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The Infectious Dose of Variola (Smallpox) Virus

Mark Nicas, Alan E. Hubbard, Rachael M. Jones, and Arthur L. Reingold

University of California—Berkeley, Berkeley, California

Abstract

Quantitative estimation of an individual's risk of infection due to airborne pathogens requires knowledge of the pathogen's infectious dose, in addition to estimates of the pathogen's airborne concentration and the person's exposure duration. Based on our review of the published literature on poxvirus infection, we conclude that the infectious dose of variola (smallpox) virus is likely one virus particle and that infection can be initiated in either the upper respiratory tract or pulmonary region. Studies of airborne transmission of poxvirus in monkeys and rabbits show that primary infection can occur in both regions of the respiratory tract. A quantitative study of poxvirus inhalation transmission in rabbits indicates that the deposition of one pock-forming unit (PFU) carried on respirable particles can cause infection. Findings in both in vitro *and* in vivo *studies of the number of virus particles comprising a PFU are consistent with a "one-hit" phenomenon—namely, the cellular uptake of just one virus particle can lead to infection of a cell or an area of cell growth, creating a pock (an infected area of cells). Variability in virulence among different virus strains may involve differences in the probability of infection per virus particle, where a highly virulent strain has a probability close to one of successful infection for each virus particle. In an analogous manner, variability in susceptibility to the same virus strain among different hosts may involve differences in the probability of infection per virus particle across different hosts.*

Introduction

Individuals with smallpox, caused by the variola virus, can transmit the infection through the air. The inhalation route was convincingly demonstrated by a nosocomial outbreak in Meschede, Germany, in 1970. A smallpox patient confined to an isolation room infected 17 individuals via airborne transmission, including one person who was present in the building lobby for only 15 minutes (Wehrle, Posch, Richter, & Henderson, 1970). Smoke tests confirmed patterns of air currents that moved from the source case's room through the interior of the hospital, as well as air currents that moved up the exterior of the building and entered patient rooms on the upper two floors of the building. This outbreak demonstrated that infection can occur without close contact. Moreover, given the tremendous dilution of the airborne virus concentration as virus-containing particles moved away from the emission point, the outbreak implies a low infectious dose for smallpox virus.

In recent discussions concerning smallpox and bioterrorism, the airborne transmission route has been deemphasized in favor of droplet transmission. This latter route involves the direct spraying of large respiratory particles via coughing and sneezing onto conjunctivae and mucosal membranes. The Centers for Disease Control and Prevention (CDC) states the following in its Smallpox Response Plan and Guidelines (version 3.0) (CDC, 2003):

> The most frequent mode of transmission is person-to-person spread via direct deposition of infective droplets onto the nasal, oral or pharyngeal mucosal membranes or in the alveoli of the lungs from close, face-to-face contact with an infectious individual. Indirect spread (not requiring face-to-face contact with an infectious individual) via fine-particle aerosols or fomites has been reported but is less common.

While the CDC recognizes that inhaling virus-containing respirable particles can cause infection, we note that droplet transmission implies that inhaling nonrespirable particles carrying virus can also cause infection. That is, particles up to 100 μm in diameter can be inspired and deposited in the upper respiratory tract. If a 100 μm particle carrying smallpox virus can be sprayed into the nose or mouth and cause infection, it follows that the inhalation and upper respiratory tract deposition of the same particle can also infect.

In determining procedures to control airborne infection, it is useful to quantitatively estimate infection risk, if possible, where risk depends on the pathogen's infectious dose and airborne concentration, and the duration of exposure. In this regard, Nicas, Nazaroff, and Hubbard (submitted) developed an exposure model to estimate the risk of person-to-person airborne infection due to pathogens emitted in a respiratory aerosol, and used the model to explain how both respirable and nonrespirable particles could be involved in transmitting pneumonic plague (caused by *Yersinia pestis* bacilli) if the infectious dose were low. In this paper, we argue that the infectious dose of variola virus is low, just one virus particle, and that infection can be initiated in either the upper respiratory tract or pulmonary region. Therefore, it is logical that airborne smallpox transmission does not require close contact. Exposure within 1 m of a source case can lead to infection due to inhaling both respirable and nonrespirable particles carrying the pathogen, while exposure at greater than 1 m leads to infection likely due to inhaling respirable pathogens only.

