operation and maintenance funds.

On the whole, the problems of China's high-level biosafety laboratory system are mainly manifested in:

(1) In terms of overall layout, the industry and economic development and the needs of special fields are not fully considered. [..]

(2) In terms of funding and operating mechanism, long-term stable maintenance funding, incomplete sharing and cooperation mechanism, lack of stable operating funding, and the disconnection between construction and operation, resulting in some laboratories not completing construction or being difficult to operate normally after completion.

(3) In terms of management and support system development, the laws, regulations and standard system of high-level biosafety laboratories need to be further improved, and the construction of supporting research conditions such as information resources and experimental data is somewhat lagging behind. The confluence of technology, management and strategy research needs to be strengthened.'

Mainstream article in the China Daily mentioning the risk of working with dangerous pathogens in labs (2015):

Discussing the challenges faced by China in its biosafety laboratories was not just limited to a circle of experts. The China Daily, an English language newspaper owned by the CCP and often used as a guide to Chinese government policy, published an article in February 2015 titled '*Be ready to fight potential risks from P4 lab*' [61].

The article welcomes the opening of the first Chinese P4 lab but ends this with a clear reminder about the existing issues with management, maintenance and supervision of high biosafety level labs, with a rather dramatic illustration that would be unthinkable in the current charged context.

'But the government will also have to tighten supervision and monitoring of research on dangerous and exotic pathogens, and strengthen the management of the facilities where such research is carried out. Besides, the tools equipped to counter risks must be battle ready and under good control to ensure that they work properly in time, and not backfire and cause harm to the people.

This is very important because as a country we cannot afford another accidental leakage of pathogens like the one in 2004.' [note: meaning the 2004 SARS lab accidents in Beijing, see 53]

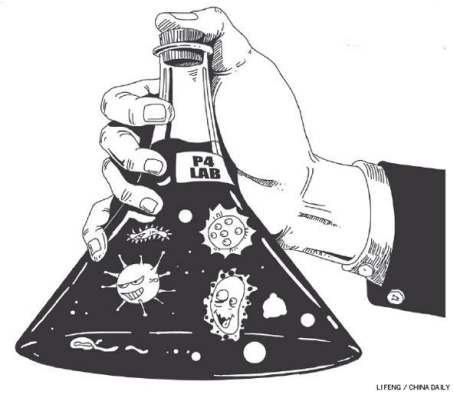


Illustration from China Daily article, Feb 2015
'Be ready to fight potential risks from P4 lab' [61]

Chinese CDC (Beijing) review of general issues with the construction and operation of BSL-3 labs in China (2014):

Part 3 of a 2014 review by the Chinese CDC of general issues with construction and operation of BSL-3s [63] offers a very pointed discussions of some structural issues:

*'1. **Failure to pass the environmental assessment**. Some laboratories were unable to pass [the environmental assessment] because they were located too close to public places and residential areas*

*2. **Insufficient construction funds and operation and maintenance funds**. [...] 43.5% of the surveyed [BSL-3] units considered insufficient construction or operation and maintenance costs as one of the main difficulties. Insufficient government investment and insufficient pre-construction research are the main reasons for this problem. There are also situations in which funds are insufficient during the construction process or the operation and maintenance funds cannot be in place after completion. [...]. All localities must adhere to the principle of adapting measures to local conditions and reasonable configuration, and not blindly build BSL-3 laboratories.*

*3. **Weak operation and maintenance capabilities.** The BSL-3 laboratory facilities and equipment are highly professional and their operation is highly risky. [...]. Among the laboratories that have been in operation, three units are operated and maintained by their own personnel, and there are only 1 to 2 maintenance personnel.*

*4. **Deviation in the principle of laboratory staffing**. [...] it should be emphasized that a high professional title and a high degree of education are not prerequisites for entering the BSL-3 laboratory. A high sense of responsibility, emphasis on biosafety, familiarity with experimental projects and personal protection operations, and regular participation in targeted training are also necessary conditions.'*

Incidentally it may be worth noting that despite these repeated acknowledgements of structural issues affecting directly laboratories safety, our count from publicly available data shows that the yearly increase in the number of new accredited lab-complexes with BSL-3s has been very stable over the last 15 years. China has effectively been building up both its labs numbers (still very low compared to the US) and its biosafety capabilities at the same time, while recognizing that it was short on both accounts.

4. Towards a rational discussion of probabilities

This paper shows that the possibility of a COVID-19 being a lab-induced pandemic cannot be discounted in the current debate.

As to the method we hope to have shown that, when exact probabilities may be much more difficult if not impossible to assess, the use of conservative probabilities may be enough to draw some insights and inform the scope of a proper investigation of the possible origins of the epidemic.

Additionally and very importantly, such a method only states initial probabilities and strongly encourages an update of these probabilities (technically a Bayesian update). It thus offers a constructive way to progress through such an investigation. One can for instance start by asking various parties to estimate some key probabilities as used here, in a way that should be consistent with their opinions as to the possible origins. One can then work on refining these probabilities over time while trying to build a consensus around them. Such an approach has the further inherent benefit of naturally leading to a risk-benefits analysis that may transcend one single lab-induced accident or random zoonotic event.

Last, we have also shown how unfortunately very common probabilistic misunderstandings may be preventing - if not forcefully shutting down - a proper consideration of the possible origins of the pandemic.

