Occupational Immunity and Natural Vaccination

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People who work with animals are frequently exposed to dangerous pathogens. Disease and subsequent immunity may result. Alternatively, occupational exposure to animals may lead to natural vaccination: the acquisition of immunity in the absence of overt disease. We use anthrax, Q fever, Campylobacter and influenza to illustrate aspects of dose, route and frequency of exposure that may be particularly favorable to natural vaccination. We then explore how exposure and immunity in those who work with animals provide clues about the epidemiology of emerging infectious diseases.

Emerging infectious diseases arise from zoonotic pathogens that transmit from animals to humans. The most obvious recent zoonotic threat to human health comes from avian influenza. But the potential for zoonotic assault spans a wide array of pathogens including SARS, Ebola, anthrax, HIV, monkeypox, and the diverse bacteria of common farm animals that sometimes cause severe enteric or neural damage in humans. Zoonotic pathogens are also among the most commonly listed agents for use as bioterror weapons.

Yet, for all the threat that zoonotic pathogens pose to humans, there are entire working classes of people who are frequently and in some cases continually exposed to zoonotic agents, including veterinarians, farmers, ranchers, tanners, and food processors. These people usually make it through the working day without incident, or so it seems. Perhaps frequent zoonotic exposure and relatively rare disease per exposure occur because successful infection is rare. But in some cases, natural vaccination may arise by infection
and subsequent acquisition of immunity in the absence of overt disease. Such immunity would alter the dynamics of infection and the spread of disease in the first line of contact with zoonotic pathogens.

We searched the literature on occupational exposure to zoonotic pathogens. We found surprisingly few reports about the patterns and mechanisms of exposure and the consequences for immunity. Because occupational exposure may be the primary source of many emerging infectious diseases, there is great need for more information about this subject. In this paper, we develop a conceptual framework to clarify what we need to know about the sporadic exposures at the source of emerging infectious disease. We use three key questions to organize the observations and concepts.

First, do occupational exposures to zoonotic pathogens actually lead to higher levels of immunity than observed in the rest of the population? For example, veterinarians encounter more zoonotic pathogens than the average individual. But do they show serological evidence that they have been infected by, and developed immunity to, those pathogens?

Second, if occupationally exposed individuals show higher levels of immunity to zoonotic pathogens, was that immunity more likely to have been acquired by illness or by subclinical infection? If occupational exposure leads to illness, the resulting immunity would not be considered, by our definition, natural vaccination.

Third, are particular aspects of exposure, such as dosage, route of inoculation, or frequency of exposure, more likely to cause in subclinical (asymptomatic) infection with resulting immunity (natural vaccination) as opposed to disease? If the answer to the third
question is yes, it might be possible to utilize these mechanisms in the prevention of zoonotic disease.

We develop four case studies. Anthrax is an occupational hazard historically confined to ranchers and tannery workers, but has recently posed challenges to postal workers and hazardous material crews. Q fever is a bacterial disease transmitted from cattle, sheep and goats. *Campylobacter jejuni* is a zoonotic bacterial pathogen that causes a significant fraction of infections leading to severe gastroenteritis. Influenza A transmits from wild birds to domestic animals, presenting an occupational threat to the farmers, veterinarians and others who work with these animals.

Each case illustrates some of the key attributes of occupational immunity and natural vaccination. Infection occurs by various routes, and the route of infection usually influences the severity of disease. Dosage varies and may be related to the route of infection, influencing whether subclinical or full-blown disease results. The frequency of exposure differs by occupation and may cause variation in the boosting of immunity. From these varied observations, we paint a picture of occupational exposure, illness and immunity.

Overall, we conclude that, for some diseases, natural vaccination probably occurs frequently, but that zoonotic pathogens differ in the amount of immunity they induce and in the pathways by which such immunity develops. We believe that the consequences of different routes of infection have been particularly neglected \(^1\). Further study of this topic will provide insight into the frequency of natural vaccination in those subpopulations most at risk for zoonotic infection, who form the front line in the spread of emerging infectious diseases.
Anthrax

Anthrax is caused by *Bacillus anthracis*, a bacterium that typically infects grazing animals such as cattle, sheep and goats. Infection by *B. anthracis* can occur through inhalation of spores from infected animals or animal products such as hides, by cutaneous infection from handling these products, or by ingestion of undercooked meat. Prompt treatment with antibiotics generally cures anthrax. Untreated inhalational anthrax has a mortality rate above 50%; gastrointestinal and cutaneous cases cause much lower mortality rates. Thus the route by which infection occurs greatly affects disease outcome.

