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## Bubonic Plague: History and Epidemiology

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“Ring around the rosies, pocket full of posies...” A very common childhood rhyme that we have all sang at one point. What we did not know as kids was that the rhyme was thought to describe the Bubonic Plague, also known as the Black Death. There is debate about whether the song was actually written about the disease. While there is evidence for both sides, many believe that the connection to the plague was made after the rhyme was written, but it does a good job of summing up the disease none the less. “Ring around the rosies” refers to the red rashes in the shape of rings that appeared on the infected person’s skin. A “pocket full of posies” protected people from catching the disease, because it was hypothesized throughout history that disease was spread by bad smells in the air and that theory held strong until scientists proved otherwise (Zietz & Dunkelberg, 2004). “Ashes, ashes” was what was left after the dead were burned because there were too many to be buried. “We all fall down [dead]” is what would eventually happen if you caught the disease (“Ring around the Rosy Rhyme;” “Ring Around the Rosie,” 2007; “Ring a Ring...,” 2008). Outbreaks of the bubonic plague had a huge impact on economical structures and the demand for public health intervention (Boiseier et al, 2002; Silva, 2001). The disease is also a prime example of a zoonotic disease.

There were three major pandemics recorded, which are studied by scientists and epidemiologists worldwide. The most recent pandemic originated in China around 1855 and became a pandemic around 1894. By the beginning of the 20<sup>th</sup> century the disease was on a rampage again, and there still was not a clear understanding of how the disease was spread and what actually caused it. Medicine up to this point was able to give a pretty accurate explanation about the general idea of how the disease was spread, but the details were not defined. During this pandemic, scientists determined that microbial infection did not appear spontaneously, that rats might be the connection to the disease, and treatments and vaccines were starting to be developed to treat the disease. 1658 was when it was first determined that a microorganism was causing the disease, but it is unclear whether the scientist was actually seeing the causative agent, because the quality of their microscopy was still very limited; *Y. pestis* identified in 1894 when an epidemic spread through Hong Kong. Before these discoveries, countries tried to take preventative measures by utilizing quarantine practices, monitoring death rates and keeping the public up to date on this information; when the death rates rose, the public left town (Zietz & Dunkelberg, 2004).

The general population has heard about Black Death outbreaks and more specifically the pandemic that started in Europe and spread worldwide between the 14<sup>th</sup>-16<sup>th</sup> centuries, but what many do not know is that this disease is still a prominent concern in modern times. Each year, 1000-3000 people die due to this disease. Cases have been reported in Brazil, Democratic Republic of the Congo, Madagascar, Myanmar, Peru, Viet Nam, and even the USA (Keeling & Gilligan, 2000; Zietz & Dunkelberg, 2004). The bubonic plague is caused by *Yersinia pestis*, and the disease is considered a zoonosis

(Keeling & Gilligan, 2000). The initial symptoms usually include fever, headache, and general illness, which progresses to painful, swollen regional lymph nodes, also referred to as buboes (National Park Service, 2005). The disease manifests quickly (1-6 days) and then spreads rapidly to the blood and then the respiratory system. The disease is highly contagious from person to person and causes primary septicemic plague and primary pneumonic plague. Septicemic plague is caused by lesioned skin coming in direct contact with infected tissue or bodily fluids, and pneumonic plague occurs when an individual inhales respiratory droplets from an infected host (Zietz & Dunkelberg, 2004). Historically, the epidemic studies focused on the disease in the human population and not determining the cause of the outbreaks. When the study of the human populace did not appear to advance the understanding of the disease the efforts were redirected to searching for the cause by focusing on the relationships between rat, flea and human populations (National Park Service, 2005). The culprit was thought to be the black rat, and while this is indirectly true, the real danger is the infected flea. Human epidemics usually followed epidemics of the rat population. The disease would ravage the rat population, leaving the fleas in search of a new live host. Unable to find another rat, their new host becomes a person (Keeling & Gilligan, 2000). Reviews of current cases indicate that, while the rat is the primary host for transporting the disease, there are multiple hosts for the flea, including shrews, squirrels and rabbits (Boiseier et al, 2002). All of these rodents have high populations, meaning that using preventative pest control measures to eliminate the hosts are impractical and futile (National Park Service, 2005). Another problem with pest control is that it cannot be done during an active epidemic. Killing the host does not kill the infected flea, meaning the flea has to find a new host, which ends up being humans, and this exacerbates the problem. As if natural occurrence of the disease was not a big enough concern, biochemical warfare contributes to epidemics of the Black Death throughout history. Several outbreaks in China during WWII were attributed to attacks by the Japanese. In addition, prisoners of war were used to test biochemical weapons.