On this subject it is worth noting that complex institutional causes may also contribute to mis-estimating the risks involved. One of the most famous examples of these factors at work was captured during the investigation of the explosion of the Challenger space shuttle:

> *'Feynman was disturbed by two aspects [..]. First, NASA management assigned a probability of failure to each individual bolt, sometimes claiming a probability of 1 in 10^8, i.e. one in one hundred million. Feynman pointed out that it is impossible to calculate such a remote possibility with any scientific rigor. Secondly, Feynman was bothered not just by this sloppy science but by the fact that NASA claimed that the risk of catastrophic failure was "necessarily" 1 in 10^5. [--]*
>
> *Feynman suspected that the $1/100{,}000$ figure was wildly fantastical, and made a rough estimate that the true likelihood of shuttle disaster was closer to 1 in 100. He then decided to poll the engineers themselves, asking them to write down an anonymous estimate of the odds of shuttle explosion. Feynman found that the bulk of the engineers' estimates fell between 1 in 50 and 1 in 200. [--]*
>
> *When describing these wildly differing estimates, Feynman [..] was upset NASA presented its fantastical figures as fact to convince a member of the public, school teacher Christa McAuliffe, to join the crew. Feynman [--] felt strongly that the recruitment of laypeople required an honest portrayal of the true risk involved'* [64].

ANNEXES

A. Probability of a non-lab related community outbreak of a human SARS-like coronavirus in Wuhan

Approximation through generalization/rescaling:

The probability we are trying to ascertain is the probability of a non-lab related (1) community outbreak of a (2) human (3) SARS-like disease (4) in Wuhan. There are simply no prior examples of such an outbreak starting in Wuhan, so we need to derive an approximation of that probability through a generalization argument and then a rescaling argument, while being careful to stay on the conservative side.

Here we argue that the only one of the 4 attributes that we can reasonably relax to get more events is (4) *'in Wuhan'*. Let's consider the 4 attributes in turn, and their potential for relaxation/rescaling:

(1) **Community outbreak:** it would not make much sense to also look at individual infections or very short chains of infections without further transmission to the community, nor would it make much sense to consider chains of infections that are not even detected. Indeed the lack of community outbreak would likely point to fundamental differences in the virus capacity to infect humans and it would be very difficult to figure out how to rescale such a generalized probability on the required subset of community outbreaks. Hence we shall only consider community outbreaks (detected and reported outbreaks with consecutive human-to-human transmissions) - a category to which the Wuhan outbreak firmly belongs.

(2) **Human**: we could try to generalize to SARS-like outbreaks affecting animals and not humans (such as pig SADS-CoV). But again it would be very difficult to rescale the resulting probability as the attribute is part of the very nature of the diseases involved.

(3) **SARS-like disease**: we could try to generalize to outbreaks of diseases with symptoms that differ significantly from SARS (HKU1 for instance, with much less mortality and little impact on healthy adults), but just as with the 'human' attribute, there is no way to easily rescale as this attribute is part of the very nature of the disease involved. [See Box 4].

(4) **in Wuhan**: the geographical attribute does not deal directly with the very nature of the disease, so we can attempt a generalization/rescaling. But even so we have to be careful; for instance shall we generalize to China, Asia, only countries with known coronavirus outbreaks (such as bird-flu, MERS-CoV)? At the very least we need to consider the homogeneity of the interactions between humans and the possible hosts and make sure that we stay on the conservative side. To that effect we decided to generalize to China and rescale conservatively based on population ratios, after considering extreme scenarios (*Eany* and *Eloc*).

Confidence Interval of estimate:

When considering the whole of China we find two human SARS-Like community outbreaks separated by around 16.5 years. The first, SARS is considered purely zoonotic, the second COVID-19 may or may not be purely zoonotic. So at most we have observed 2 SARS-like purely zoonotic community outbreak events in 16.5 years. Practically this means that we are intrinsically conservative when considering that COVID-19 is purely zoonotic for the purpose of evaluating the probability of a non-lab related community outbreak of a human SARS-like coronavirus in Wuhan. We need to keep that in mind if we find that the resulting probability for Hacc is not small - because it should logically lead us to revisit that 1 in 16.5 years interval.

Mathematically, these two events separated by 16.5 years are two events of a Poisson process and what we need to estimate is the mean of that process with a confidence interval. The Maximum Likelihood Estimate (MLE) of the mean is simply the arithmetic mean observed - so 1 event every 16.5 years - while the two-sided confidence value at the level α (for instance 5%) is:

$$Y_{lower} = \frac{\chi^2_{\frac{\alpha}{2},\, 2\times n}}{2}$$

$$Y_{upper} = \frac{\chi^2_{1-\frac{\alpha}{2},\, 2\times(n+1)}}{2}$$

Where $\chi^2_{p,\,q}$ is the chi-square distribution value with lower tail area p on q degrees of freedom, n is the sample size, $\frac{\alpha}{2}$ is the per-centage in each tail and n is the number of events for the period considered.

With n = 1 (one event every 16.5 years) and α = 10% (total in the tails) we get a confidence interval of [0.05, 4.74], meaning that the actual Poisson mean could be as low as 0.05 events in 16.5 years or as high as 4.74 events in 16.5 years at that 90% level.