There are few infected animals today in the developed industrial nations. Most recent exposure to anthrax in the US resulted from bioterrorism by spore-laden letters that infected mail recipients and postal workers. Recent outbreaks in bison and cattle in Canada arose from anthrax spores, which can live in the soil for many years; such outbreaks pose risk to ranchers and disposal crews. Rare sporadic inhalational cases develop from a variety of sources, such as exposure to spore-laden cow hides imported from Africa for constructing drums.

In developing countries, most inhalational cases are similar to those reported recently in cattle processors in Kazakhstan, which arose from exposure to cattle infected by soil-borne spores from old outbreaks. Cutaneous and gastrointestinal cases are more common and occur sporadically in many developing countries (CDC web site).

Most information about occupational exposure to anthrax comes from studies in the US during the years 1900-1960. In several studies of animal hair and hide workers, the rate of disease was low in spite of continuous exposure to air-borne spores.
One study suggested that workers may have inhaled up to 510 spores per working day. Another study reported that a significant fraction of workers had spores in anterior nasal swabs and pharyngeal washings. In three mills, up to 66% of the surfaces of the animal material handled by the workers had spores, suggesting common skin exposure. This series of papers supports the idea that exposure among animal hide and hair workers was common, but that symptomatic inhalational disease was rare.

We now turn to our three questions about occupational exposure and natural vaccination. First, can occupational exposure to anthrax actually lead to immunity? The answer is yes; we discuss the evidence in conjunction with the next question.

Second, is there any evidence of subclinical infection by anthrax? made the strongest case for this point of view, based on their study of a goat hair processing mill in New Hampshire, USA, following an outbreak of inhalational anthrax in 1957. They measured antibody titers against the protective antigen of anthrax in unaffected workers during the three months following the outbreak.

divided workers into three classes: prior anthrax victims, vaccinated individuals, and unaffected individuals. Among eleven individuals who had symptomatic anthrax more than two years before testing, only two tested positive for antibody titers. In serial studies of cutaneous anthrax, four of five individuals reverted from detectable to undetectable antibody titers after three months. Only 15 of 33 vaccinated individuals had detectable antibodies. The vaccinated individuals were sampled just before a six-month booster shot was due. The rapid waning of antibody titers in prior cases and in vaccinated individuals supports the observation that protective immunity decays over the year following inoculation.
10's most interesting result concerns unaffected workers. Among those without symptoms, 11 of 72 had detectable antibodies. Those individuals with raised titers worked mainly in the regions of the factory with the highest air-borne concentrations of spores. Given that detectable antibodies appear to wane rapidly after infection, the 11 positive tests suggest a high frequency of subclinical infection or boosting of immunity by continual exposure. In addition, among 56 unvaccinated and unaffected individuals from three other processing plants, 8 had positive titers, among which 4 worked in the most intensively exposed part of the plant. To test for the possibility of false-positive reactions, samples of 242 unexposed individuals from a military base were included in the samples examined in the laboratory, without any labeling to distinguish exposed from unexposed individuals. None of the 242 unexposed samples yielded positive titers, suggesting that false-positive results must be very rare by the methods used, supporting the conclusion of subclinical infection.

From these results, 10 conclude: “Spontaneous recovery from inhalation anthrax has been reported 12, 13 and is common in cutaneous anthrax so that it seems possible that the disease may be manifested by lesions so minor as to go unnoticed but sufficient to cause a serologic response.”

Although 10 provides a convincing and well designed analysis of subclinical infection, no other study has ever turned up such clear evidence. Subsequent authors who focused on inhalational anthrax in industrialized countries tend to invoke or reject the importance of subclinical infection in a haphazard way, without significantly advancing the subject.

Third, do particular mechanisms of infection, such as route of inoculation, bias outcome toward subclinical infection or overt disease? Most studies of anthrax focus on
inhalational inoculation, because that route has the most severe symptoms. However, cutaneous anthrax is much more common than inhalational anthrax, and gastrointestinal anthrax also occurs frequently in developing countries. The relatively common routes of cutaneous and gastrointestinal inoculation may cause seroconversion and less severe symptoms—a potential form of natural vaccination.