One of the major questions is: what puts people at a higher risk of exposure? It is hypothesized that people who live in highly populated areas with poor sanitary conditions are at higher risk of being exposed to the disease. These areas tend to have a denser population of rodents who are potential hosts for infected fleas. Many scientists are looking more in depth at the relationships between rat, flea and human populations. Public health concerns about this disease are rising. Emerging resistant strains, the use of biochemical warfare, and the re-emergence of the disease in areas that have not had outbreaks for many years may be indications that this disease could potentially become a prominent public health concern in the future (Keeling & Gilligan, 2000).

## LITERATURE REVIEW

While the pandemics that have occurred throughout history are significant markers of how much impact the disease can have, many studies are looking at present day endemics and epidemics. Understanding the pathogenesis and spread of the disease and developing preventative measures are important focuses in order to avoid another devastating pandemic. Boiseier, et al did a case study on four successive outbreaks of

the Bubonic Plague between 1995 and 1998. During this time, 1,702 suspected clinical cases were reported and 515 were confirmed by laboratory tests for *Yersinia pestis* (*Y. pestis*). Variability was introduced based on age and sex, and the researchers addressed these issues in their evaluation. There seemed to be a higher proportion of male cases, the majority of which were 25 years and younger. The death rate among patients was consistent from year to year, ranging from 6.7% to 9.3%, and there didn't seem to be any association between variable and death other than victims tended to have high temperatures. The outbreaks of the disease occurred during the coolest temperatures of the years and the number of cases decreased during the rest of the year. The article does not address a possible reason for this occurrence. Other possible environmental factors included presence of dead rats around the homes of the infected, and a demographic map of the population distribution of Mahajanga, Madagascar indicated that the most unhealthy and densely populated districts had the highest occurrence of incidences (Boiseier et al, 2002).

Since the area had not seen an outbreak of this disease in over 60 years, the sudden reemergence of the disease for so many consecutive years brought up public health concerns and questions about the etiologic causes of the disease. Through epidemiologic studies, the goal is to answer these questions in the hope of preventing a severe outbreak of the disease. This article introduces information that lays grounds for further investigation. The data presented provides supporting evidence for possible variables involved in the epidemics. Many studies suggest that higher density populations with poorer hygiene tend to be more susceptible to disease outbreaks, and the actual reason for this is still being studied. It is thought that people are living closer together and the unsanitary conditions provide a home to rodents that carry the disease infested fleas that pass the Plague to humans. This study was no exception; the crowded unsanitary district had the largest number of reports. The paper also clearly states that there seems to be a relationship involving age, but further investigation needs to be done in order to determine if the association is spurious or real. Gender is a confounding factor dependent on location, because which gender is predominant in the cases varies depending on location (Boiseier et al, 2002).

The study seems to skim the surface of a lot of ideas. It talks about temperature affects, age and gender variables, location in the city, presence of secondary diseases associated with infection, rodent populations, and topography as possible variables that influence whether an outbreak occurs and who is infected. The researchers briefly address possible discrepancies in their studies that may cause bias in the results. The case study design depends on the population sample to report information, and there is evidence that the population did not report accurately the onset and severity of the disease right away. There are also cases that never make it to the hospital that are not accounted for and out of the 1,700 potential cases, only the laboratory confirmed cases were used in these evaluations. In addition to these limiting factors, hospital records may introduce discrepancies due to poor records. The study provides supportive data that lays the groundwork for further investigation in order to determine the causative factors for this disease and the strength of the associations that seem to be present in this study. The information is also being used to set preventative measures in order to improve



public health and prevent outbreaks from spreading to surrounding areas. Suggestions to prevent the spread of the Plague due to increased trading and travel include better surveillance, rat proofing transport structures, and improving import/export regulations and monitoring (Boiseier et al, 2002).