More practically, we shall be looking at the Poisson mean which at a certain confidence level should not generate less than the observed 1 event in 16.5 years. This is given by the left-tail confidence level: $\frac{\chi^2_{\alpha,\, 2\times n}}{2}$ instead of the two-tails one. So for instance there is no more than a 10% chance that we shall observe 1 event at max in 16.5 years (the MLE of the Poisson mean) if the real mean of the generative Poisson process is at least 3.6 events in 16.5 years. We can then use this mean of 3.6 events as a conservative estimate of the real mean at 90% level.

Box 4: Human coronavirus (HCoVs):

Name	Type	Year	Location	Emergence Date MRCA (1)	Symptoms Gravity	Inter-human R0	Pattern
HCoV-229E	alpha	1966	USA	Early 19th century	Generally mild		common, seasonal
HCoV-NL63	alpha	2004	Netherland	13th century	Generally mild		common, seasonal
HCoV-OC43	beta	1967	USA	End 19th century	Generally mild		common, seasonal
HCoV-HKU1	beta	2005	Hong Kong	unknown	Generally mild		common, unknown
SARS-CoV	beta	2003	China	2002	Serious	$2 < R_0 < 3$	Epidemic Dec 02-Jul 03. Never reemerged.
MERS-CoV	btea	2012	Saudi Arabia	2012	Serious	$R_0 < 1$	Zoonotic circulation Middle East
SARS-CoV-2	beta	2019	China	2019	Serious	$2 < R_0 < 4$ (2)	pandemic

Notes:
(1) Most Recent Common Ancestor. Traité de virologie médicale Astride Vabret et Meriadeg Ar Gouilh
(2) WHO estimate as of Jun. 2020

B. Probability of a Lab Escape (inc. via Lab-Acquired Infection)

Lab accidents, including Lab-Acquired Infections, are much more common that is often appreciated [65, 66, 67]. The literature includes some estimates for the risk of Lab Escapes based on detailed records of such accidents and an analysis of the various failure points.

Conservative: 0.2% per year for a BSL-3 based on US CDC Data:

In this paper, we use the conservative probability of 0.2% chance per year for a lab actively working on a SARS-like coronavirus.

This probability was presented in a paper [43] by Lynn C. Klotz (The Center for Arms Control and Non-Proliferation, Washington DC), and Edward J. Sylvester and draws on earlier work by Kloz, based on lab incident data from the US CDC.

The authors further note that:

> *'Recent self-reported mistakes at the [US] CDC, involving a particularly deadly strain of anthrax removed from BSL-3 containment and H5N1 Asian bird flu released from the CDC laboratories altogether, lend support to our concern that the probability of escape may be much greater than the 0.2% per lab per year from just LAIs ['lab-acquired infection'].'*

The 'much greater' in the above quote makes sense. Indeed not only have there been bird flu lab escapes in the US, but in just 2 years (2003-04) there were a total of 6 Lab-Acquired Infections (some with further community transmission), including 4 in China, for one purely zoonotic outbreak (the 2003 outbreak) [Annex C].

To be perfectly exhaustive, we must note that this probability is calibrated on laboratories in the US, not China. We therefore assume that the risk for Chinese labs is not lower than the risk in US labs - an assumption which seems sustained by our review of some of the relevant Chinese literature as per point 3 of the Discussion above.

Worst case: 2.4% per year based on a Department of Homeland Security risk assessment:

In the same paper [43] Klotz & Sylvester further note:

> *'We noted above that the probability p1 = **0.2%** is conservative, estimated from the CDC data alone. The first Department of Homeland Security [DHS] risk assessment for the planned National Bio- and Agro-Defense Facility (NBAF) in Manhattan, Kansas estimated a significantly higher escape risk, over 70% likelihood for the 50-year life of the facility [68], which works out to be a basic probability of escape, p1 = **2.4% per year**. The National Research Council [NRC] overseeing the risk assessment remarked*
>
> > *"The […] estimates indicate that the probability of an infection resulting from a laboratory release of FMDv from the NBAF in Manhattan, Kansas approaches 70% over 50 years with an economic impact of $9–50 billion. The committee finds that the risks and costs could well be significantly higher than that…"*
>
> *While the DHS subsequently lowered the escape risk to **0.11%** for the 50-year lifetime, the NRC committee was highly critical of the new calculations: "The committee finds that the extremely low probabilities of release are based on overly optimistic and unsupported estimates of human error rates, underestimates of infectious material available for release, and inappropriate treatment of dependencies, uncertainties, and sensitivities in calculating release probabilities.'*

Incidentally it is interesting to note how the DHS lowered its risk assessment by a factor of about 630 (from an initial 70% over 50 years to a final 0.11% over 50 years), thus moving from a major risk to a very small risk.

C. Probability of an outbreak given a Lab Escape

We shall first note that the probability of a pandemic given a lab escape shall be dependent on:

- **Characteristics of the infectious disease**

  The type of coronavirus studies conducted in Wuhan, with a focus on virus candidates with an affinity for human transmissions, reinforces the risk of outbreak as it involves highly contagious diseases (high R_0).

- **Characteristics of the accident**

  The possibility of a lab escape due to bad disposal of laboratory wastes can increase the risk of an outbreak, as such escape may go undetected for potentially weeks. This is a risk for which Chinese authorities have recently shown great awareness [42].