In support of^{10}'s suggestion that cutaneous inoculation and subclinical infection may have played a role in the resistance of certain workers to the outbreak of inhalational anthrax in the goat hair processing mill, found direct evidence that cutaneous anthrax caused seroconversion for the protective antigen. Cutaneous symptoms can often be rather mild, with small skin lesions that heal without significant clinical consequences. It would be interesting to know how often animal workers get inoculations into cuts that induce or boost immunity without noticeable symptoms. Vaccine research supports the idea that cutaneous exposure can be protective: an epidermal patch protects laboratory animals against subsequent challenge by inhalational exposure.

Among gastrointestinal anthrax exposures, subclinical or mild and misdiagnosed cases likely occur, but few studies have focused on this problem. Seroconversion may occur in subclinical cases. Oral vaccines are considered a promising approach to inducing protective immunity to anthrax, which suggests that a better understanding of the effects of naturally occurring gastrointestinal exposure would be interesting.

In summary, some evidence supports mild or subclinical cases of anthrax by routes of infection that differ from the most severe inhalational form of the disease. Occupation or lifestyle likely influences the patterns of exposure and dosage by different routes. The main limitation with regard to occupational immunity and natural vaccination probably arises
from the short-lived course of protective immunity following exposure. Whether repeated boosting by continual exposure can maintain protective immunity remains an open question. More generally, we discussed anthrax because of the available evidence on alternative routes of infection with different consequences for disease. We suspect that other pathogens share anthrax’s variable consequences among routes of infection but also have longer-lasting immunity. If so, then natural vaccination may be a significant factor in the dynamics of some zoonotic infections. Our next case continues to build the circumstantial evidence in favor of this view.

**Q fever**

Immunity to anthrax wanes over time, whereas immunity after a bout of Q fever appears to be lifelong. Effective natural vaccination against anthrax may require repeated exposure; for Q fever, a single exposure is probably sufficient for natural vaccination to occur.

Q fever is a disease of humans caused by the zoonotic bacteria *Coxiella burnetii*. The primary reservoirs of *C. burnetii* are cattle, sheep and goats. Humans at risk of occupational exposure include veterinarians, meat processors, dairy workers and livestock farmers. Human infections vary in severity; about half of cases are subclinical. When symptoms do occur, infected individuals suffer fever, sore throat, chills, coughing, nausea, vomiting, diarrhea or chest pain. Mortality ranges from 1%-2%. Recovery results in immunity that is thought to be lifelong (CDC web site).

We now turn to our three questions. First, does occupational exposure to *C. burnetii* lead to more frequent infection than occurs in the rest of the population? Two studies suggest this is so. In a random sample of 583 people across geographic regions of Cyprus,
53% of individuals were reported as seropositive. Rural, semi-urban, and urban areas differed, with rates of 61%, 48%, and 34%, respectively, presumably because of greater exposure to animals in the rural regions. In particular, contact with sheep or goats increased risk by 80% 21. In the second example, 22 found seropositive reactions in 14% of 267 veterinarians in Japan, compared with seropositivity in 4% of 2003 blood donors and 5% of 352 medical workers. The methods to determine positive reactions varied between the above studies; the important results concern differences between geographic location or occupation within studies, rather than the absolute levels of seroprevalence. Both studies support the idea that people who are exposed to zoonotic pathogens are also being infected by them.

Second, are individuals occupationally exposed to C. burnetii more likely to be infected subclinically than those who became infected by a chance exposure? And third, do the mechanisms of infection, such as route and dose, differ between those who become infected subclinically and those who become clinically ill?

We found relatively little direct information about our second and third questions. Thus, even though Q fever poses a significant occupational hazard to a variety of human workers, we lack basic information about dose, route of infection, and severity of symptoms. There is, however, a substantial literature on various aspects of transmission and dosage that do help us to access the probability of natural vaccination in indirect ways. We first review the most common mode of Q fever transmission, inhalation, then follow with the less common routes of ingestion and tick-borne transmission.

It is widely believed that nearly all symptomatic human cases of Q fever arise from inhalation of bacteria 23-25. If occupational exposure involves frequent inhalation of small
doses of bacteria in the workplace, then natural vaccination instead of disease could result if disease symptoms occur more frequently at higher doses. A single inhaled bacterium is sufficient to initiate infection in both humans and guinea pigs. However, we found no studies that relate the number of inhaled bacteria to the severity of symptoms in humans. Dose-response studies have been done in guinea pigs, which appear to be a good model for the pathology of human infections. Humans and guinea pigs have similar dose-response curves for the time between inhalation and the onset of fever.