Background and Poxvirus

The genus *orthopoxvirus* contains a number of morphologically identical viruses, including variola virus, vaccinia virus, and animal-associated poxviruses such as cowpox, all of which show extensive serological cross-reactivity and cross-protection in animals; they also share a large DNA segment in their genomes (Fenner, Wittek, & Dumbell, 1989). Variola virus, now eradicated in the human population (Fenner, Henderson, Airta, Jezek, & Ladnyi, 1988), included a variety of strains that arose in geographic isolation but had two primary phenotypes: (1) variola major, which produced a case fatality rate of 5% to 40%, and (2) variola minor, which produced a case fatality rate of 0.1% to 2%. The origin of the vaccinia virus, which is used for making smallpox vaccine, is in dispute, although all hypotheses are variations on the theme of attenuation or alteration of variola virus and/or cowpox virus as a result of serial passage in humans and animals (Fenner, Wittek, & Dumbell, 1989).

Much of the informative laboratory work with regard to infectious dose of poxvirus has been done with vaccinia virus, which introduces concern about extrapolating results from vaccinia virus to variola major virus. The virology literature considers vaccinia virus to be the prototypical *orthopoxvirus* and does not explicitly discuss the comparability of vaccinia with variola major. However, there are two lines of evidence that suggest similar infectivity. First, studies with different species and strains of poxvirus show similar ratios between the concentration of viral particles as counted by microscopy and the concentration of infectious units as assayed by pock formation (Table 1). Second, the variable segments of poxvirus DNA, which are located at the strand termini, are found to be associated with virulence and host range but not with infectivity (Bloom, Edwards, Hager, & Moyer, 1991; De Silva & Moss, 2003). This observation suggests that infectivity is conserved across *orthopoxvirus* species.

Throughout this paper, the term *infectious unit* is used to denote the smallest number of virus particles needed for infection under the conditions of the assay. The number of infectious units per volume is a standard measure of activity or titer for a virus inoculum (Luria, Williams, & Backus, 1951). For poxvirus, an infectious unit has traditionally been equated with a pock-forming unit in the chick chorioallantoic membrane assay (CAM) or a plaque-forming unit (PFU) on a cell culture layer. *Infection* refers to viral uptake by a cell that leads to pock or plaque formation. In some cell culture assays where plaque formation is not reported, viral DNA proliferation is a surrogate marker of infection.

Table 1
Infectivity of *Orthopoxvirus*

Virus Particles per Infectious Unit	Virus Type	Assay System	Virus Counting Method	Reference
7.5-40	Cowpox (red)	Rabbit Dermis	EM	(Dumbell, Downie, & Valentine, 1957)
9.6-27	Cowpox (white)	Rabbit Dermis	EM	
37-167	Cowpox (red)	CAM Egg	EM	
44-170	Cowpox (white)	CAM Egg	EM	
366	N. Carolina rabbit adapted Vaccinia	Rabbit Dermis	Nitrogen content and Turbidity	(Sprunt, Marx, & Beard, 1940)
41.9	Vaccinia	Rabbit Dermis	Light Microscopy	(Parker & Rivers, 1936)
16-500	N. Carolina egg adapted Vaccinia	Guinea Pig Dermis	EM	(Overman & Sharp, 1959)
16-79	N. Carolina egg adapted Vaccinia	Rabbit Dermis	EM	(Overman & Sharp, 1959)
12.3-27	Downie Vaccinia	CAM Egg	EM	(Dumbell, Downie, & Valentine, 1957)
12	Vaccinia	L cell	Tritium labeling	(Dales, 1963)
10.9-18.6	Tissue Vaccinia	CAM Egg	EM	(Kaplan & Valentine, 1959)
10.6	WR Vaccinia	L cell	EM	(Galasso & Sharp, 1964)
8.3-25	Downie Vaccinia	Rabbit Dermis	EM	(Dumbell, Downie, & Valentine, 1957)
4.2 (2.4-9.2)	CL Vaccinia	Rabbit Dermis	Virus Dry Weight	(Smadel, Rivers, & Pickels, 1939)
3.4-22.5	LC Vaccinia	CAM Egg	EM	(Kaplan & Valentine, 1959)
3.4-8.9	N. Carolina calf lymph Vaccinia	CAM Egg	EM	(Overman & Sharp, 1959)
1.2-10.7	RV Vaccinia	CAM Egg	EM	(Kaplan & Valentine, 1959)
0.66 (0.5-1)	NY Calf Lymph Vaccinia	CAM Egg	EM	(Overman & Tamm, 1956)