We then refer to Merler *et al* [39], who used an agent-based model that specifically considers laboratory workers and their contacts in microsimulations of the epidemic onset due to an urban lab escape (Rotterdam). Part of their results is the tabulation of the probability of outbreak under an uncontrolled scenario (no intervention), and a reference scenario with countermeasures (closure of lab, quarantine of lab workers households, etc).

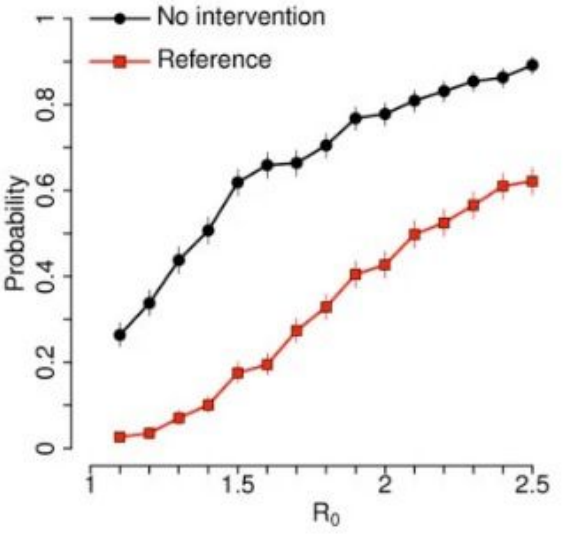


Figure reproduced from Merler *et al* [39].
Probability of outbreak for different values of R_0 by assuming no intervention scenario (uncontrolled epidemics) and reference scenario (countermeasures)

Clearly many factors may affect such a simulation, some which may or may not apply to the case at hand, behind a simple urban / non-urban distinction. To try to stay on the conservative side we therefore use a probability of outbreak given lab escape for an initial R_0 of 1.75 and not the common estimate of around 2.2 for COVID-19. This gives us a probability of outbreak (despite countermeasures) of around 25%.

We shall note that this probability is actually based on simulations using an urban lab in Rotterdam, a fairly small city of 0.7mln and a density of around 3,100/km^2. Merler *et al* [39] further give breakout

probabilities for various European of different sizes and density (but none even approximately matching Wuhan over both population (10 mln) and density (1,500 / km^2). However their simulations show little variability across the cities considered for a R_0 of 2.2. This result seems to be corroborated by observations which emphasize instead the likely impact of other factors (such as quality of health care systems and adherence to countainment guidelines) [69, 70].

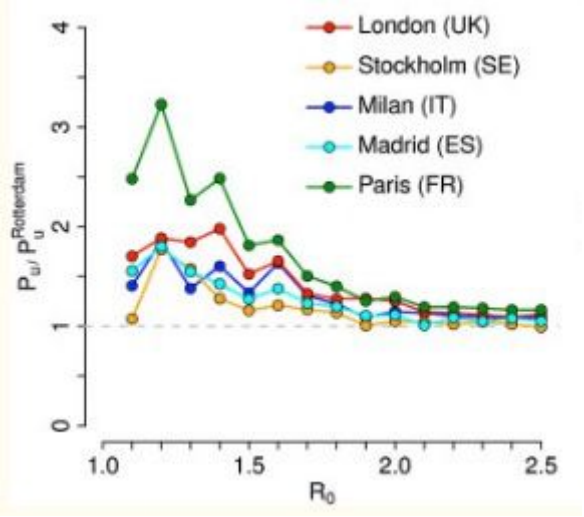
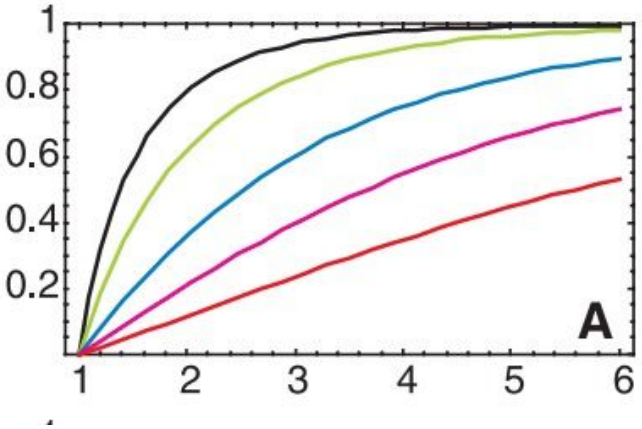


Figure reproduced from Merler *et al* [39].

Ratio between probability of outbreak in different urban areas and probability of outbreak in Rotterdam for different values of R_0 for reference scenario of countermeasures.

Klotz [71] using an approach more limited in scope found results of the same order. Incidentally both Klotz and Merler *et al* emphasize the non-negligible probability of non detection of the lab escape until too late to prevent a pandemic.

As part of a detailed early evaluation of transmission dynamic of SARS, Lipsitch *et al* [49] used Branching Theory to derive the probability of an outbreak of SARS in a given population based on a variety of scenarios, including a single initial infectious case introduced in that population (A below) based on a mean R_0 and a variance-to-mean ratio for R_0 ranging from 1 (black line) to 20 (red line) (with 2/green, 4/blue and 10/magenta). That variance-to-mean ratio (which is unfortunately very difficult to estimate from typical epidemiological data) can be thought of as the variance in the number of secondary cases at the beginning of the transmission chain - the higher the variance the more chances that the transmission is stopped early by a low draw for R_0. Taking a mean R_0 of 2.2 and the high variance-to-mean ratio of 10, this effectively returns an outbreak probability of around 25%, once again compatible with the 25% we used.