By looking at history, recent outbreaks, and changing behaviors of *Y. pestis*, Keeling and Gilligan carried out a metapopulation model of the zoonosis for the bubonic plague. The researchers evaluated the disease dynamics in rat, flea and human populations, and the postulated "...that bubonic plague persists even in quite small rodent populations and therefore the observed historical dynamics are caused by fluctuations in the number of rat cases rather than random imports of infection." The plague is found throughout the United States, southern Asia, southern Africa and South America. As previously stated, 1000-3000 deaths a year occur because of this disease, and understanding the zoonosis of the disease will help prevent historical pandemics from reoccurring. The process of transmission is detailed in the study and connections between rat, flea and human populations help to describe the pattern of outbreaks among the human population. The disease is transmitted between rats via the flea, and when there is an epidemic among the rat population, it decreases drastically. When the rats die, the fleas are left to look for a new host which is usually another rat. Coexistence of human and rat populations, in densely populated areas, gives fleas a second host to choose from if they cannot find another rat. It is claimed that the dynamics of the human population do not affect the behavior of the disease; the rat epidemic just continues in the human population during an outbreak. Evidence shows that human outbreaks of the disease lag behind rat epidemics consistently throughout history. When the disease appears in the human population, it usually indicates the disease is on a rampage in the rat population, meaning there is a substantial infectious flea population (Keeling & Gilligan, 2000).

There are other factors that contribute to the likely hood of an outbreak, but these are likely to be confounding factors rather than causative agents. Outbreaks seem to be seasonal. Temperatures and humidity affect flea activity and because of this, the flea populations increase and are more active during ideal environmental conditions. The susceptibility of the rodent population to disease also seems to have an impact on whether the disease becomes present in the human population. If the rats are more susceptible, they are devastated by the disease more quickly and the disease begins to infiltrate the human population. Past studies have focused on the diseases progression through the human population, but they have not reviewed the etiologic factor of the disease. This caused misconceptions about how the disease was transmitted. It was claimed that the disease was brought into areas by introducing foreign rats, but through evaluation of rat populations, it has been determined that native rat populations maintain an endemic level of the disease that persists for years with seemingly random epidemics. These random outbreaks are then mirrored in the human population if the disease was devastating enough to the rat populations (Keeling & Gilligan, 2000).

Concentrations of wild rat populations and human population density seem to be important factors for exposure. For example, it is estimated that there is at least one rat for every person in New York, meaning there are potentially 4500 rats per square kilometer. Therefore, if the rat population suffers a devastating enough epidemic, it

could cause severe public health problems for the human population in that city. The dynamics of the disease in the rat populations are influenced by four primary factors:

- i. in the absence of the disease, the proportion of susceptible rats increases;
- ii. epidemics and endemics can infect neighboring susceptible populations;
- iii. highly susceptible subpopulations give rise to short-lived epidemics
- iv. moderately susceptible subpopulations can often lead to endemic persistence.”

These dynamics can set up grounds for an epidemic in the rat population that can lead to an outbreak in the surrounding human population. Distribution of the disease plays a role in these factors as well. The disease persists in rat populations, because endemics of the disease are found in sporadic regions. Neighboring rat populations would most likely be more susceptible, and this allows the disease to persist and eventually can develop into an epidemic (Keeling & Gilligan, 2000).

The study shows that the Plague is unique to other zoonotic diseases, because the occurrence of the disease in the human population is dependent on mortality of the rat population rather than the presence of the rodent. Not determining the actual rat population in a region introduced a possible variable into the study. Another stated concern was determining the chance that an infected flea will go from its rat host to a human host is dependent on many other variables that were not controlled for in this study. The study looked at patterns of rat and human outbreaks and determined patterns using mathematical explanation; it did not focus on establishing statistical support for its claims. Since the disease is caused by infected fleas going from rat to human populations when the rat population is devastated by an epidemic, killing rats when the disease appeared in the human population would exacerbate the problem rather than resolve it. To address the risk factors, the researchers suggest preventative measures for control of the rat and flea populations before an outbreak occurs. If the disease cannot spread to neighboring populations, then the disease is less likely to progress to epidemic proportions in the rat population which can then spread to the surrounding human population (Keeling & Gilligan, 2000).

