Phage therapy dosing: The problem(s) with multiplicity of infection (MOI)

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ABSTRACT
The concept of bacteriophage multiplicity of infection (MOI) – ratios of phages to bacteria – historically has been less easily applied than many phage workers would prefer or, perhaps, may be aware. Here, toward clarification of the concept, I discuss multiplicity of infection in terms of semantics, history, mathematics, pharmacology, and actual practice. For phage therapy and other biocontrol purposes it is desirable, especially, not to solely employ MOI to describe what phage quantities have been applied during dosing. Why? Bacterial densities can change between bacterial challenge and phage application, may not be easily determined immediately prior to phage dosing, and/or target bacterial populations may not be homogeneous with regard to phage access and thereby inconsistent in terms of what MOI individual bacteria experience. Toward experiment reproducibility and as practiced generally for antibacterial application, phage dosing instead should be described in terms of concentrations of formulations (phage titers) as well as volumes applied and, in many cases, absolute numbers of phages delivered. Such an approach typically will be far more desirable from a pharmacological perspective than solely indicating ratios of agents to bacteria. This essay was adapted, with permission, from an appendix of the 2011 monograph, Bacteriophages and Biofilms, Nova Science Publishers.

Introduction
For many phage workers, multiplicity of infection (MOI) has a standard meaning: The ratio of phages added to bacteria, or $\text{MOI}_{\text{input}}$1. This “modern” concept of MOI, however, overly simplifies a more meaningful “historical” definition, as equivalent to $\text{MOI}_{\text{actual}}$1. Specifically, defining MOI in terms of the number of phages that have been added to bacteria can be misleading, and especially so when densities of bacteria are low or phage adsorption slow. Furthermore, MOI is not easily defined if not all bacteria may be equivalently reached, such as when applying phages to biofilms.2,3 The use of $\text{MOI}_{\text{input}}$ as the sole means of describing dosing during phage-mediated biocontrol of bacteria4-6 can as a consequence be problematic such as during phage therapy, that is, the use of bacterial viruses clinically as antibacterial agents.7-9 Here I consider these problems from a number of perspectives, semantic, historical, mathematical, pharmacological, and practical, building on various prior discussions.1,10-14

Semantics
Multiplicity of infection literally means the ratio of phages to bacteria when counting only those phages that have actually adsorbed/injected bacteria,15 i.e., “Multiple infection.”16-18 Less literally, the concept of MOI was invented prior to an understanding of many of the limitations to phage infection.18 In particular, not all adsorbing phages succeed in successfully infecting such as due to bacteria expression of anti-phage resistance mechanisms.19 Thus, effective phage adsorption does not necessarily translate into effective phage infection. Many authors nevertheless employ the terms infection and adsorption more or less synonymously. Notwithstanding these complications, in most instances the concept of MOI as literally defined is equivalent to that of multiplicity of adsorption, i.e., “Multiple adsorption,”17 the ratio of adsorbed phages to bacteria. From 18 (p. 113, emphasis theirs), “…the ratio of adsorbed phage particles to bacteria in the culture is named the multiplicity of infection.”

The qualification “infection,” particularly relaxed to mean simply adsorption, therefore is critical to appreciating the concept of MOI. Consistently, “actual” in $\text{MOI}_{\text{actual}}$ should be interpreted as considering only those phages that have actually adsorbed/injected bacteria. Indeed, if a phage has not adsorbed a bacterium...
then it cannot be considered to have contributed to a multiplicity of infection in literal or, for that matter, historical terms.

History

Phage genetical or physiological characterization traditionally has been done mostly employing cultures of relatively high bacterial densities, e.g., \(\sim 10^8\) bacteria/ml.\(^{16,17}\) Under these conditions, rates of phage adsorption tend also to be high, typically resulting in a rapid adsorption of free phages.\(^{20}\) This means that the ratio of phages which have been added to bacteria and the ratio of phages that have adsorbed bacteria can be similar.\(^{18,21}\) Thus, MOI\(_\text{input} \approx \text{MOI}_{\text{actual}}\). As a consequence, phage workers employing relatively high bacterial densities along with phages that adsorb reasonably quickly can get away with defining actual multiplicities of infection (MOI\(_\text{actual}\)) in terms of initial free-phage-to-bacterium ratios (MOI\(_\text{input}\)).