Graph from Lipsich *et al* [49]

The probability of an outbreak of SARS in a susceptible population for
a range of values of R, approximated by the probability of non-extinction of a branching process

D. Lab safety considerations

Relevant Biosafety Levels:

Cellular research with live SARS-like coronavirus cultures is normally done in BSL-3 conditions. Animal experiments involving SARS-like live strains are normally done in ASBL-3 conditions.

Only [A]BSL-3 and [A]BSL-4 are considered High Level biosafety labs. BSL-2 labs are normally supposed to handle only clinical samples of coronaviruses but have nevertheless been known to be handling experiments with live SARS-like coronavirus cultures too [41].

Pathogens		Handling of biohazard materials				
Name	Risk group	Culture	Animal trials	clinical sample	Inactived samples	Non-infectious samples
Mouse leukemia virus	1	BSL-1	ABSL-1	BSL-1	BSL-1	BSL-1
Hepatitis B virus	2	BSL-2	ABSL-2	BSL-2	BSL-1	BSL-1
High pathogenic avian influenza virus	3	BSL-3	ABSL-3	BSL-2	BSL-1	BSL-1
Ebola virus	4	BSL-4	ABSL-4	BSL-3	BSL-2	BSL-1

Table 2 - reproduced from Yiping Zhu, Chinese Academy of Sciences [72]

Table 1: Recommended Biosafety Levels for Laboratories Working with Human Pathogens

Biosafety level	Agent	Practices	Primary barriers and safety equipment	Facilities (secondary barriers)
1	Not known to consistently cause diseases in healthy adults	Standard microbiological practices	None required	Laboratory bench and sink required
2	• Agents associated with human disease • Routes of transmission include percutaneous injury, ingestion, and mucous membrane exposure	BSL-1 practice plus • limited access • biohazard warning signs • "sharps" precaution • biosafety manual defining any needed waste decontamination or medical surveillance policies	Primary barriers: • class I or II biosafety cabinets (BSC) or other physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials Personal protective equipment (PPE): • laboratory coats, gloves, and face protection as needed	BSL-1 plus • autoclave* available
3	• Indigenous or exotic agents with potential for aerosol transmission	BSL-2 practice plus • controlled access • decontamination of all waste • decontamination of laboratory clothing before laundering • baseline serum	Primary barriers: • class I or II BSCs or other physical containment devices used for all open manipulation of agents PPE: • protective laboratory clothing, gloves, and respiratory protection as needed	BSL-2 plus • physical separation from access corridors • self-closing, double-door access • exhaust air not recirculated • negative airflow into laboratory
4	• Dangerous exotic agents that pose a high risk of life-threatening disease • Aerosol-transmitted laboratory infections have occurred; or related agents with unknown risk of transmission	BSL-3 practices plus • clothing change before entering • shower on exit • all material decontaminated on exit from facility	Primary barriers: • all procedures conducted in class III BSCs or class I or II BSCs in combination with full-body, air-supplied positive pressure personnel unit	BSL-3 plus • separate building or isolated zone • dedicated supply and exhaust, vacuum, and decontamination systems • other requirements outlined in the BMBL text

Source: BMBL, 5th edition.

*An autoclave is a device to sterilize equipment and supplies by subjecting them to high-pressure steam at 121° C or higher.

Table reproduced from US GAO Report

'High-Containment Laboratories - National Strategy for Oversight Is Needed' [73]

The importance of processes:

While facilities and physical equipment are very important for biosafety, they are actually not in any way a guarantee of biosafety. Most often Lab-Acquired Infections (LAI) and Lab Escapes are due to faulty behaviours or processes, either exclusively or as a key compounding factor. So while good facilities and equipment (with a proper maintenance budget) are important, only good processes and their correct implementation can truly insure biosafety in a lab.

> *'Laboratory safety is 90% personal attitudes and individual actions, 10% facilities and equipment'. Dr Yiping Zhu* [72]

Unfortunately following good procedures requires experienced personnel, which can be a problem when any country quickly starts operating many BSL-3 labs [74]. It is also a problem when part of the personnel is just part-time or students with a limited training in biosafety [59, 60, 52, 63, 42, 75].

To be fair, let's note that this is not a problem peculiar to China. Indeed the US itself went through a similar burst of construction of many new BSL-3 and BSL-4s following the anthrax attacks of 2001. This resulted in the US Government Accountability Office (GAO) issuing a report to Congress recommending a strategic evaluation of high containment laboratories based on cost-benefits and a better oversight [76, 77, 73].

Previous SARS lab accidents:

A total 6 cases of Lab-Acquired Infection with SARS were recorded in 2003-04, in Taipei, Singapore and Beijing [38]. The Taiwan accident was at a BSL-4 lab [78] while the Singapore case involves a student working within a BSL-3 who was only given 20 minutes of training and was in street-clothes.