Experimental Airborne Infection

A series of documented smallpox outbreaks have demonstrated person-to-person airborne transmission, including the previously described outbreak in Meschde, Germany (Wehrle, Posch, Richter, & Henderson, 1970), but few studies have investigated the infectious dose via airborne transmission. Poxvirus has been transmitted by inhalation exposure involving investigator-generated poxvirus aerosol or respiratory aerosol emitted by infected animals. Hahon (1961) reported that four species of monkeys—*Macaca cynomolgus,* M. *irus,* M. *rhesus,* and *Saimiri sciureus*—are susceptible to infection via inhaling variola virus aerosol, resulting in generalized exanthem without local lesions. In a study of the pathogenesis of variola virus infection in *M. irus* following airborne exposure, Hahon and Wilson (1960) isolated virus from the nares, nasopharynx, trachea, and lungs. The investigators concluded that the lungs were a primary site of infection because virus multiplication in the lungs followed a typical growth curve. However, primary infection in the trachea of *M. irus* is possible; generalized exanthem was observed in monkeys inoculated in the trachea with 15 infectious units (Hahon & Wilson, 1960). *M. irus* is also sus-

ceptible to infection via inhaling vaccinia virus, which results in ulcerations and inflammation in the bronchiole region, in addition to viral pneumonia (Hahon, 1961).

Airborne transmission of rabbit poxvirus was demonstrated by Bedson and Duckworth (1963), who found that 3 of 9 test rabbits held in cages separated from infected rabbits became infected with rabbit poxvirus after 24 hours of exposure. The investigators also found that even when test rabbits were caged together with infected rabbits for 12 or 24 hours, resulting infections occurred via inhalation. Rabbit poxvirus was found in the upper and lower respiratory tract of 18 of 19 cross-infected test rabbits examined 2 to 7 days post exposure. Among rabbits examined 2 to 4 days post exposure, 11 of 12 had virus present in the respiratory tract, while only 4 of 12 rabbits had virus in their livers. These experiments demonstrate that initial infection can occur either in the upper or lower respiratory tract. In humans, the former site involves the deposition of nonrespirable particles with diameters in the 10 μm to 100 μm range, and the latter site involves the deposition of respirable particles having diameters <10 μm.

The only study to quantify the airborne infectious doses of poxvirus was performed by Westwood et al. (1966) using Downie's vaccinia virus strain and the Utrecht rabbitpox strain. Rabbits were exposed to the virus in the form of a cloud of dry particles generated by the Henderson apparatus; it was reported that 98% of the aerosol particles were less than 1 μm in diameter. Dose was calculated as the number of PFUs inhaled based on the time of exposure, the estimated breathing rate, and concentration of PFUs in the cloud. The lowest estimated inhaled dose of vaccinia virus was 4 PFUs, which produced infection in 3 of 3 rabbits. The lowest estimated inhaled dose of rabbit poxvirus was 7 PFUs, which produced infection in 7 of 7 exposed rabbits. The investigators noted that studies in monkeys and guinea pigs indicate that only 25% of inhaled respirable particles are retained in the lungs. In turn, this deposition fraction implies that the infectious dose of vaccinia virus was 1 PFU, and less than 2 PFUs for rabbit poxvirus.

