Establishing herd immunity against Ebola through vaccination

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**A R T I C L E   I N F O**

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**A B S T R A C T**

Objectives: In response to recent concern regarding Ebola outbreaks, this study aims to (1) determine the relationship between vaccination coverage and herd immunity, (2) determine the vaccination coverage necessary to establish herd immunity for previous Ebola viruses, and (3) recommend vaccination coverage thresholds for future Ebola viruses.

Methods: Herd immunity thresholds needed to block transmission of Ebola virus were determined using vaccine efficacy and number of secondary cases per infected case during an entire infectious period.

Results: In past Ebola outbreaks 42.2–63.0% of the population would need to be vaccinated in order to prevent transmission and outbreaks. Assuming 80% vaccine efficacy as reported by phase I clinical trials, 52.7–78.7% of the population would require vaccination coverage in order to establish herd immunity. In recent ring vaccination trials which considered the vaccine to be 100% effective after 10 days, 42.2–63.0% of the population would need to be vaccinated.

Conclusion: For future Ebola outbreaks, the spread of the virus can be prevented by vaccinating certain percentages of the population depending on vaccine efficacy and number of secondary cases per infected case.

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1. Introduction

In 2014 the largest Ebola epidemic in history spread through West Africa with additional cases reaching the United States [1]. The first case of Ebola was recognized in 1976 in the Democratic Republic of Congo as a rare and severe illness with fatal potential. The virus is transmitted from wild animals to people and spreads through the population from human-to-human transmission. Due to the dangerous nature of the virus, it is important to prevent its transmission through vaccination. Vaccination can reduce the risk of Ebola virus contraction and its related complications, physician visits, hospitalizations and death. By vaccinating a certain proportion of the population against the virus, transmission of Ebola in the community can be blocked through the establishment of herd immunity.

Vaccines can affect more than just the individual who is vaccinated; vaccines can also protect people who have not been immunized. The concept of “herd immunity” refers to an indirect protection of an entire community from disease by immunizing a critical proportion of the population. Herd immunity breaks the chain of an infection’s transmission so that outbreak does not occur [2]. For example, transmission of measles can be blocked by vaccinating 92–95% of a given community [3]. The remaining 5–8% of the community who are unvaccinated and susceptible to measles receive “conferred immunity” from the vaccinated individuals. Given the proportion of vaccinated individuals, in terms of vaccination coverage, above a pre-determined herd immunity threshold, transmission of measles is blocked within the community.

The threshold for herd immunity needed to block transmission of Ebola virus in the population is currently unknown. Herd immunity is established when the prevalence of protected persons (\( I \)) is higher than the herd immunity threshold (\( I > I_c \)) [3,4]. When this occurs, Ebola virus transmission is blocked within the given population. However when prevalence is lower than the threshold, the number of infections is able to grow exponentially, thus spreading the virus within the population. Recent early phase trials of Ebola vaccinations report the efficacy of the vaccines, which can be used to determine the percentage of the population that requires vaccination in order to reduce community outbreaks and prevent transmission [5,6].

The objectives of this study are to determine the relationship between Ebola vaccination coverage and herd immunity,
determine the vaccination coverage necessary to establish herd immunity for previous Ebola viruses, and provide suggestions for vaccine coverage needed for future Ebola viruses.

2. Methods

This study mathematically determined the herd immunity threshold required to prevent transmission of Ebola. It was determined by accounting for the number of secondary cases per infected case ($R_0$) during the entire infectious period in a completely susceptible population, or basic reproductive number, in past outbreaks and the vaccine effectiveness. When $R_0 > 1$, outbreaks and resulting epidemics occur.

When vaccinations are administered within a specified population or community, the vaccine protects only a proportion ($E$) of the vaccinated individuals. The proportion of protected individuals who were vaccinated represents the effectiveness of the vaccine against infection transmission.

Using the mentioned variables, the critical proportion of protected individuals needed to establish herd immunity in a completely susceptible community can be determined from the equation $I_c = 1 - (1/R_0) [2, 4]$. The critical vaccination coverage ($V_c$) needed to establish herd immunity can next be determined by dividing the herd immunity threshold ($I_c$) by the level of vaccine effectiveness ($E$); $V_c = I_c/E = [1 - (1/R_0)]E [2, 4]$.

Citing $R_0$ values from past Ebola epidemics (Table 1), it is possible to mathematically derive the herd immunity threshold, and the number of protected persons required to establish herd immunity in a completely susceptible population.