The phrase “Get away with” is key to what MOI\(_\text{input} \approx \text{MOI}_{\text{actual}}\) truly signifies. Unless determined experimentally, that is, then MOI\(_\text{input} \approx \text{MOI}_{\text{actual}}\) represents a shortcut. It does not follow that such ratios – of addition versus of infection – should be equivalent under all circumstances. In fact, it is especially under conditions of low bacterial densities, poor phage adsorption, or inconsistent phage penetration to target bacteria that multiplicity of “adsorption” and starting phage-to-bacterium ratios will be most different. Tellingly, the syllabus to the Cold Spring Harbor Phage Course, as published in 1950,\(^{18}\) warns that, “Since adsorption of phages is never 100%, the actual multiplicity has to be determined for each experiment” (p. 114, emphasis mine).

An additional but confusing historical aspect of MOI discussions stems from use of the term, "traditional."\(^1\) Specifically, I refer to MOI\(_\text{input}\) as a “modern” definition of MOI while Kasman et al.,\(^1\) refer to MOI\(_\text{input}\) instead as a “traditional” description of MOI. The latter assertion, however and unfortunately, is in error. Thus, the historical meaning of MOI as MOI\(_\text{actual}\) at some point appears to have been altered, creating a new tradition, MOI\(_\text{input}\), which continues into modern times. My argument is that historically it was understood that at best MOI\(_\text{input}\) was an approximation of MOI\(_\text{actual}\) (= MOI). With time, however, that institutional understanding to a degree may have been lost, resulting in a mistaken “tradition” that MOI\(_\text{input}\) instead is what one uses as MOI.

Nonetheless, it is important to heed Benzer et al.’s advice from over 65 years ago\(^{18}\) that what we now call MOI\(_\text{input}\) cannot simply be assumed to be MOI\(_\text{actual}\). Rather, such claims of equivalence must “be determined” to be the case.

Further, unless MOI\(_\text{input} \approx \text{MOI}_{\text{actual}}\) then the former term really does not have much meaning,\(^1\) except as an indication of relative numbers of phages applied. For instance, MOI\(_\text{input} = 100\) means that tenfold greater numbers of phages have been added than for MOI\(_\text{input} = 10\). Yes, a multiplicity of greater than 1 also means that more phages have been added than bacteria are present, which is potentially an important piece of information. Such an observation, however, has little meaning unless many or most added virions adsorb and all bacteria are readily reached, i.e., again, such that MOI\(_\text{input} \approx \text{MOI}_{\text{actual}}\).

MOI\(_\text{input}\) can serve as an approximation of MOI only under a narrow set of conditions. These conditions, however, are routinely violated when phages are employed as biocontrol agents of bacteria. As a consequence, MOI\(_\text{input}\) as an approximation of MOI should not be employed when reporting phase therapy experiments without explicit qualification of intended meaning. Such qualification can include using the construct MOI\(_\text{input}\) while citing Kasman et al.\(^1\) and then, ideally, explaining to the reader the limitations of the concept as a stand-in for MOI\(_\text{actual}\). These are requirements for high bacterial densities, efficient phage adsorption, environment homogeneity, relative lack of virion inactivation, and determination that most free phages in fact have adsorbed. Far better instead to experimentally determine MOI\(_\text{actual}\) in situ, though in many cases this can be difficult if not impossible—or at least to predict this value mathematically.

Mathematics

The absolute rate at which uninfected bacteria become phage adsorbed within an environment – in other words, the rate at which new infected bacteria are created – is relatively straightforward to calculate. It is the product of phage density (\(P\)), density of unadsorbed bacteria (\(U\)), and the phage adsorption rate constant (\(k\)), that is, \(PUk\).\(^{4,10,11,20,22-25}\) The rate at which individual free phages are lost to adsorption, however, is equal to the product of the virion adsorption rate constant and the overall density (\(N\)) of adsorption-susceptible bacteria. These are both not- phage-infected and phage-infected bacteria,
that is, for the latter, assuming that individual cells can be multiply adsorbed. Thus, individual phages are lost to adsorption at a rate that equals \( N k \). Another way of stating this is that the more adsorbable the bacteria that are present in a culture, then the more rapidly a free phage population will be lost to adsorption.

