Interrupting the Transmission of Respiratory Tract Infections: Theory and Practice

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Interrupting transmission has always been one of the most attractive approaches (and in many situations, the only feasible approach) to control of infections. The quarantine system was developed as an attempt to control transmission long before the germ theory of disease put the process into a scientific framework. While many of the measures used to separate infected persons from susceptible persons did achieve the goal of control, others did not. From our perspective, some of the methods, such as systematic use of fumigants to disinfect letters and parcels, seem silly, but they were in fact based on the flawed transmission theory of the time.

Transmission theory has expanded steadily, but there has often been a lack of communication between those working in that realm and those involved in the often pragmatic arena of disease control. Strategies have sometimes been developed by trial and error, when theory could have been used to guide decisions. This article examines some recent experience with control of transmission and the interplay between theory and practice. Emphasis is placed on the purely respiratory infections, but systemic infections transmitted by the respiratory route are noted for comparison.

Transmission Theory: The Basic Reproductive Number

The scientific theory of transmission now has a strong mathematical basis, and modeling of the dynamic process can have a major role in deciding, for example, how to distribute vaccine in a period of shortage—that is, what age groups or other possible risk groups should be vaccinated. From a pragmatic standpoint, decision-makers will respond better to recommendations that are mathematically substantiated than to simple intuitive judgments. Many equations have been generated to describe transmission, but central to them all is Ro, or the basic reproductive number [1, 2]. In a totally susceptible population, Ro approximates the classic average secondary attack rate, although it is not limited to contact units such as the family. The Ro is a characteristic of a particular agent but is not fixed and is affected by such variables as population density, as is the secondary attack rate. These complex relationships are one of the reasons that modeling disease spread has been so difficult, since reducing a dynamic situation to a series of equations is required. In any event, highly transmissible conditions such as measles have a high Ro.

As shown in table 1, adapted from an article by Anderson and May [3], the Ro of measles is ~16. For comparison, influenza has been added to this list of basically childhood vaccine–preventable diseases as an example of an agent that is truly respiratory, not only in terms of route of transmission. If the Ro is one, it means that only one contact case may occur in a totally susceptible population. The closer the Ro is to one, the more likely that transmission will eventually cease, especially if it is possible to increase the proportion that are susceptible.

The Ro’s in this table were not estimated from contact studies of infection occurrence. Such information is rarely available. Rather, Ro has been estimated from seroprevalence studies in which data on the age by which individuals experience their first infection are determined. Those infections with a higher Ro will produce a higher frequency of infections at a younger age. The estimates for influenza are derived from family studies done in Tecumseh, Michigan, which included serology to detect asymptomatic infection, another phenomenon to be considered with a true respiratory tract virus [4, 5]. This places influenza conservatively at a Ro of 3–4. It should be
Table 1. Transmission properties of selected viral and bacterial infections.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Average age (y) at infection*</th>
<th>Critical average vaccination level (%) required to block transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>4–6</td>
<td>15–17</td>
</tr>
<tr>
<td>Pertussis</td>
<td>4–5</td>
<td>15–17</td>
</tr>
<tr>
<td>Mumps</td>
<td>6–7</td>
<td>10–12</td>
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<tr>
<td>Rubella</td>
<td>9–10</td>
<td>7–8</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>11–14</td>
<td>5–6</td>
</tr>
<tr>
<td>Polio</td>
<td>12–15</td>
<td>5–6</td>
</tr>
<tr>
<td>Influenza</td>
<td>. . .</td>
<td>3–4</td>
</tr>
</tbody>
</table>

NOTE. Table is modified from [3].
* On the basis of data from developed countries, before availability of vaccine.
† The number of new cases infected by a single case when all contacts are susceptible; the basic reproductive number.

remembered that polio, unlike many of the other infections included in the table, is not transmitted by the respiratory route.