Martin Furmanski [79] provides a more detailed review of lab accidents. Amongst others, the author mentions that:

> *'[...] there have been six separate [SARS] "escapes" from virology labs studying it: one each in Singapore and Taiwan, and in four distinct events at the same laboratory in Beijing.'*

and then gives a detailed account of the four Chinese labs SARS escapes:

> *'On April 22, 2004 China reported a suspected case of SARS in a 20-year-old nurse who fell ill April 5 in Beijing. The next day it reported she had nursed a 26-year old female laboratory researcher who had fallen ill on March the 25th. Still ill, the researcher had traveled by train to her home in Anhui province where she was nursed by her mother, a physician, who fell ill on April 8 and died April 19. The researcher had worked at the Chinese National Institute of Virology (NIV) in Beijing, which is part of China's Center for Disease Control (CDC), and which was a major center of SARS research.*
>
> *The investigation at NIV also uncovered an unrelated laboratory infection in a 31-year old male laboratory researcher at the NIV who fell ill on 17 April. The entire NIV institute was closed and all of its 200 employees placed in quarantine in a hotel. Subsequent investigation confirmed these first three cases as SARS, and eventually identified a total of nine cases, in three generations, including health care workers and their family contacts. Neither of the two primary patients had worked with live SARS virus, and WHO investigators had "serious concerns" regarding biosafety procedures at the NIV.*
>
> *[--] A joint China CDC and WHO investigation found many shortcomings in biosecurity at the NIV, and traced the specific cause of the outbreak to an inadequately inactivated preparation of SARS virus that was used in general (not biosecure) laboratory areas in the NIV, including the one in which the two primary cases worked. It had not been tested to confirm its safety after inactivation, as it should have been. The WHO also found more general shortcomings in the handling of live SARS virus and a lack of surveillance of laboratory personnel for laboratory infections.*
>
> *Li Liming, director of the China CDC and his deputy directory, the director of the NIV and his deputy director, and the director of the division where the two index cases worked were removed from their positions and found guilty of negligence in overseeing safety at the institution. The Chinese government also decided to move the China CDC campus from its position in a residential neighborhood to an area "more remote from downtown," and to allocate funds for more advanced laboratory equipment and infrastructure.'*

Peng, Bilal and Iqbal [80] recently put together a detailed summary of LAIs in Asia Pacific. We reproduce their table below while noting that the 2004 SARS infection of a Taipei lab worker actually happened at a BSL-4 lab of the National Defense University [78].

Year	Country	Microorganism	Affected Worker	Laboratory Type/Level
2016	Taiwan	*Ralstonia pickettii*	-	-
2014	South Korea	Dengue	Laboratory staff	Research/BSL2
2011	Australia	Dengue	Scientist	Research/BSL2
2010	India	Buffalopox virus (BPXV) (Z)	Researcher	-
2009	Malaysia	*Brucella melitensis*	Laboratory staff	Clinical
2006	Taiwan	*Shigella* spp. (Z)	Graduate student	Research
2006	PR China	Seoul virus and hantavirus (Z)	8 postgraduate students	Research
2004	Taiwan	Dengue type 1	Graduate student	Research
2004	Taiwan	SARS-CoV (Z)	Researcher	Research
2004	PR China	SARS-CoV (Z)	8 human cases, 1 died	Research
2003	Singapore	SARS-CoV (Z)	Graduate student	Research/BSL3
2002	Taiwan	*Arthroderma benhamiae* (Z)	Scientist	Research
2002	Australia	*S. aureus*, MRSA, EMRSA (Z)	Laboratory staff	Clinical
2001	Japan	*Arthroderma benhamiae* (Z)	Researcher	Research
2000	South Korea	*Orientia tsutsugamushi* (Z)	Worker	-
1999	Taiwan	*Vibrio parahaemolyticus* (Z)	Laboratory staff	-
1998	Japan	*Helicobacter pylori* (Z)	Bacteriologist	-
1996–2000	Australia	*Brucella suis* (Z)	Various	Clinical
1996	Malaysia	*Salmonella typhi*	Laboratory staff	-
1992	Australia	*Pseudomonas pseudomallei* (Z)	3 Laboratory staff	Diagnostic
1990	South Korea	*Rickettsia typhi* (Z)	Laboratory staff	Clinical
1990	India	*Mycobacterium leprae* (Z)	Worker	Clinical
1989	South Korea	*Rickettsia typhi* (Z)	Laboratory staff	Research
1987	Australia	Newcastle disease virus (Z)	Laboratory staff	Research/BSL3
1986	Australia	*Brucella melitensis* (Z)	Researcher	Research
1985	Japan	*Mycobacterium tuberculosis* (Z)	Pathologist	Research
1982	Australia	*Shigella flexneri* (Z)	Laboratory staff	Clinical

Table 3 - reproduced from Peng, Bilal and Iqbal [80]
Data collected from the American Biological Safety Association [38]

E. Lab Counts

Count of BSL-3 lab-complexes in Wuhan working on SARS-like coronaviruses:

We counted 5 Wuhan BSL-3/ABSL-3 lab-complexes working on coronavirus:

Very active:

- Wuhan Institute of Virology, Xiao Hong Shan site
- Wuhan University - inc. the Center for Animal Experiment
- Huazhong Agricultural University (State Key Laboratory of Agricultural Microbiology)

Level of activity not clear:

- Wuhan National Biosafety Laboratory, Chinese Academy of Sciences, Wuhan Institute of Virology, Zhengdian site
- Hubei CDC

Each lab-complex has typically more than one individual lab involved. For instance the BSL-3 at the Zhengdian site (also called the NBL-3) has 3 cellular biosafety labs (i.e. BSL-3s), 1 small-sized animal lab and 1 medium-sized animal lab, hence 5 individual P3 labs including 2 ABSL-3. [11].