Infected guinea pigs by inhalation with six dose levels, increasing by factors of 10 from $2 \times 10^1$ to $2 \times 10^6$. All animals seroconverted, indicating infection with an immune response. The intensity of fever and pathology of the lungs, liver, and spleen, increased steadily with dose. At the lowest dose, almost no pathology was detected; at the highest dose, moderate pathology occurred in all tested tissues. These results suggest that low doses may often lead to subclinical or mild disease, whereas high doses may lead to severe cases.

Further clues about subclinical infection and the potential for natural vaccination come from studies of non-inhalational infections of Q fever. Human infections by *C. burnetii* can occur by ingestion of unpasteurized milk. Most evidence suggests that ingestion often leads to seroconversion but rarely to symptomatic disease, although the occurrence and severity of clinical symptoms by this route of infection remain open problems. Longitudinal serological studies of farm families or others who routinely drink unpasturized milk could help shed light on whether natural vaccination is occurring in these populations.

Ticks comprise the final route of infection discussed in the literature. Field surveys show that ticks often carry *C. burnetii*. In experimental settings, tick bites successfully
infect guinea pigs \textsuperscript{24}. Ticks could, therefore, be a source of human infection, but almost all discussion in the literature concludes that tick-borne transmission of Q fever to humans is rare. \textsuperscript{32} did find in two patients simultaneous bacteremia of \textit{C. burnetii} and the tick-borne pathogen \textit{Rickettsia conorii}, suggesting that tick-borne transmission of \textit{C. burnetii} may occur; similarly, \textsuperscript{33} found three patients simultaneously infected by these two bacteria. Thus, although tick-borne transmission is widely discounted in the literature and may indeed be rare, the actual evidence on this topic is rather limited.

We find these studies of tick-borne transmission intriguing because they suggest how occupational exposure via cutaneous inoculation might lead to natural vaccination against Q fever. Experimental transmission of \textit{C. burnetii} by ticks into guinea pigs shows that subcutaneous inoculation can be highly effective in causing infection. Various subcutaneous vaccination strategies provide good protection against subsequent challenge \textsuperscript{23, 24, 28}. In animals, killed bacteria provide effective vaccines \textsuperscript{23}, suggesting that cutaneous exposure to dead bacteria may produce or boost immunity.

Animal workers must often be exposed to bacteria through cuts in their skin. Among veterinarians and their assistants, scratches and bites from handling animals commonly occur \textsuperscript{34}. How often does accidental inoculation through skin cuts lead to infection and seroconversion? What is the dose-response relationship between cutaneous infection and the severity of symptoms? Can accidental cutaneous inoculation of dead bacteria lead to natural vaccination or the boosting of immunity induced by prior infection?

In summary, the necessary conditions for natural vaccination against Q fever may occur. Occupational exposure, infection and immunity occur frequently. Many infections are subclinical. But the relative extent to which exposure by different routes or doses leads
to illness versus subclinical infection remains unknown. Immunity without overt disease may be obtained occupationally by exposure via skin cuts and scratches. Cutaneous inoculation is in fact a common method of vaccination against many pathogenic organisms.

**Campylobacter jejuni**

Our third example is campylobacteriosis, an acute gastroenteritis caused primarily by *Campylobacter jejuni* 35. Campylobacteriosis is one of the most common causes of human diarrhea. Most infections result from handling or eating raw or undercooked poultry. Campylobacteriosis is an occupational hazard to meat processors. Non-occupational exposure occurs in the home during food preparation and in petting zoos. The risk of exposure is heightened by the fact that infected animals often exhibit no signs of illness (CDC web site).

This example particularly highlights the ways in which different routes of inoculation may influence the probability of subclinical infection following occupational exposure. We now turn to our three questions.