The data on seroprevalence were derived from studies conducted in developed countries before the introduction of vaccine; it would be quite different in developing countries at that time. This indicates that improving the environment plays a greater role in reducing fecal-oral transmission than in changing respiratory transmission. The ultimate calculation derived from this compilation is the vaccination level required to block transmission. That is the point at which elimination of transmission will take place: when, through vaccination, sufficient numbers of susceptible persons enter a state of immunity.

Role of Reinfection and Antigenic Change

However, there are exceptions to the above analysis. To render the real, complex world of hosts and parasites into a form that can be modeled in a relatively uncomplicated fashion, many simplifications have to be made, especially when dealing with respiratory agents. Reviewing them helps to provide a framework for generalizing these observations and for identifying the kinds of information needed for decision-making. They can be divided into factors related to the host and those related to the agent. The first point related to the host is that with all infectious agents, protective immunity is not necessarily life-long; traditional concepts suggesting that this was the case (for example, with measles) were the result of inapparent reinfections not being recognized [6]. With removal of the agents from general circulation, the truism that there is no such thing as life-long immunity has become more obvious.

In contrast, with typical respiratory and other surface viral infections, this was always apparent, with reinfections occurring frequently and in an easily detectable form. The phenomenon of reinfection was reported very shortly after the first descriptions of respiratory syncytial and parainfluenza viruses, but its extent was not recognized until community studies were carried out [7]. In the Tecumseh Study of Respiratory Illness, the yearly infection rate was determined serologically for parainfluenza virus types 1, 2, and 3 [8]. If there was a rise in antibody titer for one or more types, it was considered as one parainfluenza infection, a conservative measure in view of the known possibility that a single infection can produce a nonspecific antibody response to more than one type. Calculated on a person-year basis, results indicated that children in the age group of 1–4 years had at least 39 infections per 100 per year, and among those 5–9 years of age there were at least 43 infections per 100 per year. This suggests that in the latter age group, reinfections may be occurring at least every other year.

Such reinfections are often asymptomatic as is carriage, the parallel in the world of bacteria. They are critical in considerations of spread and elimination strategies because both can potentially lead to transmission. However, it is known that the amount of viral agent released into the environment from asymptomatic cases is less than that from symptomatic cases, for a number of reasons. These include the lack of symptoms such as sneezing and coughing that are responsible for spread, as well as a reduced titer of antibodies. Thus, it is likely that asymptomatic patients will be less contagious.

Elimination of Haemophilus influenzae type b transmission after vaccination programs with conjugated vaccines began was a major bonus not easily incorporated into the standard transmission theory, and it was taken by some to indicate the relatively precarious situation of the bacterium in the carrier state [9, 10]. The fact that it did not occur with use of the unconjugated vaccines should remind us that the specific type of immunizing preparation does matter and may have profound and unexpected implications [11]. This also confirms that the carrier state or asymptomatic infections often do not have the same consequence as symptomatic disease with regard to transmission. Diphtheria is another case in point for bacterial infections. The toxoid used for control should not necessarily affect the carrier state of nontoxigenic strains.

Another related point in terms of the host is the issue of partial protection. Nearly all models put individuals into dichotomous categories of “immune” and “susceptible.” For respiratory infections, we know that most of the population is partially immune, which in many cases can be quantified by measuring antibody titer. Infection may occur if the infectious dose given to the partially immune individual is sufficient. However, that occurrence is less likely until the antibody titer declines to a sufficient point. This rate of decay of antibody post-infection or post-vaccination has critical implications on the probability of transmission and indicates again why the immunogenicity of a vaccine is important, not only for individual protection but also for community protection.

In terms of agent factors, the simplest to recognize, if not to deal with, is that of true antigenic change. Antigenic variation is often hypothesized to be involved when there are out-
breaks of an infectious disease in a vaccinated population, but it rarely turns out to play a significant role. Influenza is another matter, and pandemic shift is the most dramatic situation. In fact, the year-to-year gradual changes are more common and more consistently important in terms of control issues. The other agent factor is not one in which transmission theory is of much help in anticipating: replacement of one agent by another of similar characteristics, as transmission of the first agent is reduced or eliminated. In the world of viruses, interference is well recognized and, in terms of influenza, has actually been modeled in simultaneous outbreaks of different subtypes, an occurrence frequently recognized when surveillance is accurate [12].