Overall, the experimental inhalation studies demonstrate that poxvirus infection can be initiated in the upper and lower respiratory tract as a result of investigator-generated aerosol exposure and animal-to-animal transmission. Further, a single PFU (as operationally defined in the CAM assay) appears capable of producing infection through the airborne route. The number of virus particles comprising the infectious unit is now examined.

Studies of the Infectious Unit

The numerical value of an infectious unit has been estimated using a variety of virus types, strains, counting methods, and culture methods as shown in Table 1. As expected, due to variation in the methods used (e.g., varied strain virulence, adaptation to the host (Overman & Sharp, 1959), virus disruption due to experimental methods (Dales, 1963), topographical effects of host cells (Abel, 1962), and variance in the virus and pock or plaque counts), a range of estimates has been reported. Only Parker and Rivers (1938) and Sprunt, Marx, and Beard (1940) reported a count of vaccinia virus per infectious unit that did not include 20 virus or less. Both of these studies, however, had methodological limitations. In particular, Parker and Rivers (1936) were unable to purify virus solutions sufficiently to permit accurate counting (Parker, Bronson & Green, 1941), while Sprunt, Marx and Beard (1940) used observations on vaccinia virus made by other researchers with different virus strains. In addition, the large range observed by Overman and Sharp (1959) with vaccinia virus on rabbit and guinea pig dermis is qualified by two observations. First, the investigators did not use vaccinia virus adapted to these hosts, and second, guinea pigs are particularly resistant to vaccinia virus infection. Neglecting the aforementioned studies, Table 1 indicates that most investigators found that one infectious unit of vaccinia virus is associated with 10 virus particles.

On its face, an activity level of 1:10 is consistent with two alternative models. Model I assumes that 10 active virus particles must be taken up by a cell to cause infection, and is termed a "10-hit" phenomenon. Model II requires just one virus particle to be taken up by a cell to cause infection, but assumes that only 10% of the virus particles are active and capable of replication and infection; in the alterna-

tive, Model II permits 100% of virus particles to be active, but assigns each virus a 10% probability of success at infecting the cell. Model II is termed a "one-hit" phenomenon.

Model I is algebraically described as follows. Let μm denote the average number of virus particles encountered by a cell. The integer number of virus particles encountered is treated as a Poisson random variable with mean μm, such that the probability that n virus are encountered is: $[(\mu_N)^n \exp(-\mu_N)] \div n!$ The probability that a cell is infected is the complement of the probability that the cell encounters fewer than 10 virus particles:

Equation (1) $$\Pr(\text{Infection}) = 1 - \sum_{n=0}^{9} \frac{(\mu_N)^n \exp(-\mu_N)}{n!}$$

In contrast, Model II assumes that only one virus particle is necessary for infection. Let $p = 0.1$ denote the proportion of virus particles that are active and able to infect, or in the alternative, the probability of successful infection per virus particle. The probability that a cell is infected is:

Equation (2) $$\Pr(\text{Infection}) = 1 - \exp(-p \times \mu_N)$$

Although the alternative constructs for Model II are biologically distinct, they are mathematically equivalent as outlined in Appendix I. Note that the virulence of a virus strain might involve the value of the parameter p, and in addition, the value of p might also vary across hosts. Different *in vitro* and *in vivo* experiments indicate that Model II, the one-hit phenomenon, is the appropriate descriptor for variola virus infection.

In Vitro Studies

Galasso and Sharp (1963; 1964) investigated the yield of vaccinia virus in L-cell cultures. Based on the steep slope of the virus particle growth curve, they reported that an inoculated dose of 10 virus particles per cell seemed to infect all cells, though they did not explicitly report the percentage of cells infected. If the average dose of virus particles per cell was 10, then by Poisson probabilities, about 54% of cells should have received 10 or more virus, and about 46% should have received 9 or fewer virus. Although these percentages are not exact for a finite number of virus added to a finite number of cells, they indicate that only about 50% of cells should have encountered sufficient virus to be infected per Model I, not the approximate 100% of cells observed. Given an average dose of 10 virus particles per cell, only 0.045% of cells should have encountered no virus particles. Therefore, the observation that practically 100% of cells were infected is more consistent with the infectious unit being one or two virus particles, not 10 virus particles.

