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The False Promise of Herd Immunity: Herd Immunity Might Not Protect Against Lab-Enhanced 2009 H1N1 Pandemic Influenza Viruses

Summary and Conclusions

When epidemics and pandemics end, a key reason is that herd immunity prevents further infection in the population. The immune population contributing to herd immunity is comprised of those who have survived the infection and those who have been vaccinated. Vaccination is not a major contributor to herd immunity in poor nations, as most people are not vaccinated.

The 2009 influenza pandemic (pdm09 H1N1) infected 20-27% of the world's population¹ before the pandemic ended. Pre-existing herd immunity to this virus and subsequent vaccination using derivatives of this strain may not provide protection against new infections from an accidental release into the community of a lab-enhanced more virulent strain of pdm09 H1N1. If enhanced virulence is accompanied by enhanced airborne or contact transmission, then the basic reproductive number, R_0 , would increase, and the number of people infected would then increase until the new herd-immunity threshold is reached. This is the key observation of the simple analysis here.

There are many published studies creating pdm09 H1N1 virus strains with enhanced virulence and with circumstantial evidence for enhanced airborne or contact transmission (see Table 1). A release from a laboratory of such an enhanced strain could lead to nearly a billion new infections world-wide with potentially higher case-fatality rates than the 2009 pandemic since the new strains are more virulent. A potential billion new infections is a highly worrisome, big number and should be a concern to all of us.

Adding significantly to our concern, some of this research was carried out at low BSL2 containment, where the probability of a laboratory release is likely much greater than BSL3. Apparently, BSL2 was deemed sufficient because of presumed herd immunity acquired from the 2009 pandemic. Do not fall for the false promise of herd immunity.

There is considerable variation in the basic reproductive numbers for the 2009 pandemic and there were many other variables such as population and H1N1 strain heterogeneity, so an accurate quantitative analysis is not possible. Consequently, the analysis here should be viewed only as a means to alert us to concerns over the pandemic risk of seasonal or pandemic influenza virus research where a lab-created

increase in R_0 may occur shifting the herd-immunity threshold even though the surface hemagglutinin protein has not changed.

Herd-immunity threshold theory and reproductive numbers

The reproductive number, R_0 , is the average number of people infected by a single-infected-person. The zero subscript indicates that this is the reproductive number at the beginning of a new epidemic, that is, the infection- and vaccination-naïve reproductive number. It is called the basic reproductive number.

Reproductive number decreases as the epidemic grows. This decreasing reproductive number is called the effective reproductive number, R_E . It decreases because an infected person encounters fewer susceptible people to infect as some of the people encountered will be immune from having already been infected and survived or have been vaccinated.

As the fraction of immune people in the population, i , increases, the effective reproductive number is given by

$$R_E = (1-i) R_0 \quad (1)$$

From equation (1) when $i=0$ and $s=1$, $R_E = R_0$, where s is the susceptible fraction of the population. (For this simple two-state representation, $s+i=1$.) Equation (1) also has the property that R_E decreases as i increases in a way that makes sense; that is, it states that an infected individual can only infect encountered susceptible people by subtracting out from R_0 the encountered immune people.

R_E eventually falls to $R_E < 1$, where the infection will soon end because each infected individual can then infect less than one person on average², so the epidemic grinds to a halt in a short time³. When $R_E > 1$, the number immune will continue to increase until $R_E = 1$, the so-called “herd-immunity threshold.” Below the threshold, the fraction of immune persons in the population will soon not increase as the virus soon disappears despite the fact that there are still susceptible people in the population.

The fraction immune in the population at the threshold is denoted by the letter H .

Setting $R_E = 1$ and $i = H$, equation (1) becomes

$$1 = (1-H) R_0$$

which when solved for H yields

$$H = 1 - (1/R_0) \quad (2)$$

This is the literature equation⁴ relating herd-immunity to basic reproductive number.