The extreme situation here involves vaccinating against one agent while the potential for the spread of other agents still exists. This replacement in fact did occur in the military for a time when only adenovirus type 4 vaccine was available; type 7 and other adenoviruses known to have potential for spread in this population took their place until appropriate vaccines could be developed [13]. A current question involves use of conjugated pneumococcal polysaccharide vaccines for young children. It is known that the number of groups or types with invasive potential is approximately double the number for which a conjugated vaccine can be produced. These other types, which are clearly in circulation, could replace those in the specifically designed vaccine.

Direct and Indirect Protection: Rubella Vaccine

One of the great advantages of use of vaccine is that protection may extend beyond those directly vaccinated to others in the population. Returning to the concept of Ro, indirect protection, as a result of what has generally been called herd immunity, is more likely to occur for infections with low Ro’s than for those with high Ro’s, as programs immunize greater proportions of susceptible persons. This concept does have practical consequences, even when it is applied intuitively. Smallpox eradication became possible when it was realized that the Ro was far lower than previously anticipated and that protection would be required only in limited regions around detected cases.

It is useful to examine what would be predicted to occur with different approaches to vaccination, on the basis of the Ro. The history of rubella vaccination is illustrative, since policies did vary in regions of the world when the vaccine was introduced, resulting in dramatically different outcomes. Rubella was actually one of the first illnesses that, although traditionally thought to provide lifelong protection after infection, was demonstrated to produce only partial or time-limited immunity. This was shown in the mid-1960s during the course of vaccine trials, when individuals thought to be immune as a result of previous natural infection were first demonstrated to have a rise in antibody titer after exposure, similar to the situation with the classic respiratory viruses such as parainfluenza virus [14]. The same situation was also demonstrated in vaccinated persons, in whom reinfection after natural exposure could be documented almost immediately after vaccination [15].

This unexpected finding was particularly troubling and resulted in different implementation decisions. The key here was that there was no viremia associated with reinfection, which was seen as the principal issue in terms of the later prevention of congenital rubella. Also demonstrated in these careful studies was that respiratory viral shedding was much lower in rubella reinfection than in primary infection [16].

Armed with this piece of information and the fear of using vaccine in women, even very young women, who might be pregnant, the United States launched an attempt to control transmission by universal vaccination of young children. This had the result of decreasing the frequency of primary infection while temporarily leaving many in the childbearing years still susceptible. In retrospect, this was the right decision. In the United States, frequency of both rubella and the congenital rubella syndrome dropped rapidly and stayed down. Well known are the results of not using vaccine to control transmission, with continuation of outbreaks.

In retrospect, the interruption of rubella transmission by indirect protection can now be analyzed, and in this analysis transmission from inapparent infection is confirmed to be consequential, allowing eventual interruption. Also critical to the success of childhood vaccination is the low Ro of rubella, which in prevaccination antibody prevalence studies was shown to infect at far later ages than measles [17, 18]. This indicates again what is known intuitively: if women in childbearing years are still developing primary infections, rubella must be an agent whose transmission is not that intense.

Indirect Protection: Influenza

The only common respiratory virus for which there is a vaccine is influenza. In many ways, influenza is an unlikely target for control through indirect protection because of the issues of partial immunity and antigenic change. It is interesting that violations of one of the basic assumptions of indirect protection—namely, random mixing—has made this approach possible. Observations on the occurrence of this and other respiratory infections have demonstrated the importance of schoolchildren in spread [19]. As mathematical models became more sophisticated with the development of more powerful computers, it was possible to design them with various mixing groups to approximate real conditions. These models have confirmed that by reducing illness and therefore shedding of virus by schoolchildren, transmission can be reduced [20].