The rate at which uninfected bacteria are lost to phage adsorption will not, by contrast, necessarily change as a function of bacterial density. This is because bacteria become phage adsorbed, on a per-bacterium basis, at a rate that is equal to \( Pk \). This is the product of phage density and the phage adsorption rate constant, where the expression \( Pk \), of course, is not dependent on bacterial density (neither \( U \) nor \( N \)). This expression, however, comes with two caveats. First, it assumes that free phage densities will remain constant over time,\(^{13} \) i.e., at \( P \). This, though, can be a reasonable approximation given low bacterial densities since rates of phage adsorption, and therefore of free phage losses, consequently can be low. Second, it assumes that all target bacteria are equally susceptible to phage adsorption, i.e., that \( k \) is consistent. The latter is only true, however, given homogeneous bacterial populations and environments. Notwithstanding these concerns, the rate at which individual bacteria become phage adsorbed is primarily a function of phage density rather than of bacterial density. Therefore, the larger the phage titer that one applies to bacteria, then the sooner a desired minimum \( \text{MOI}_{\text{actual}} \) may be achieved.

The impact of changes in bacterial density on \( \text{MOI} \) thus is not straightforward. Holding numbers of added phages constant, then \( \text{MOI}_{\text{input}} \) as equal to \( P_0/N_0 \) will decline given higher initial bacterial densities (\( N_0 \)). This claim should hold even though individual added phages (\( P_0 \)) should adsorb more rapidly given higher numbers of added bacteria. For a specific \( \text{MOI}_{\text{input}} \) and adsorption interval, however, \( \text{MOI}_{\text{actual}} \) instead can be larger given greater bacterial densities. The latter occurs primarily because we are fixing the ratio of phages to bacteria, i.e., at \( \text{MOI}_{\text{input}} \), such that adding more bacteria results in adding more phages, which then as a population adsorb bacteria faster. In any case, \( \text{MOI}_{\text{actual}} \) will always be smaller than \( \text{MOI}_{\text{input}} \) unless 100% phage adsorption occurs.\(^1 \) Bacterial density, furthermore, is a key variable in determining how much smaller. For lower bacterial densities and holding \( \text{MOI}_{\text{input}} \) constant, then \( \text{MOI}_{\text{actual}} \) can be much smaller whereas with higher bacterial densities the two values will be more similar.

Though the rate of phage adsorption of homogeneous populations of planktonic bacteria is equal to \( Pk \), the total number of phages that bacteria will come to adsorb (\( A \)) also has a time component. This time component is the duration (\( t \)) of association of free phage populations with target bacteria. Thus, \( A = Pkt \). \( \text{MOI}_{\text{actual}} \) is the ratio of adsorbed phages (\( A \)) to total adsorbable bacteria (\( A/N \)). On a per-bacterium basis, which implies for purposes of calculation that \( N = 1 \), then \( Pkt \) also will equal \( \text{MOI}_{\text{actual}} \).\(^{24,27} \) That is, \( \text{MOI}_{\text{actual}} = A/N = A/1 = Pkt/1 = Pkt \). Phage therapy success ultimately is a function of both the rate (\( Pk \)) and actual degree (\( Pkt \)) of phage adsorption to bacteria. MOI therefore is relevant to that success, but particularly MOI as calculated as a function of phage titer (\( P \)) along with phage properties (\( k \)), i.e., \( \text{MOI}_{\text{actual}} \) as defined by \( Pkt \). Ultimately, it is the generation or penetration of sufficient local\(^{26} \) \textit{in situ} phage titers\(^{13} \) (\( P \)) in combination with sufficient \textit{in situ} rates of phage adsorption (\( k \)), along with a phage’s bactericidal and/or productive range of activity,\(^9 \) that are crucial toward pharmacologically defining the potential for a given phage treatment to be efficacious.\(^{8,12,29} \)