A key observation from equation (2) is that H increases as R_0 increases.

The post-pandemic situation for pdm09 H1N1.

Since the 2009 H1N1 pandemic has long passed, the relevant fraction of the population immune today, PI, would be those immune after the 2009 pandemic. In developed nations, $PI=H+V$, where V is the fraction effectively vaccinated. For poor nations, where there is little to no vaccination, $PI=H$.

Reproductive numbers vary from less than 1 to over 3 for seasonal and pandemic influenza⁵. For the pdm09 H1N1 pandemic virus, the median reproductive number was 1.46 with a range 1.30–1.70.⁶ (See caption to Table 4 in Biggerstaff, *et al.*). From equation (2) for $R_0 = 1.46$, the threshold to herd immunity, H, is reached when 32% of the population is immune.

Now, taking into account vaccinations, about 27% of the U.S. population was vaccinated against the pdm09 H1N1 virus⁷, a percentage likely similar for all developed nations. However, vaccinations are not always effective at protecting against infection. For the pdm09 H1N1 virus, vaccine effectiveness varied depending on vaccine type and the sub-population vaccinated. The overall effectiveness of the pandemic vaccines was 56%.⁸

Thus, the percentage of the population immune post-pandemic is $PI=0.32+(0.27 \times 0.56)=0.47$ or 47%. This percentage, of course, assumes that the R_0 value is accurate and that the population is homogeneous.

There is considerable variability in pdm09 H1N1 basic and effective reproductive numbers as seen in Table 4 of Biggerstaff, *et al.* This is the main reason an accurate quantitative analysis is not possible. Consequently, the following analysis should be viewed only as a means to alert us to concerns over the pandemic risk of this research.

Furthermore, in Biggerstaff's Table 4 the median basic reproductive number, R_0 , is less than the median effective reproductive number, R_E , the opposite from what is expected.⁹ This could be due to issues in data collection and analysis.

Literature evidence for enhanced virulence and transmissibility of lab-created pdm09 H1N1

There are many published research studies creating in the lab pdm09 H1N1 strains with enhanced virulence. If enhanced virulence is accompanied by enhanced airborne or contact transmission, then R_0 would increase, and infection would increase in the population until the new larger herd-immunity threshold is reached (equation 2).

Using the single search term "2009 H1N1 pandemic influenza mutagenesis virulence," a Pub Med search identified fifteen publications of lab-created pdm09 H1N1 virus strains with enhanced virulence. Table 1 lists publication titles, biosafety level, countries creating and conducting the research, along with an assessment of whether the lab-enhanced virulent strains are likely accompanied by increased R_0 from increased airborne or contact transmission.