Sebbane et al focused on what the flea of rodents was actually passing on when transmitting the disease. Their results came from controlled laboratory testing of the *Y. pestis*. What they discovered is that the bacteria can cause the bubonic plague and primary septicemic plague. It all depends on whether a plasmid-encoded cell-surface plasminogen (Pla) is present on the bacteria. The results suggest that the bubonic plague was an evolutionary development of this Pla. When the Pla is present it causes primary septicemic plague, and in its absence, the bubonic plague persists and a secondary disease that may develop from this is septicemic plague. The researchers used a wild type of *Y. pestis* and mutated form of the bacteria that was Pla negative. They injected the bacteria intradermally (ID) or transmitted the disease using fleas into groups of ten mice. The fleas mimicked how the disease is transmitted in nature. The bacteria is transmitted “...from a peripheral fleabite site via the lymphatic system to the regional lymph nodes.” From here, depending on whether Pla is present or not, the disease progresses to the bubonic plague or to primary septicemic plague. With the bubonic plague, inflammation causes edematous, necrotic, swollen and painful lymph nodes called buboes. Primary septicemic plague goes straight to the blood and causes a pathogenesis of the blood

(Sebbane et al, 2006).

Without the Pla, the bacteria cannot overcome the lymph node barrier, meaning the bubonic plague does not become systemic as quickly as the Pla positive bacteria. By using a wild type of the bacteria in fleas, it was determined that both diseases developed, so this suggests that the fleas are transmitting both forms of the bacteria to their hosts, which leads to the bubonic plague and primary septicemic plague. Another observation made was that mice infected with the Pla negative bacteria lived longer, and this may explain why the disease persists in rat populations. This persistence would provide a longer opportunity for the disease to spread and become an endemic or even an epidemic in the population. Since the Pla negative bacteria seems to be an evolutionary modification, it is believed that rats carry both forms of the bacteria and could cause either disease in the host it passes the infection to. One variable that the researchers did address was whether the saliva of the flea influenced how the bacteria diffused throughout the host, and their results indicated that the "...salivary gland extract did not enhance the infectivity or affect the dissemination route of the ID-injected bacteria." (Sebbane et al, 2006).

There are concepts that are not answered by this study that need to be looked at more closely. It is unclear whether the Pla positive bacteria travels through the lymph nodes first before emptying into the blood or if the bacteria diffuses through the tissue and directly into the blood stream. Because the flea's mouth is not long enough to penetrate into the dermis where the blood supply is found, it is unclear how the bacteria could be deposited directly in the blood. One of the next steps for this study would be to look at the actual process of transmission in order to better understand the pathogenesis of the disease. The researchers did not address possible variables in their study and did not define what further investigation should be done to improve the validity of their studies. Since this is a controlled, scientific study, the results should be repeatable thus increasing the validity of the study. There is always the risk that the disease does not act in nature like it does in the lab, so even if the researchers can figure out the bacteria's behavior, it may not completely prepare them for disease among the general population (Sebbane et al, 2006).

Molecular epidemiology provides many benefits to epidemiology studies. Continued surveillance of the disease and the use of more advanced analyses are being used as this disease continues to prevail worldwide. Lowell et al used molecular epidemiology to explore the sources of human exposure to *Y. Pestis*, and their primary focus was to "...identify the source of human exposure and to assess the exposure site for potential continuing risk." After the bacterium was genome sequenced, researchers were able to identify several markers in the bacteria that showed variability. This variability is what they used to pinpoint the source of infections in different cases. The possible sources were determined from the case histories about the person and where they had been before the disease manifested. In this paper, the cases were reviewed on an individual basis, and then the challenges of a population outbreak were briefly discussed. An outbreak in 2002 caught the attention of many people, due to its unusual location, New York. Since there are significant concerns with bioterrorism, it was important to identify the source of the disease. Before knowing the genome of the bacteria, it was difficult to

figure out the source for sure, since there can be multiple sources (Sebbane et al, 2006).

When determining the bacteria sources, researchers collected fleas from sites where the person could have been exposed and other possible sources of the disease. For example, in one case they studied, they determined that the source was from a cat who had pneumonia plague (this was not confirmed because the cat had died before an investigation could be performed). Identifying the source was dependent on the number markers that were different. The fewer differences, the more likely the sample was from the source of the disease. The researchers in this paper indicated that if only 1-2 markers were different, then that was a positive identification of the source. The reason that there is any difference is due to the high mutation rate of the bacteria. Even if the source is identified, it is recommended that public health officials do not determine their action of intervention based on these results alone. Using this molecular technique directs where further investigation should be concentrated, and with additional information, a plan of intervention can be developed to prevent an outbreak of the disease (Sebbane et al, 2006).