First, does occupational exposure lead to a higher level of immunity against *Campylobacter* than is observed in the rest of the population? Occupational exposure among food processing workers is associated with high antibody titers against *Campylobacter jejuni* 36. Only 2% of prenatal patients from Manchester, England and 5% of similar patients from more rural areas had detectable antibodies. By contrast, sampling detected antibodies in 27-68% of poultry workers from five different sites, 36% of workers exposed to cattle, and 18% of veterinary assistants. In a poultry abattoir, short-term workers employed less than one month had significantly lower levels of IgG antibodies against *Campylobacter jejuni* than did long-term workers 37.
It is not known whether detectable antibodies against *Campylobacter* indicate protective immunity. Various lines of circumstantial evidence suggest that infection yields protection against subsequent exposure. Experimental oral infections in animals and in human volunteers lead to increased antibody titers. Naturally occurring infections cause increased levels of specific IgG antibodies at one year post-infection. In developing countries, young children frequently harbor the bacteria, but disease is rare among those over two years of age, and antibody levels increase with age. mention that “It is anecdotal among poultry abattoir workers that during the first period of employment they suffer from episodes of diarrhoea. However, over time the number of diarrhoeal episodes apparently decreases, suggesting acquired immune protection.”

U.S. military personnel were screened for antibodies against *Campylobacter* before and after travel to Thailand. Those with higher titers before travel had significantly lower incidence of diarrhea during their time in Thailand. Symptomatic seroconversion during travel occurred four times more frequently among those with low initial titers. *Campylobacter* were the most commonly identified enteropathogens in stool samples. Thus, high antibody levels before travel appeared to provide protection against *Campylobacter enteritis*. On the whole, it appears that the tendency for increased antibody titer with greater exposure correlates with better protection against disease—in other words, occupational immunity appears to be common.

Second, are occupationally exposed individuals more likely to acquire immunity by illness or by subclinical infection? We were unable to find any studies of *Campylobacter* that directly address this question. Subclinical infection does occur (CDC web site), but we did not find reports of the frequency of subclinical infection in particular groups.
Third, do aspects of exposure, such as route and dose, differ between those who become infected subclinically and those who become clinically ill? The primary route of symptomatic infection is by ingestion. The CDC web site reports that it takes fewer than 500 *Campylobacter* cells in an ingested inoculum to initiate infection. In industrial abattoirs of developed countries, special worker clothing and training probably minimize cutaneous exposure via cuts. But in less regulated food processing environments, infection through cuts would provide another route of infection, with yet another relationship between dosage, symptoms, and protective immunity. No studies have focused on all of these issues in natural cutaneous exposure.

Some studies suggest significant airborne concentrations of *Campylobacter* in industrial poultry abattoirs, with worker exposure from airborne droplets. Such droplets may be ingested by the typical oral route of infection.

If ingestion of airborne droplets is indeed a significant source of infection in abattoirs, then two differences likely occur between occupational exposure and sporadic exposure of typical members of the population. First, the distribution of dosages likely differs—perhaps airborne droplets in the moist workplace more often inoculate workers with subclinical doses compared with sporadic ingestion via food. Second, previously exposed workers likely get a continual boost of immunity by repeated exposure, whereas sporadically infected individuals would not receive boosting inoculations so often.

Pulmonary inoculation apparently rarely leads to symptomatic infections, but it would be interesting to study how repeated inhalation of subclinical doses affects protective immunity. Wilson suggests that UV treatment of air in abattoirs may improve the health of workers, but if repeated inhalation actually boosts protective immunity for long-term
workers, then cleaning the air might alter the dosage and infection profiles in ways that actually increase symptomatic disease. That is, of course, a speculative idea—the point is that some fascinating and important questions remain open with regard to how occupational conditions affect exposure and natural vaccination.

In summary, long-term immunity following infection with *Campylobacter* probably occurs, although boosting by repeat infection may play a role. There is no direct evidence with regard to the frequency or causes of subclinical infection. Among animal workers, it would be particularly interesting to know whether cutaneous or pulmonary exposure could cause subclinical infection and protective immunity, and whether frequent small doses by ingestion of airborne droplets affect the long-term maintenance of protective immunity.

**Avian and swine influenza**

Influenza A viruses derive from wild birds. Much has been written about the pathways of transition between wild birds and humans. One recurring theme concerns infections of humans through contact with domestic animals that harbor avian-derived viruses. This theme leads to our topic of occupational exposure.

Several recent sporadic infections of humans have derived from contact with domestic animals. In these cases, a small number of people became infected, but the virus did not spread widely in human populations. We use those sporadic cases to address the same three questions we applied to anthrax, Q fever and *Campylobacter*.