Tracking Number	Article Title	BSL Level	Countries of Research	Increased Airborne or contact transmission?
1	A PB1 T296R substitution enhance polymerase activity and confer a virulent phenotype to a 2009 pandemic H1N1 influenza virus in mice	BSL3	China	Likely, lung cells infected
2	Impact of the H275Y and I223V Mutations in the Neuraminidase of the 2009 Pandemic Influenza Virus In Vitro and Evaluating Experimental Reproducibility	unknown, (BSL2?)	Canada	Possible, study on Madin-Darby canine kidney (MDCK) cells only, no lung cell or animal experiments
3	The contribution of PA-X to the virulence of pandemic 2009 H1N1 and highly pathogenic H5N1 avian influenza viruses	BSL3	China, UK	Likely, viral replication in A549 lung cells increased
4	PB2-588I enhances 2009 H1N1 pandemic influenza virus virulence by increasing viral replication and exacerbating PB2 inhibition of beta interferon expression	unknown, (BSL2?)	China	Likely, Virus titer in lungs of mice was increased
5	Asparagine substitution at PB2 residue 701 enhances the replication, pathogenicity, and transmission of the 2009 pandemic H1N1 influenza A virus	BSL2	US	Yes, but only 3 ferrets used in WT experiments and 3 ferrets in mutant pdm09 H1N1 experiments
6	Substitutions T200A and E227A in the hemagglutinin of pandemic 2009 influenza A virus increase lethality but decrease transmission	unknown, (BSL2?)	US, Netherlands	No, ferret transmission experiments were performed
7	Mutations in polymerase genes enhanced the virulence of 2009 pandemic H1N1 influenza virus in mice	unknown, (BSL2?)	China	Likely, virus titer in lungs of mice was increased
8	Impact of mutations at residue I223 of the neuraminidase protein on the resistance profile, replication level, and virulence of the 2009 pandemic influenza virus	unknown, (BSL2?)	Canada, UK	Unlikely, found no significant differences between WT and mutants
9	Synergistic adaptive mutations in the hemagglutinin and polymerase acidic protein lead to increased virulence of pandemic 2009 H1N1 influenza A virus in mice	unknown, (BSL2?)	Germany, US	Likely, increased virus titer observed in human lung epithelial cell line (A549)
10	The 2009 pandemic H1N1 D222G hemagglutinin mutation alters receptor specificity and increases virulence in mice but not in ferrets	unknown, (BSL2?)	Canada	Likely, contact transmissibility measured but levels compared to WT may be the same. Higher lung viral titers observed.
11	PA residues in the 2009 H1N1 pandemic influenza virus enhance avian influenza virus polymerase activity in mammalian cells	unknown, (BSL2?)	US	Possible, virus containing the 851 mutation grew faster in human A549 cells
12	Impact of amino acid mutations in PB2, PB1-F2, and NS1 on the replication and pathogenicity of pandemic (H1N1) 2009 influenza viruses	unknown, (BSL2?)	US, Japan	Unlikely, virus titers in respiratory organs were comparable to those of the wild-type virus
13	Virulence-associated substitution D222G in the hemagglutinin of 2009 pandemic influenza A(H1N1) virus affects receptor binding	unknown, (BSL2?)	Netherlands, US, UK	Unlikely, no enhanced transmissibility from the lab-created mutants compared to WT
14	D225G mutation in hemagglutinin of pandemic influenza H1N1 (2009) virus enhances virulence in mice	BSL3	China	Likely, higher viral titers in lung homogenates. No transmission experiments performed
15	Introduction of virulence markers in PB2 of pandemic swine-origin influenza virus does not result in enhanced virulence or transmission	BSL3+	Netherlands, US,	Unlikely, the impact of key known virulence markers in PB2 in the context of current S-OIVs was surprisingly small
16	Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets	BSL3+	US, Japan	Possible, droplet transmission with H5 in (A/California/04/2009, CA04) background, but might not be more transmissible or virulent than WT

Table 1. Titles of publications of lab-enhanced pdm09 H1N1 strains with increased virulence, along with biosafety level and location of the research, and an assessment of whether the research produced increased airborne or contact transmission strains. The publication No. 16, was referred by Dr. Simon Wain-Hobson. When biosafety level is reported as “unknown,” it usually means that the research was carried out at BSL2. Publication titles may be used to download the publications.

Two interesting observations from Table 1:

- 11 of the 16 studies were likely carried out at low BSL2 containment.
- Increased airborne or contact transmission is reported as “yes” or “likely” in 8 of the 16 studies and “possible” in 3 of the 16 studies.

From the publications, the circumstantial evidence for a likely increase in airborne or contact transmission is increased viral titers in lung-derived cells *in vitro* or in lung cells in ferrets or mice. Increased viral titers and virus shedding from lungs and the upper respiratory tract could increase

transmission. Unfortunately, this circumstantial evidence supporting increased transmission cannot provide R_0 values, as R_0 cannot be determined in a closed laboratory setting with only a few animals.