The biggest source of discrepancy seems to be with determining a positive match between the source and the bacteria present in the case. For this reason, the molecular epidemiology investigations provide useful information in order to direct further investigation. To advance the validity of the study, the researchers could have addressed the issue of disagreement between experts about what identifies a positive source. The paper also does not address variability that could be introduced by the cases. If the researchers do not get a full history, they could miss an important source. In an epidemic that spans a large demographic, the ability to identify a specific source becomes even more difficult. This was due to the fact that a widespread outbreak probably occurred due to multiple sources, and the need for other epidemiology study techniques are needed to get a better understanding of the activity of the outbreak before officials can even begin to address prevention actions (Sebbane et al, 2006).

DeWitte, et al looked at the cause and spread of the disease from a different perspective; the researchers looked at whether a person was more susceptible to contracting the disease if they were considered frail. In the study, frail was defined as "... the presence of at least one skeletal lesion (porotic hyperostosis, cribra orbitalia, linear enamel hypoplasia, periosteal lesions of the tibia, or short femur length)...," and this was "...associated with earlier episodes of infection, under-nutrition, or other forms of physiological stress" (DeWitte & Wood, 2008). The study claimed that mortality caused by the Bubonic Plague was affected by the environmental factor of frailty, but the association wasn't exclusive. In other words, everyone was susceptible to exposure and the risk of contracting the disease, but there were other environmental factors that created variety in what groups were more affected by the disease. Paleoepidemiology was used to analyze this hypothesis, and the researchers used skeletons from two different locations to do a case-study type analysis that looked at the mortality rate and biological indicators of the condition of the skeletons upon death. The case group was gathered from East Smithfield cemetery, which was created exclusively for the purpose of burying Black Plague victims between 1347 and 1351. A control group was created in order to look at the death patterns in populations that were not devastated by the Black Plague.



To avoid the influence of residual disease effects, the control population was taken from medieval Denmark cemeteries that provided an accurate sample of the population prior to the epidemic. This location was chosen, because at the time it had a very close socioeconomic structure to England, where the East Smithfield cemetery is located (DeWitte & Wood, 2008).

Two-hundred-ninety-one skeletons in the control population and 490 skeletons in the case population were evaluated for skeletal frailties. The results indicated there were significant correlations between all of the frailties that were evaluated and mortality except for short femurs among the populations. The results also indicate that the association between frailty and death was much higher in the Denmark population versus the London population. By comparing the London population to the Denmark population, researchers can begin to determine whether the Black Plague truly behaved indiscriminately or whether the disease behaved in a normal endemic pattern of a disease. While there was evidence that the Black Plague affected frail people more, it still was indiscriminate to a certain degree. There were a significantly higher proportion of skeletons among the London population that did not have indications of frailty but still died because of the bubonic plague. Since the skeletons that showed frailties had a higher density, this would indicate that the frail died more than the healthy. Ultimately, the paper concludes that it is very unlikely to find a causative agent condition that is not influenced by health conditions. Other studies on warfare and severe famine show that the frail are more affected by the conditions than the healthy. Frailty may actually be a confounding factor in these conclusions, because evidence suggests that it is associated with increased mortality, but there is not actually a causal relationship between mortality and frailty (DeWitte & Wood, 2008).

Since the researchers chose their populations from skeletons in specific cemeteries, this could introduce a possibility for bias, which was addressed throughout the article. The most evident concern is the introduction of selection bias. The study populations were not chosen at random from a whole population, histories were not provided for the subjects since they were already dead, and other variables like age, race, and socioeconomic standing were not determinable during the study. Since these differences were not determined, there are many variables that could be confounding the conclusions of this study, and the researchers address this by stating the results provide evidence that there is a consistent pattern suggesting a relationship between frailty and the risk of infection, but the data may not be statistically significant. Factors that may contribute to bias include that fact that older people tend to be more susceptible to disease, and there is not a way to know the health characteristics of individuals before they died. What actually caused the lesions on the skeletons may introduce further variability, especially between the controls and the cases. Causes of periosteal lesions of the tibia may be different depending on whether the individual lived in Denmark or London. The researchers tried to account for this by picking two locations with similar demographics during that time period. To eliminate some of the other variables that arise when studying populations from the past, paleontologists select from catastrophic skeletal samples. When a large number of people die at a point in time, it is easier to determine whether the cause in question is the causative agent. The researchers took