Map showing the main Biosafety Labs in central Wuhan

Count of Chinese biosafety labs:

As background information, we also tried to get a good count of High Biosafety Level labs in China. This proved rather difficult as there is no official count and the few numbers published can be rather contradictory.

Note that there may be two ways of counting the labs:

- One can count **individual labs**. For instance the P3 of the Wuhan National Biosafety Laboratory at the Zhengdian site (NBL-3) has 5 BSL-3 individual labs [11].
- One can count **lab-complexes** in the same building. In this case the 5 individual BSL-3 labs at the NBL-3 should be counted as one.

One reason for doing a lab-complexes count may be that all the BSL labs of the same level in the same premises likely share some of the same physical infrastructure, especially as to waste disposals. However this way of counting may result in an understatement of the risk, as the risk of Laboratory Acquired Infection should roughly be proportional to the number of researchers in these labs, hence roughly to the number of individual BSL-3 labs.

Some institutions do not indicate the number of individual-labs in their lab-complexes. In this case we counted only one individual lab for such a lab-complex. The true count of individual labs (for the lab complexes that we identified) is therefore likely higher than the one we give,

We also wish that available LAI risk estimates in the literature were a bit more precise on this point. In this paper we use the lab-complexes count which is a conservative way of interpreting the available LAI risk estimates.

BSL-3:

- We were able to determine that at least 112 individual [A]BSL-3 were operating in China as of August 2020, across 62 lab-complexes (excluding mobile laboratories).
- An article in the Southern Metropolis Daily (南方都市报) [81] mentions that:

  > *'According to Ankang, a representative of the National People's Congress and chairman of Hualan Bio, there are currently 89 domestic biosafety level 3 (BSL-3) laboratories (hereinafter referred to as P3), of which 55 are cell laboratories.'*
  >
  > *According to incomplete statistics from the "Caijing" magazine, there are currently 68 P3 laboratories in mainland China, of which 55 are cell research laboratories (BSL-3) and 13 are infectious animal laboratories (ABSL-3).'*
  >
  > *'Bai Chunli, Secretary of the Party Leadership Group and Dean of the Chinese Academy of Sciences, published a signed article "Providing Strong Scientific and Technological Support for Comprehensively Improving the National Biosafety Governance Capability" in the "Flag" magazine in April 2020. China revealed that there are currently 81 P3 laboratories in China that have passed the review of the Ministry of Science and Technology, and 2 P4 laboratories are officially in operation.'*
- The 'National Biosafety Systems' review [82] by the University of Pittsburgh Medical Center (UPMC) for Health Security (2016) mentions 63 accredited BSL-3/ABSL-3 labs in China.
- Yuan Zhiming [59] gives a detailed count as of end 2013:

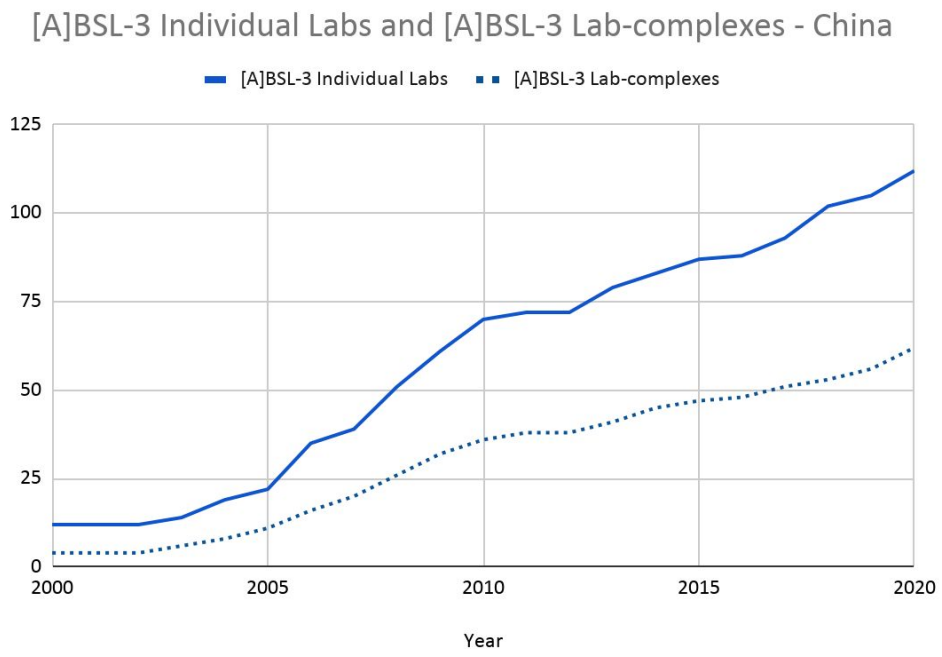
  > *'As of December 31st 2013, 53 BSLs, including 42 BSL-3s, had been fully accredited in China and more laboratories have completed the accreditation in recent years.*
  >
  > *In addition, more than 1000 BSL-2 labs are currently being operated in universities, research institutions, hospitals and R&D entrepreneurship centers.*
  >
  > *In addition, four mobile BSL-3 laboratories were imported from Labover (Montpellier, France) and distributed to institutes in Beijing, Shanghai, and Guangdong for the nation-wide surveillance of pathogens and the emergency response of post-disaster and global public health events. In addition, a self-designed and self-constructed mobile BSL-3 was composed of two 9125 mm containers and met the biosafety requirements for pathogen diagnosis.'*

  Note: the text is not entirely clear: In *'53 BSLs including 42 BSL-3s'*, the 53 BSLs must mean 53 [A]BSL-3+, so most likely the author means 42 BSL-3 and 11 ABSL-3.
- At least 30 [A]BSL-3 laboratories built and more 10 planned, based on respondents to a Nov 2013 survey [63].
- 'In addition, as of August 31, 2013, there were 42 BSL-3 laboratories in China', as per 2016 paper co-authored by Yuan Zhiming [60].
- South China's Guangdong Province is gearing up to plan and construct 25 to 30 P3 laboratories [by 2025] and at least one P4 laboratory within five years [83].