Release into the community from a BSL2 lab is much more likely than from a BSL3 lab, as the biosafety procedures are far less stringent than BSL3. Even if all lab personnel were vaccinated, which is likely the case, release from a BSL2 lab could occur if vaccination was not effective, or when virus is transported out of the lab into the community on the bodies and clothing of lab personnel. Ineffective vaccination is an Achilles heel as far as lab-releases are concerned.

Calculation of potential new infections

Increased viral titers observed in lung cells *in vitro* and in lungs of mice and ferrets could imply a significant increase in R_0 . If a new strain with increased R_0 arises through creation of a more virulent and likely more transmissible strain in a laboratory, the herd-immunity threshold rises. *Consequently, the number of people infected could rise until the new immune threshold is reached.*

As a hypothetical illustration, divide the world's nations into two camps, nations with a $0.27 \times 0.56 = 0.15$ or 15% effective vaccination rate and poor nations with no vaccination. Assume a modest increase to $R_0 = 1.8$ for a post-pandemic lab release of a transmission-enhanced pdm09 H1N1 virus. This is an increase from the 2009 pandemic median of $R_0 = 1.46$. From equation (2), the new herd-immunity threshold rises to $H = 0.44$, increasing from $H = 0.32$.

From equation (1), for a vaccinated nation, $R_E = 1.8 \times [1 - (0.32 + 0.15)] = 0.95$ at the start of the new wave of infection, so herd immunity plus vaccination might protect the population from significant further infection, since in this hypothetical analysis R_E is just under the 1.0 threshold. Assume the vaccinated nations are mainly the U.S. and Europe, which comprise about 20% of the world's population¹⁰.

For unvaccinated nations, $R_E = 1.8 \times (1 - 0.32) = 1.22$ at the start of the new wave of infection, so infections will increase significantly until the new herd immunity threshold is reached. Unvaccinated nations comprise about 80% of the world's population or 0.8×7.6 billion = 6 billion people. The number susceptible to infection would be $(0.44 - 0.32) \times 6$ billion = 0.72 billion additional people could be infected until the new threshold is reached.

Since these lab-enhanced strains are more virulent than the wild-type strains, the case-fatality rate may increase as well. Potential new infections of 0.72 billion is a highly worrisome, big number and should be a grave concern for us all. Do not fall for the false promise of herd immunity.

Comparison of pandemic risk for math5N1 and pdm09 H1N1 with enhanced transmission

Controversy over lab-created pandemic risk was initiated in 2011 when Dutch researcher Ron Fouchier¹¹ and American virologist Yoshihiro Kawaoka¹² submitted manuscripts to Science and Nature where they described how to create strains of H5N1 avian influenza that were mammalian airborne transmissible (math5N1). Does the pandemic risk from the lab-enhanced pdm09 H1N1 virus strains described here rival that of the math5N1?

For pdm09 H1N1, reproductive-number ranges are known.¹³ Wild-type strains of pdm09 H1N1 had spread throughout the world. The more virulent strains listed in Table 1 could have greater reproductive numbers, which we cannot estimate. For math5N1, the virus is airborne transmissible between ferrets in the laboratory, so it is reasonable to assume the virus would be airborne transmissible in humans as well; however, there is no way of estimating reproductive numbers in human populations.

For pdm09 H1N1, the world case-fatality rate was a surprisingly low 0.001–0.011%,¹⁴ from which 76,000 to 836,000 deaths can be calculated based on a world population of 7.6 billion. The case-fatality rate could increase substantially for these more virulent lab-created strains, but cannot be estimated. For avian H5N1, the case-fatality rate is 60% for poultry workers and others directly infected by handling infected birds. The case-fatality rate in the population for the math5N1 virus cannot be estimated. It could be much lower than 60%, but could still cause fatalities in the millions with 1% case-fatality rate.

Both lab-enhanced pdm09 H1N1 and math5N1 present a risk of significant population infection with high fatalities.