After determining herd immunity thresholds for previous epidemics, data was pulled from phase I and III clinical trials in order to determine the critical vaccination coverage needed to establish herd immunity in past outbreaks given vaccine efficacy. Vaccine efficacy in early phase I clinical trials was measured by percentage of subjects with positive enzyme-linked immunosorbent assay results at week 12 after vaccination. Antibodies directed against specific antigens were measured throughout the trial and an end point titer with a background-corrected optical density reading of $\geq 30$ was considered a positive result [7]. A more recent phase 3 trial of Ebola ring vaccination determined efficacy of ring vaccination based on zero cases of Ebola virus disease at 10 days or more post-randomization and vaccination [8].

3. Results

In past Ebola virus epidemics, the prevalence of protected persons needed to establish herd immunity ranged from 42.2% in the most recent epidemic to 63.0% in earlier epidemics (Table 1).

The required vaccination coverage to establish herd immunity for past Ebola epidemics varied depending on vaccine efficacy. The required vaccination coverage to establish herd immunity for these past Ebola epidemics ranges from 52.7% to 78.7% assuming the vaccine is 80% effective as reported by a phase 1 clinical trial [7]. A 2015 phase-3 ring vaccination cluster-randomized trial reports the efficacy of the vaccine in different scenarios. In individuals who randomly received the ring vaccination, the vaccine was considered to be 100% efficacious after 10 days [8] which requires 42.2–63.0% of the population to be vaccinated in order to provide herd immunity. The 2015 study reports an estimated 75.1% and 76.3% overall vaccine efficacy in all eligible participants, which equates to a critical vaccination coverage of 56.2–83.9% and 55.2–82.6% respectively.

To account for real-world human error and varying degrees of efficacy, Table 2 reports the vaccination coverage that would have been required to establish herd immunity against past epidemic Ebola viruses for different levels of vaccine effectiveness.

The vaccination coverage required to establish herd immunity against future Ebola viruses for varying levels of vaccine effectiveness and differing $R_0$ values is demonstrated in Fig. 1. For example, when the number of secondary cases per infected case, $R_0$, is equal to 1.1 and the vaccine is approximately 90% effective, only about 10% of the given population will have to be vaccinated in order to provide herd immunity against the virus.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>$R_0$ CI</th>
<th>Vaccine coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Democratic Republic of the Congo</td>
<td>2.7 (1.5–2.8)</td>
<td>63.0% (47.37–64.3%)</td>
</tr>
<tr>
<td>Uganda epidemic</td>
<td>2.7 (2.5–4.1)</td>
<td>63.0% (60.0–75.6%)</td>
</tr>
<tr>
<td>Liberia epidemic</td>
<td>1.73 (1.66–1.83)</td>
<td>42.2% (39.8–45.4%)</td>
</tr>
</tbody>
</table>

Where $I_c = [1 - (1/R_0)]$, $I_c$ = herd immunity threshold and $R_0$ = basic reproductive number.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>60%</td>
<td>100%</td>
<td>100%</td>
<td>70.3%</td>
</tr>
<tr>
<td>80%</td>
<td>78.7%</td>
<td>78.7%</td>
<td>52.7%</td>
</tr>
<tr>
<td>90%</td>
<td>70.0%</td>
<td>70.0%</td>
<td>46.9%</td>
</tr>
<tr>
<td>100%</td>
<td>63.0%</td>
<td>63.0%</td>
<td>42.2%</td>
</tr>
</tbody>
</table>

Where $V_c = I_c/E$, $V_c$ = vaccine coverage and $I_c$ = herd immunity threshold.
4. Discussion

This study explored the relationship between Ebola vaccination coverage and herd immunity while assessing the vaccination coverage necessary to establish herd immunity for previous Ebola epidemics. The results suggest that higher levels of vaccination coverage would have been needed in order to provide herd immunity against previous Ebola epidemics. Given that the recent 2014 Ebola epidemic had a lower R0 value, it may suggest that less vaccine coverage than previous epidemics would be needed in order to prevent transmission.

Additionally, results of this study suggest that future Ebola virus transmission can be blocked by vaccinating susceptible populations. Fig. 1 demonstrates vaccination coverage needed in order to prevent future Ebola outbreaks in a 100% susceptible population given varying R0 values and vaccine effectiveness. As seen in Fig. 1, it is easiest to prevent an outbreak when a virus has a low R0 value and high vaccine efficacy. This study suggests that for Ebola viruses with R0 ≥ 3 and vaccine effectiveness of 70%, nearly all of the population would need to be vaccinated in order to establish herd immunity. With a lower R0 value and a vaccine efficacy of 70%, a smaller percentage of the population would need to receive the vaccine in order to prevent outbreak.