A serial dilution experiment can easily distinguish between Models I and II. Consider that an average dose of 10 virus particles per cell is delivered. Based on the 10-hit process (Model I), the expected percent of cells infected is 54%. Based on the one-hit process with $p = 0.1$ (Model II), the expected percent of cells infected is 63%. Given the inherent variability in experimental methods, these two percentages might be difficult to distinguish. Now, decrease the dose of virus delivered to an average of one virus particle per cell. The expected percent of cells infected decreases to 9.5% based on Model II, but decreases to .00001% based on Model I. Although these exact percentages would not be observed experimentally, they should be distinguishable. Further, at average virus doses less than 0.5 per cell, Equation (2) predicts an approximate linear relationship between the proportion of cells (or cell growth areas) infected and the average dose of virus per cell.

In this vein, Abel (1962) performed a series of experiments looking at the proportion of cells that scored as infective centers, which signifies that virus particles penetrated and replicated in the cells. For rabbit poxvirus in KB-cells, the proportion of cells scoring as infective centers was 90% at an average dose of 10 virus particles per cell, and 40%, 3%, and 0.3% for average doses of 1, 0.1, and 0.01 virus particles per cell, respectively. When the same assay was performed with rabbit poxvirus on chick embryo fibroblast cells, the proportion of infected cells was 30%, 9.4%, and 0.16% with average doses of 5, 1.25, and 0.15 virus particles per cell, respectively. These results are more consistent with Model II. An approximate linear relationship was also observed by Hahon (1965) with the Yamada strain of variola vi-

rus on McCoy cells, and by Postlethwaite (1960) with the Lister strain of vaccinia virus on chick embryo cells.

The results of Cairns (1960) further support Model II. Fluorescein-coupled viral antibodies and autoradiography were used to image sites of viral synthesis in KB-cells infected with the VMA strain of vaccinia virus. When virus was introduced at a dose of 0.03 virus particles per cell (with the dose estimated from the number of cells infected with dilute inocula), nearly all cells showed a single site of viral synthesis. Cairns (1960) occasionally observed pairs of closely adjacent sites that may have resulted from multiple infections due to a clump of virus particles. Given an average dose of 0.03 virus particles per cell, the Poisson probability that 10 or more viruses infected a single cell is on the order of 10^{-22}.

As described by Cairns (1960), poxvirus infection is a three-phase process: (1) viral penetration into the cell, (2) initiation of cellular preparation, and (3) viral DNA replication. Penetration of poxvirus occurs through phagocytosis (Dales, 1963), and initiation is thought to involve viral uncoating (Joklik, 1962). Cairns reported that the effect of multiple sites of viral synthesis in a cell (presumably due to infection by multiple virus particles) was to increase the synchronicity of viral replication, but not to decrease the lag time until replication began. Cairns interpreted this observation to mean that the length of the second phase (the initiation of cellular preparation) is fixed, but that multiple virus penetration decreases the lag time until cellular preparation is initiated. Once cellular preparations had been initiated, all virus particles begin replication at the same time. This overall sequence is consistent with infection by a single virus particle.

Cairns would perhaps dispute the application of the Poisson model to his data, as he found that the proportion of cells showing viral DNA synthesis at different times subsequent to virus introduction was not strictly compatible with a Poisson distribution. However, the deviation from the one-hit model was apparently small, because it is not discernible in the graphically displayed data in Cairns' (1960) paper.

In Vivo Studies

The one-hit model for poxvirus infection was first suggested by Parker (1938), who examined the distribution of positive dermal lesions produced by intradermally inoculating rabbits with serial dilutions of three strains of vaccine virus. Parker found the distribution of positive lesions was more consistent with a one-hit phenomenon than with an infection process requiring two or more virus particles per positive lesion.