- The mainstream Chinese press seems to be seriously underreporting the number of BSL-3 labs. See for instance a reference to *'more than 20 BSL-3'* as of May 2020 in the Global Times [84].

Date	2013-08	2013-11	2013-12	2016-?	2020-08	2020-08
Count	42 BSL-3	from survey: 30 built 10 planned	42 BSL-3 11 ABSL-3?	63 [A]BSL-3	89 [A]BSL3 with 55 BSL-3, 20 more under construction	at least 112 [A]BSL-3, with 84 BSL-3, across 62 lab complexes
Lab-complex or individual lab	Not clear	Not clear	Not clear	Not clear	Likely individual	Individual when possible
Source	60	63	59	82	81	Authors

Summary of [A]BSL-3 counts



[A]BSL-3 Lab-count, using publicly available data [authors]

It is important to put these numbers into their proper context. The US has about 1,500 [A]BSL3 labs, so a much higher number (see for instance 73, page 25, for a similar graph for the US as of 2008). What matters here is not necessarily the number of [A]BSL-3 labs itself but the adequacy between the number, the available number of experienced workers, the proper implementation of biosafety processes (including working at the right BSL level) and the proper maintenance of these labs - all of which are potential risk factors if deficient - as seen in Annex D above.

BSL-4s:

While this paper does not include BSL-4s in the probabilities, we shall still give a count for reference. We counted two active BSL-4s from available public data: the Wuhan National BSL-4 and the Harbin BSL-4 [85, 86]. Additionally the National Development and Reform Commission of People's Republic of China set the goal of building 5 to 7 BSL-4s by 2025, as part of the 'High-level biosafety laboratory system construction plan for 2016-2025' [87, 62].

F. Equivalent Results via Bayes' Theorem

The above probabilistic treatment is a simple application of Bayes Theorem, albeit with a more intuitive presentation. For reference here we derive the same result using the strict formality of Bayes Theorem:

Noting WO for 'community outbreak in Wuhan', we have:

$$P(Eacc \cap WO) = P(WO \mid Eacc) \times P(Eacc) = P(Eacc \mid WO) \times P(WO)$$

$$P(Eacc \mid WO) = \frac{P(WO \mid Eacc) \times P(Eacc)}{P(WO)}$$

$$P(Eacc \mid WO) = \frac{P(WO \mid Eacc) \times P(Eacc)}{(P(WO \mid Eacc) \times P(Eacc) + P(WO \mid Erand) \times P(Erand))}$$

In the Reference scenario:

- $P(Eacc)$ = *0.6% per year for 3-BSL3 labs*
- $P(WO \mid Eacc)$ = *20%*
- $P(Erand)$ = *1 in 10 year (for China)*
- $P(WO \mid Erand)$ < *1%*

Hence in the Reference scenario:

$$P(Eacc \mid WO) > 20\% \times 0.6\% / (20\% \times 0.6\% + 1\% \times 0.1)$$

$$P(Eacc \mid WO) > 54\%$$

And conversely $P(Erand \mid WO) < 46\%$.

G. Notes on some key terms

On biosafety levels:

- **BSL:** Biosafety Level
- **ABSL:** Animal Biosafety Level
- **P3 lab:** used to mean a level 3 lab, either BSL-3 or ABSL-3. We instead use **[A]BSL3** in this paper.
- **Cell lab**: abbreviation for cellular research lab (with a BSL level), by opposition to animal research (with an ABSL level)

On viruses and diseases:

- **SARS**: Severe Acute Respiratory Syndrome - a class of infectious disease
- **SARS-CoV:** Severe Acute Respiratory Syndrome Coronavirus, official name given to a coronavirus that caused the SARS epidemic of 2002, also sometimes called SARS-CoV-1
- **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2, official name given to the novel coronavirus that caused the COVID-19 pandemic with initial outbreak in Wuhan.

- **COVID-19:** Infectious disease caused by SARS-CoV-2

From outbreak to pandemic:

- **Outbreak:** An outbreak is an initial apparition of cases of a certain disease (potentially new) within a defined period of time, place and population. An outbreak may be detected or not.
- **Community Outbreak:** A community outbreak is a detected outbreak with multiple levels of human-to-human infections in the community. A community outbreak may lead to an epidemic or may die naturally or after countermeasures.
- **Epidemic:** An epidemic is a rapid multiplication of new outbreaks over a larger geographic area and larger population. An epidemic may lead to a pandemic.
- **Pandemic:** A pandemic is an epidemic that is largely out of control and spreading to multiple countries. A pandemic starts in new countries typically through new community outbreaks.

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