Potential risk = (likelihood) x (potential consequences), so even if the likelihood of a release from a laboratory seeding a pandemic is small, the potential consequences are high for both lab-created pdm09 H1N1 and math5N1. It doesn't matter whether lab-enhanced pdm09 H1N1 or mat H5N1 is the greater potential risk. They are both influenza viruses with the ability to spread throughout the world. That alone should give us concern. Furthermore, since the benefits of the research are uncertain, there are good reasons for concern over conducting this research at all on live viruses.

Thanks to Simon Wain-Hobson for important comments on the manuscript.

¹ *One fifth of the world had swine flu due to 2009 pandemic – WHO report*, <https://www.rt.com/news/swine-flu-pandemic-who-815/>

² The average interval between successive cases in a chain of transmission is called the "time period" or "serial interval." For influenza, the serial interval ranges from one to ten days depending on influenza subtype.

³ The total number of infected from a single infected person, S_N , after N serial intervals is

$$S_N = R_E^1 + R_E^2 + R_E^3 \dots R_E^N = R_E (1 + R_E^1 + R_E^2 + R_E^3 + \dots R_E^{N-1})$$

From the well-known formula for a geometric series

$$S_N = R_E \times (1 - R_E^N) / (1 - R_E)$$

And for a very large number of serial intervals N ,

$$S_N = R_E / (1 - R_E).$$

As an illustration of why $R_E < 1$ leads to the infection dying out, let $R_E = 0.95$ and $N \rightarrow \infty$, $S_\infty = 20$. Thus, the number infected from this one person levels-off around 20, implying the infection and virus has died off. Almost no new infections occur after 100 serial intervals. Twenty new infections after R_E becomes less than one is a small number compared to when $R_E > 1$ where numbers infected grow exponentially and each infected person could seed hundreds of new infections.

⁴ "Herd Immunity": A Rough Guide (<http://op12no2.me/stuff/rough.pdf>)

⁵ Biggerstaff, et al., *Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature*. (<https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-14-480>)

⁶ *Ibid.* This median is a mix of basic, R_0 , and effective, R_E , reproductive numbers for the 2009 pandemic.

⁷ *Effects of Vaccine Program against Pandemic Influenza A(H1N1) Virus, United States, 2009–2010*, Table 1 (<https://wwwnc.cdc.gov/eid/article/19/3/pdfs/12-0394.pdf>)

⁸ Griffin MR, Monto AS, Belongia EA, Treanor JJ, Chen Q, et al. (2011) *Effectiveness of Non-Adjuvanted Pandemic Influenza A Vaccines for Preventing Pandemic Influenza Acute Respiratory Illness Visits in 4 U.S. Communities*. PLoS ONE 6(8): e23085. doi:10.1371/journal.pone.0023085.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0023085>

This multicenter large study calculated the overall effectiveness of the pandemic vaccine at 56%. For the inactivated vaccine, vaccine effectiveness was 89% in those aged 10 to 49. Effectiveness in children aged 6 months to 9 years was 32%, and for people over 50 it was 6%.

⁹ Biggerstaff, *et al.* defines effective reproductive number as we do: “the effective reproduction number (R_E) is calculated in a population with underlying immunity and accounts for a population’s reduced susceptibility to infection.” So definition differences do not appear to explain the $R_E > R_0$ result.

¹⁰ https://en.wikipedia.org/wiki/List_of_continents_by_population

¹¹ S Herfst, *et al.*, *Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets*, Science 22 Jun 2012:

Vol. 336, Issue 6088, pp. 1534-1541, DOI: 10.1126/science.1213362

<http://science.sciencemag.org/content/336/6088/1534.full>

¹² M Imai, *et al.*, Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets, Nature volume 486, pages 420–428 (21 June 2012)

doi:10.1038/nature10831 <http://www.nature.com/articles/nature10831>

¹³ Biggerstaff, *et al.*, *op. cit.*

¹⁴ Dawood, F. S., *et al.*, Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis. Volume 12, No. 9, p687–695, September 2012

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