It is important to note that there are several limitations to this study. The study utilizes a simple threshold theorem which makes several assumptions: (1) random vaccination within the population, (2) homogenous mixing of persons within the population, (3) homogeneous distribution of vaccine-induced protected and infected persons within the population, and (4) fully susceptible population [2]. It can be speculated that because this model assumes a fully susceptible population, vaccination coverage needed to establish herd immunity in a population with individuals already protected due to natural infections would be less than the proposed thresholds within this study. Additionally, this study assumes that vaccine efficacy is equal to the percentage of patients from previous trials with positive enzyme-linked immunosorbent assays when this value may not truly correlate to the vaccine efficacy and immunity.

This study relies heavily on the accuracy of the basic reproductive values (R0) reported for past Ebola outbreaks that are included in Table 1 and used to calculate the results in Table 2. As seen in Table 1 of this study, the R0 value of the 1995 DRC and 2000 Uganda epidemics are 2.7 whereas the most recent 2014 Liberia epidemic’s value was significantly lower at 1.73. Although the strains for the outbreaks were the same, the varying R0 values can vary due to several factors because it is a property that combines the process of contagion within a population and the patterns of contact within the population. Some variables that affect R0 may include the number of susceptible people in the population that the affected patients are in contact with, containment and control measures for the virus, and stages of outbreak [9]. In 2014, the World Health Organization (WHO) redesigned frame work and created intensive public health containing measures to be implemented from both local and international levels [10]. The R0 value for the 2014 epidemic was calculated from data collected during July and September 2014, after said measures were initiated. It is possible that containment measures were improved in the most recent outbreak thus resulting in a decreased R0 value.

Currently, there are known contraindications to Ebola vaccination for specific age ranges. Of note, the phase 1 trial by Sarwar, which this study utilized for vaccine efficacy data, was limited to adults aged 18–60 years [7]. Applying the data from our study we can speculate that if 52.7–78.7% of a mixed age population of individuals was vaccinated this would provide community protection to the young and the older adults who were ineligible to receive the phase 1 trial vaccine in that population. Due to the restrictions in age, a larger percentage of the adult population needs to be vaccinated in order to protect those who cannot be vaccinated. If children and older adults were also eligible to be vaccinated, it would be easier to reach the herd immunity threshold by being able to vaccinate more individuals.

The most recent phase 3 trial of Ebola vaccination in Guinea involved ring vaccination in a cluster-randomized style. Ring vaccination involves administering vaccination only to a cluster of high risk individuals who are in close contact with a confirmed isolated infected person [8,11]. Although different from traditional methods of vaccination this method demonstrates notable efficacy. Eligible individuals in the clusters were given either immediate or delayed Ebola vaccination. Of the immediately vaccinated individuals the vaccine was 100% effective as determined by no symptoms of Ebola virus disease 10 days after vaccination. Of all eligible individuals who received immediate or delayed vaccination (21 days after randomization) the vaccine was 75.1% effective and 76.3% effective depending on cluster [8]. Because this was a cluster trial of individuals in close contact with isolated infected person(s) the R0 value of the virus is likely higher than in populations where individuals are not in close proximity. Therefore, it is possible that critical vaccination coverage values may be lower in other communities. Importantly, the basic reproductive value of the outbreak in Guinea was not reported so it is difficult to conclude exactly how the critical vaccination coverage would be affected.

In future outbreaks with a 100% efficacious vaccine, as reported by the Guinea ring vaccination trial, 42–63% of the population would have to be vaccinated to prevent transmission. There are several stressors that could affect the ability to vaccinate individuals against Ebola in the future. When outbreak occurs, access to adequate supply of vaccine to vaccine sufficient number of individuals is not always possible within desired time range to control transmission. Thus, it is important that future Ebola outbreak protocols include intensive measures for containment to prevent transmission. If supply is a potential issue it would be wise to distribute vaccine supply in levels of priority. Similar to vaccination protocols within hospitals an important target population to vaccinate would be healthcare workers [12]. The Guinea trial demonstrates the value of ring vaccination in Ebola and the importance of vaccinating individuals who have been or will be in close contact with the virus. This can include contacts of sick individuals such as family and friends, caregivers, and contacts of contacts.

5. Conclusions

The novel data within this study can have future impacts in preventing outbreaks and transmission of the rare but dangerous Ebola virus. As clinical trials are still underway for development of Ebola vaccines, the information from this study can be utilized in the future with novel vaccine efficacy data to determine vaccine coverage needed to prevent outbreaks.

Conflict of interest: None declared.

References