Evaluation of the effect of vaccinating school-age children has been done on two occasions, widely separate in time and place. The first was in Tecumseh, Michigan. It was carried out when the type A(H3N2) viruses first appeared and the availability of vaccine was limited [21]. The experiment was conducted in the study town of Tecumseh, in which vaccine
was offered to school-age children. The neighboring city of Adrian remained unvaccinated since no vaccine was yet commercially available when the pandemic began. This allowed the community to be an observed comparison. The vaccine was of relatively low potency, containing less than half the amount then used for annual vaccination. It was also monovalent and contained only the expected new pandemic variant.

Antibody levels achieved were relatively low, which, as indicated above, would not be ideal for producing indirect protection. On the positive side, vaccination rates were high, actually 92% among the youngest children. In retrospect, given transmission patterns, this was probably ideal since the 5- to 9-year-olds would be expected to have peak infection rates. Surveillance for illness was conducted at the individual level. The average illness frequency during the outbreak was overall threefold higher in the comparison community than in the vaccinated one. The reduction was not limited to the vaccinated age group, which would demonstrate direct protection. It also included the unvaccinated age groups, indicating that indirect protection had been achieved.

Shortly after this designed study, an unplanned event occurred in the Northern Territory of Australia that further confirmed this experiment. Again, standard inactivated vaccine was involved. By chance, the type A(H3N2) outbreak arrived unexpectedly before the vaccination program was completed throughout the territory. The result again indicated that indirect protection had been produced in the heavily vaccinated area [22].

A more recent example of the role of indirect protection involves studies in which University of Michigan researchers collaborated with colleagues at the Centers for Disease Control and Prevention and in Russia [23]. The intent was to conduct a study comparing the direct protection of the Russian live influenza vaccine and inactivated influenza vaccine with placebo, as well as to evaluate the extent of indirect protection when vaccine was offered to an entire school (that is, when randomization was done on the school level). It would be expected that school transmission would decrease as the percentage vaccinated in that school increased. The effect was measured on the unvaccinated students or the staff, who were ineligible for vaccination.

A regression line was constructed, comparing the percentages vaccinated in schools where live vaccine, inactivated vaccine, or placebo was administered with the illness rates of the students who chose to remain unvaccinated or the staff. There was a significant relationship only for those schools in which live vaccine was used. No similar relationship existed for either inactivated vaccine or placebo. A question arises concerning why no effect was shown for inactivated vaccine in this study, when it was shown previously on two other continents. There are two possible explanations. Antibody titers produced by the Russian inactivated vaccines were modest, but so were the titers produced in Tecumseh. A more likely explanation involves the percentage of children vaccinated, which was lower than that reached in the Tecumseh experiment. On the live vaccine side, the question of why indirect protection was achieved probably relates to the effect this vaccine has in reducing shedding of virus, even when complete protection against infection is not produced.

Respiratory Transmission and Future Vaccines

These observations indicate that the principles of transmission should guide us in designing experimental studies and in programmatic use of vaccines. As models improve, based on resulting real observations, they will be able to guide us further. We do need more data on how to interrupt transmission, especially in areas where we have had little experience. The rubella story is a case in point, concerning success of a vaccine viewed as suspect at the time. A new vaccine against respiratory syncytial virus for infants, for example, would be expected to protect against only severe disease. However, use of such a vaccine more generally among young children may produce indirect protection by decreasing shedding, which could then delay the first infection still further, beyond the critical period of the first months of life.

The next new group of respiratory vaccines will be conjugated pneumococcal polysaccharides. Here the issue of replacement by additional invasive types not in the vaccine is a real concern. However, by the time the serotypes in the vaccine are eliminated, with the optimistic assumption of an effect against the carrier state, new vaccine approaches not based on the polysaccharide may be ready. The message, then, is to include the issue of transmission in our planning for vaccine intervention but not to be paralyzed into inaction by possible theoretical worries. Different approaches to control in different parts of the world may help to determine which of the possible methods is the most appropriate.

References