Bryan and Beard (1940) argued that Parker had actually observed a distribution in the host response, which coincidentally led to results fitting a one-hit model. However, host susceptibility was examined by Parker et al. (1941), who titrated vaccinia strains of different virulence in the rabbit dermis, mouse cerebrum, guinea pig dermis, and CAM systems. When the positive lesions in a group of animals were summed across animals, results with a high virulence strain (New York Board of Health strain) best fit the one-hit model. Titration with the moderate virulence CVII strain in mice after intracerebral inoculation showed no discernible relationship between virus concentration and infection. Results for the moderately virulent strain deviated from the one-hit model, such that the infectious unit was found to comprise more virus particles than observed with the more virulent strain. The experiments with the moderately virulent strain, however, were also inconsistent with the multi-hit infection process, because the percentage of positive lesions did not decrease rapidly with dilution, as predicted by Model I.

To investigate variation in susceptibility among hosts, Parker et al. (1941) examined the frequency of positive lesions in multiple test sites on individual animals. They found that while the number of virus particles producing a 50% infectious dose (i.e., 50% of the test sites on an animal showed lesions) varied between rabbits, the distribution of lesion counts across test sites within each rabbit best fit the one-hit model for strains of moderate (CVII) and low (CVI) virulence. Similar conclusions were reached by Sprunt and McDearman (1940), who observed that pseudopreganant and castrated rabbits receiving estrogenic hormones were more resistant to vaccinia virus than castrated and normal males, but that among both resistant and less-resistant animals, the distribution of positive lesions best fit the one-hit model. These investigators concluded that a single virus particle can infect, provided that it reaches a susceptible cell, but that a particle's chance of reach-

ing a susceptible cell in a resistant animal is less by a constant proportion than in a susceptible animal (Sprunt & McDearman, 1940). This idea is consistent with Model II if the parameter p varies between hosts. Further evidence for this conclusion is provided by Galasso and Sharp (1964) who observed no difference between the quality of virus that remained unadsorbed to cells following inoculation of a cell culture, and the quality of virus in the original inoculum. This result suggests that all virus particles (adsorbed versus unadsorbed) are viable.

The one-hit model has also been tested by observing the relationship *in vivo* between the frequency of pocks (synonymous with the term plaques) and serial dilutions of virus concentration. Again, Equation (2) indicates that at low virus doses per cell or per area of cell growth, one should observe an approximately linear relationship between the number of pocks and the average dose of virus delivered (Dulbecco & Vogt, 1954); were two or more virus particles required for infection, the frequency of pocks or plaques would appear as an approximate power relationship. An approximately linear relationship was observed by Slonim et al. (1967) with Czechoslovak vaccine virus on CAM and by Westwood et al. (1957) with Downie's strain of vaccinia virus on CAM.

Conclusions

On balance, we believe there is adequate *in vitro* and *in vivo* evidence that infection can be produced by a single particle of variola virus. Across different experimental systems the number of poxvirus per infectious unit has been found to vary, but it appears that favorable conditions enable all virus particles to infect (Overman & Tamm, 1956; Parker, Bronson, & Green, 1941; Sprunt & McDearman, 1940). Further, we see no biologically plausible reason that the one-hit model would not apply to inhaled virus. Conditions in the upper or lower respiratory tract may increase or decrease the probability that a given virus particle initiates a focus of infection, but infection is possible in either region. Primary infections have been observed in the upper and lower respiratory tracts of monkeys (Hahon & Wilson, 1960) and rabbits (Westwood, Boulter, Bowen, & Maber, 1966). A rabbit inhalation study found that 3 of 3 rabbits were infected by an estimated deposited dose of 1 PFU of vaccinia virus (Westwood, Boulter, Bowen, & Maber, 1966). We also note that the one-hit model has been applied to other mammalian viral infections including waterborne human gastrointestinal viruses (Teunis, van der Heijden, vander Giessen, & Havelaar, 1996) and poliomyelitis virus in monkey cell culture (Dulbecco & Vogt, 1954).