First, does occupational exposure to zoonotic influenza in domestic animals lead to a higher level of immunity against those foreign viruses than is observed in the rest of the human population? Several recent reviews demonstrate increased antibody titers among
individuals occupationally exposed to swine. For example, found higher seropositivity to swine-adapted influenza viruses in swine farmers, their families and employees than controls not having contact with swine. found that, for swine isolates of H1N1 and H1N2, farm workers, veterinarians, and meat-processing workers all had greatly elevated seroprevalence compared with controls.

Serological studies of poultry workers present mixed results, partly because of the technical complexity of such studies. However, several studies do clearly show strongly elevated antibody titers among occupationally exposed poultry workers. For example, in the H7N7 poultry outbreak in the Netherlands during 2003, raised titers were observed in 49% of 508 poultry cullers and 64% of 63 people exposed to humans infected with H7N7. In a comparison of 42 veterinarians with 66 controls for antibody titers against nine different avian influenza strains, the veterinarians had significantly elevated titers against three of the nine strains.

The recent human infections by the H5N1 avian influenza virus also present mixed serological results. Studies of poultry workers, cullers and health care workers involved in the initial outbreaks in 1997 showed elevated seropositivity, suggesting that there had been some degree of subclinical infection by H5N1. However, studies of later outbreaks failed to show similar results (need more citations). The current view is that H5N1 has difficulty starting an infection in humans, which would explain the low seropositivity and the relatively few cases per contact with infected animals (see review by ). However, sampling has been limited and the serology seems to be particularly difficult to interpret for this virus.
In summary, several lines of evidence suggest that occupational exposure to avian and swine influenza viruses may lead to a higher level of seropositivity than observed in the general population. Differences in seropositivity occur between various avian-derived strains and between the type of animal exposure. Swine exposure presents clearly elevated antibody levels among animal workers; poultry exposure presents a more complex picture.

Second, if occupationally exposed individuals show higher levels of immunity to zoonotic influenza viruses, was that immunity more likely to have been acquired via illness or by subclinical infection? The high levels of seropositivity reported above from swine and poultry exposures were not associated with widespread clinical symptoms. Thus, subclinical infections can lead to seropositivity. However, positive tests for serum antibodies does not necessarily mean protective immunity. The relation between serology and immunity remains a key issue in interpreting the current literature.

Third, do particular aspects of infection, such as dosage, route of inoculation, or frequency of exposure, influence the probability that exposure results subclinical infection with resulting immunity (natural vaccination) as opposed to disease? No direct evidence addresses this question in humans. ⁵⁶ reported a laboratory study of mice that contrasted the intensity of symptoms between two different routes of inoculation. They found that pulmonary inoculation of mice with H1N1 influenza viruses led to lethal infections at moderate doses, whereas nasal inoculations caused death only at very high doses. This result on the less severe consequences of nasal inoculation leads to an interesting general problem with regard to occupational exposure. Could animal workers be exposed frequently to viral particles in inhaled dust? Would such exposures sometimes act as nasal vaccines? Similarly, how would workers be affected by cutaneous exposures through
scratches and cuts? Apart from the specific issues of natural vaccination, we simply do not have much information about routes of exposure, symptoms, and immunity.

Conclusions

In recent years, emerging infectious diseases have grown in importance and attracted increased research attention. Because occupationally exposed individuals often provide the first line of zoonotic transmission into human populations, it will be particularly important to learn more about infection and immunity in animal workers. To set the background, we developed the conceptual framework of occupational immunity and natural vaccination. That framework provided the basis on which to organize existing information about the key problems for future study.

In particular, we emphasized three aspects of exposure and immunity for which it would be important to know more. First, to what extent do occupationally exposed individuals actually develop infections and immunity? Second, how often do occupational infections go undetected because they cause relatively mild symptoms? Third, how do unusual aspects of dosage and route of inoculation among animal workers cause those individuals to develop infection, symptoms, and immunity?

Each of our four pathogen examples provides some information about these questions. From our review, it appears that occupational exposure does typically cause increased infection and immunity among animal workers. Several studies suggest that occupational infections are sometimes, perhaps often, subclinical. Interestingly, the routes of inoculation that may be particularly prevalent among workers, such as cutaneous exposure through cuts and scratches or nasal inhalation, may be particularly likely to cause subclinical infection and natural vaccination. However, the consequences for different
routes of exposure and different dose levels have rarely been studied. On the whole, our concepts and review of the literature show the importance of the subject and what we need to learn in order to move ahead.

More references needed in text??

Annotate bibliography

Figures??

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