**Pharmacology**

Most antibacterial agents are not dosed as ratios of drug to bacteria. This is because – except under the most controlled circumstances – bacterial densities in the course of antibacterial treatments constitute an uncontrolled variable. Alternatively, this is because most drugs are dosed so that densities remain at levels which optimize a combination of efficacy, safety, and dosing convenience, that is, rather than in terms of ratios to anything other than patient body mass. Phage therapy doses in most instances may be similarly administered such that phage densities do not substantially decline over the course of treatment, and this is rather than toward establishment of some hypothetical added-phage-to-bacterium ratio.\(^{12} \)

What phage density should thus be maintained over the course of treatment? The answer to that question is complicated by the fact that phages often are able to increase their numbers in the course of impacting bacteria.\(^{4,12} \) Thus, in deciding that phages should be present during therapy at a certain, minimum titer, it is possible to achieve that titer via more than one route, that is, via traditional dosing or, instead, via the \textit{in situ} amplification of phage numbers through phage replication. The density sought, however, should be similar regardless of how it is reached, at least immediately local to target bacteria, i.e., as over micrometer scales.
What density that should be is a function of how fast we want phages to reach bacteria, resulting in what we hope is an MOI\textsubscript{actual} in the range of 10.\textsuperscript{1} Assuming a Poisson distribution of adsorbed phages to bacteria, then the fraction of homogeneously susceptible bacteria that would survive such an onslaught will be expected to be equal to $e^{-10} = 5 \times 10^{-5}$, or more than a 10,000-fold decline in viability. That is, due to the random (stochastic) nature of phage adsorption in combination with the ability of individual bacteria to adsorb multiple phages, it is necessary to adsorb most bacteria many times over to achieve substantial overall killing. An MOI\textsubscript{actual} of 1, by contrast, will be expected to allow a population of bacteria to survive, following phage adsorption, at a rate of $e^{-1} = 37\%$.

Regardless of bacterial densities, I and others\textsuperscript{29,30} have suggested that a reasonable phage density capable of impacting bacteria in a timely manner is one of $10^8$/ml. That is, \textit{in situ} and immediately local to target bacteria.\textsuperscript{28} Such densities then need to be sustained over relatively long periods – e.g., hours, days, weeks depending on circumstances – so that phage penetration to all bacteria may be possible.\textsuperscript{3} The resulting $Pkt = MOI\textsubscript{actual}$ for $10^8$ phages/ml, assuming a value of $k$ of $2.5 \times 10^{-9}$ ml min$^{-1}$ (the latter from reference 20), one hour of adsorption, and a homogenous population of target bacteria, will equal $10^9 \times 2.5 \times 10^{-9} \times 60 = 15 = MOI\textsubscript{actual}$. This, $e^{-15}$, implies a $3 \times 10^{-7}$ survival rate for those bacteria which phages can reach, i.e., over a million-fold reduction. The resulting impact would be lower, however, given lower initial phage densities, declines in phage densities over time, slower phage adsorption, or poor phage penetration. Thus, in practical terms, rather than striving for a specific MOI in our dosing, we should be striving instead toward sustaining phage densities – through dosing along with \textit{in situ} phage replication – at some minimum titer as found in the \textit{immediate vicinity} of target bacteria, with $10^8$ phages/ml a suggestion of what that titer might be.

\textbf{Practicality}

Problems can arise with the use of MOI\textsubscript{input} as a measure of phage dosing especially in the biocontrol of food microorganisms or when phages are used prophylactically. This is because bacterial contaminants under these circumstances tend to be present at fairly low densities.\textsuperscript{22,30} Especially when bacteria are present at low densities, then MOI\textsubscript{actual} will be more a function of phage density than of bacterial density (references 1,10,13,30 and above). Thus, with a \textit{fixed} MOI\textsubscript{input} – where arriving at some optimal and thereby somewhat fixed MOI\textsubscript{input} presumably is one purpose of calculating phage therapy dosing based on MOI\textsubscript{input} – then more phage particles would be added the more \textit{bacteria} that are targeted. The result, paradoxically, can be greater rates of phage-mediated killing of individual bacteria the greater the densities of bacteria that are targeted, even ignoring expectations of increased rates of phage replication when host bacteria are more plentiful.\textsuperscript{4}