Given a specified infectious dose for variola virus, it is possible to estimate smallpox infection risk due to person-to-person transmission of virus in emitted respiratory aerosol, and due to virus-containing materials aerosolized by normal laboratory handling procedures or by accidents. The risk of person-to-person airborne infection is a multivariable function involving the virus concentration in respiratory fluid, the expiratory event rate, the size and volume distribution of the particles emitted per expiratory event, the receptor's breathing rate and exposure duration, and the receptor's location in the room relative to the source case (Nicas, Nazaroff, & Hubbard, submitted). The risk of laboratory airborne infection involves the virus concentration in the materials being handled, the size and volume distribution of the aerosolized particles, and the receptor parameters of breathing rate, exposure duration, and location relative to the aerosol release. Admittedly, nearly all these inputs are uncertain; in particular, we have found no published data for the concentration of variola virus in respiratory fluid. Due to uncertainty in the input parameters, the numerical risk estimates are also uncertain. At the same time, even uncertain risk estimates permit categorization of exposure scenarios as "relatively low" risk versus "relatively high" risk, and thereby inform biosafety officers in their decision-making about infection control procedures for health care workers and laboratory personnel.

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Appendix I

The Mathematical Equivalence of Two Constructs for the One-Hit Model

Assume that a fraction f of virus particles are active, and that if an active virus particle encounters a cell, the probability is one that the virus will be taken up by the cell, replicate, and cause a focus of infection. Let μ_N denote the average number of virus particles encountered by a cell, such that the expected number of active virus particles encountered by a cell is $f \times \mu_N$. The integer number of active virus particles encountered by a cell is a Poisson random variable with mean $f \times \mu_N$. The probability that at least one active virus particle encounters a cell, which case infection ensues, is the complement of the probability that no active virus particles encounter a cell. Therefore, the probability that a random cell is infected is:

Equation (A1)
$$\Pr(\text{Infection}) = 1 - \exp(-f \times \mu_N)$$

In the alternative, assume that all virus particles are active, and that each has probability p of being taken up by a cell, replicating, and causing a focus of infection. Consider a cell that encounters n virus particles. The probability that none of the virus particles infect the cell is $(1 - p)^n$, in which case the conditional probability of infection is the complement: $1 - (1 - p)^n$. Given that μ_N is the average number of virus particles encountered per cell, the probability that the cell encounters n virus particles is the Poison probability $[(\mu_N)^n \exp(-\mu_N)] \div n!$ The unconditional probability that a cell is infected is found by summing over all values of n:

Equation (A2)
$$\Pr(\text{Infection}) = 1 - \sum_{n=0}^{\infty}(1-p)^n \frac{(\mu_N)^n \exp(-\mu_N)}{n!}$$

The sum term on the right-hand side of Equation (A2) is simplified as follows. The constant $\exp(-\mu_N)$ is brought outside the sum, and the terms $(1 - p)^n$ and $(\mu_N)^n$ are combined:

Equation (A3)
$$\sum_{n=0}^{\infty}(1-p)^n \frac{(\mu_N)^n \exp(-\mu_N)}{n!} = \exp(-\mu_N)\sum_{n=0}^{\infty}\frac{[(1-p)\times\mu_N]^n}{n!}$$

The sum term on x the right-hand side of Equation (A3) is the Taylor series expansion around zero of the function $\exp((1 - p)^n \times \mu_N)$. Therefore:

Equation (A4)
$$\sum_{n=0}^{\infty}(1-p)^n \frac{(\mu_N)^n \exp(-\mu_N)}{n!} = \exp(-\mu_N)\times\exp((1-p)\times\mu_N) = \exp(-p\times\mu_N)$$

This identity is substituted into the right-hand side of Equation (A2):

Equation (A5)
$$\Pr(\text{Infection}) = 1 - \exp(-p \times \mu_N)$$

It follows that if the values of f and p are the same, Equations (A1) and (A5) are identical.