several steps to minimize the variability in their study and thoroughly addressed possible discrepancies in their study. Using objective observations of the skeletons added validity to the patterns that were observed; indicating that there is a direct or indirect association between frailty and exposure to the disease. In the discussion it is suggested that the association is most likely indirect. The claim that the disease is indiscriminate is valid to a certain degree because healthy skeletons and skeletons with the evaluated lesions were present in higher densities in the case population (DeWitte & Wood, 2008).

LJ Silvia addressed the issue of public health and its role in preventing or addressing emerging disease. Since there is a present concern for the bubonic plague becoming a prominent problem again (Keeling & Gilligan, 2000), the ideas presented in the paper provide significant information about the need for effective public health intervention. One of the turning points in public health intervention occurred in Brazil when the bubonic plague reached Santos, Rio de Janeiro at the end of the 19<sup>th</sup> century. The devastating results of the outbreak lead to the formation of the country's first biotechnology center. Concerns for this country focused on their economic dependence on coffee growing. Since this was an epicenter for growing and trade of coffee, the area was more susceptible to infectious disease including indigenous disease and foreign ones. A clear conclusion that has become apparent after all the infectious disease outbreaks that Sao Paulo has experienced is that constant public health intervention is needed, even after a disease has been dealt with. Populations are always changing; travel is becoming a more common practice worldwide, meaning infectious diseases can migrate faster and further; and microbes are constantly mutating as well. Reemerging diseases in the late 20<sup>th</sup> century confirmed that once the problem is "fixed" does not mean that it can be forgotten. Advancing medicine, changing ecosystems and changing population distributions are occurring at a rapid pace, and in order for public health to keep up with changes and to protect the public, epidemiologic studies are essential. The concern is that the changes are happening so quickly and that epidemiology generally focuses on past trends may be an inhibiting factor about the quality of the information provided by these studies. This all applies to the Bubonic Plague as evidenced by the persistence of the disease in present day, and because of recent epidemics worldwide. There have been three pandemics that were detrimental to the human population, and scientists want to prevent a fourth from happening. Being aware of the concepts and concerns presented in this paper will contribute to actions against the disease (Silva, 2001).

## SUMMARY

After looking at the Black Plague from many different aspects, it has been determined that fleas on rodents are the main concern for transmitting *Y. pestis*. Rats are the main carriers of the fleas, and they are commonly found in populated cities with poor sanitation. These conditions provide homes and food to the pests so they can thrive (Boiseier et al, 2002). With continuous outbreaks in the rodent population, the disease continues to resurface, and when a particular wave devastates the rat population, the next closest host, humans, becomes the target. An important variable in the transmission of the disease is frailty of the person. In general older or frailer people are more susceptible to disease, but these factors do not have direct impact on the transmission

of this disease. Since there is a persistence of the disease among the human population, and there have been epidemics within the past 30 years, scientists and public health officials are working to understand the pathogenesis of the disease, and trying to find a way to prevent another pandemic (Keeling & Gilligan, 2000). Zietz et al shows how the knowledge of transmission and Sebbane shows how the bacteria causes disease in the body.

For prevention, the National Park Service-U.S. department of the Interior has a set of guidelines in an attempt to prevent infection in the first place, and it outlines how to get rid of the pests. The key is to get rid of the flea, not just the rat. Insecticides are a common way that the flea population is reduced. By keeping areas clean of garbage and potential homes for the rodents, people can lower their possibility of exposure. With suspected exposure, antibiotics can be used to prevent the clinical symptoms. It is clear that even if the disease seems to be cleared from an area, there is a possibility for the disease to come back; it is just a matter of time. This was a hard lesson learned in Madagascar, and this occurrence enlightened the rest of the world to continue awareness and surveillance of rat populations and disease occurrences even if the disease is not present at the time.

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