A second practical issue is an obscuring of the minimum density of added phages that are required to achieve antibacterial efficacy, such as to achieve a bacteria-killing inundation threshold that is independent of phage’s potential to replicate.\textsuperscript{4,12,13} That is, what that threshold might be may be obscured were it to be inadvertently exceeded as a consequence of changes in the density of target bacteria, again while holding MOI\textsubscript{input} constant. For example, if a fixed ratio of 100:1 added phages to bacteria is employed, then in principle one could see greater per-bacterium likelihood of bacteria killing starting with $10^6$ bacteria/ml rather than $10^4$ bacteria/ml since $10^8$ rather than $10^6$ phages per ml would be applied, respectively, or a mere $10^4$ phages/ml given a bacterial challenge of only $10^5$ bacteria/ml, e.g., such as to food. In other words, if basing dosing on a constant MOI\textsubscript{input}, then when more target bacteria are present the densities of added phages could come to exceed bacteria-killing inundation thresholds without our necessarily being aware, from a phage dosing perspective, that in fact this has occurred. Greater potential to kill bacteria specifically because bacteria are more common, of course, is completely counter to standard antimicrobial practice where lower rather than higher starting densities of target organisms generally are desired, such as when dealing with foodborne pathogens or contaminated wounds. Here, however, this contradiction would occur because of an \textit{implicit} raising of antibacterial dosing, an approach which would be inconsistent with typical pharmacological practice.

A third practical issue is that only after establishing a consistent bacteria-infecting efficiency for a given phage-addition protocol, under well controlled conditions,\textsuperscript{21} may an often well-qualified MOI\textsubscript{input} be legitimately employed as a description of phage dosing. This is because only then can one have some reasonable sense of how fast phages are reaching bacteria.
This assertion should come as no surprise since it is standard practice, before use, to normalize indirect estimations, such as MOI_input, e.g., as when using culture turbidity as a gauge for bacterial viable counts. In addition, it can be necessary to modify even well-established normalizations whenever experimental conditions have been modified. Thus, if there is an indication that conditions have changed – such as when going from in vitro-determined rates of phage adsorption to novel in situ conditions in the course of phage therapy – then estimations of MOI_actual that are based on MOI_input should be assumed to be suspect.

Presumably, that is, a second goal of employing MOI estimations during phage therapy is toward appreciation of the number of phages that directly affect individual bacteria. For multiple reasons, however, MOI_input can be a poor predictor of that number. So too, it should be added, can phage titer, but at least with titer the only explicit claim being made is one of numbers of phages.

**Conclusions**

Phage titers are readily measured and to a degree controllable in the course of phage dosing. In addition, phage titer, at least at the point of phage application, is less of a function – unlike MOI – of other parameters such as duration of phage exposure, phage adsorption rate constant, or bacterial density. Furthermore, if presented solely in terms of MOI, then after-the-fact dosing calculation in terms of titers, that is, numbers of phage virions per some unit volume, requires knowledge by readers of bacterial densities, which in many cases can be difficult to ascertain from published methods. Indeed, what I primarily look for in phage therapy reports are (1) phage doses applied (in volumes and titers, or, for systemic application, instead per-animal and/or per-kg absolute numbers), (2) how often phages are applied, (3) where and how phages are applied, (4) time delays between bacterial challenge and phage application, and then (5) clinical, microbiological, and toxicological results.

Unless it can be shown that most added phages are adsorbing, that most target bacteria are equivalently phage susceptible, and that densities of target bacteria are knowable more or less in real time, then reliance solely on MOI_input as a measure of phage dosing can serve, at best, as a means of representing relative numbers of phages applied to bacteria. Often, furthermore, the result is an obscuring of actual phage doses. Description of dosing in terms of phage titers readily indicates relative dosing as well, but without such obfuscation. Dosing in terms of phage titers also is more standard from a pharmacological perspective, allows greater ease of comparison between studies, and more readily translates to phage dosing during real-world implementation of biological control or phage therapy. In short, the titers and volumes of phage formulations used should, if at all possible, always be provided when reporting the methods of phage therapy studies. Consistently, in my opinion, MOI, whether as MOI_input or MOI_actual should never be used as the sole measure of phage dosing in phage therapy experiments.

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