# This paper is the one to recreate

**Superspreading and the effect of individual variation on disease emergence**

* IN DB
* See document, handwritten notes

# For the next section

* Use ResearchRabbit to search for article of interest
* Lookup citations
* Rank by citations

# On ticks, generally

## [**Ticks**](https://www.sciencedirect.com/book/9780323911481/ticks): Biology, Ecology, and Diseases

* (Johnson, 2023)

## Chapter 1 - A brief introduction to ticks

* IN DB
* “Ticks are related to [spiders](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/araneae) and mites, placing them in the class [Arachnida](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/arachnid) and sharing the common feature of eight legs in the adult form.”
* “All tick species have four life stages, egg, larva, nymph, and adult ([Fig. 1.1](https://www.sciencedirect.com/science/article/pii/B9780323911481000010" \l "f0010))”
* “All mobile life stages must locate a host, attach to it, and take a blood meal”
* “Ticks are found wherever their vertebrate hosts are present. The greatest diversity is found in tropical regions where ticks have adapted to predation on virtually all vertebrate groups of species”

## Chapter 2. Tick classification and diversity

* IN DB
* “The Ixodidae contains the largest number of species with representatives found in all biogeographical regions. Many transmit an array of pathogens to humans, [livestock](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/farm-animal), and domestic pets. They are distinct by the morphological structure of the scutum or hard shield that covers the whole dorsal (upper) surface in males but only partially covers the surface in females. The capitulum, or [mouth](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/mouth) parts, is prominent and projects forward from the body and can be viewed dorsally. The hypostome is typically longer than those found on soft ticks and has more numerous denticles or backward facing “teeth.” Eyes, if present, are found close to the side of the scutum. Hard ticks have three life stages, larva, nymph, and adult, with each stage taking a single blood meal. Adult males may or may not take a blood meal depending on whether the species requires this for sperm development. The adult female generally feeds once on the host over the course of a number of days and can become engorged to many times its original size. This single feed enables the female of many Ixodid species to oviposit (egg laying) thousands of eggs. Hard ticks are found throughout the world, even in some of the most extreme environments such as Antarctica.”

## Chapter 3. The tick life cycle

* IN DB
* “The tick life cycle is dominated by the need to obtain nutrition. While this is true for all organisms, in the case of ticks, especially for hard ticks, this is a single event that must be completed before moving to the next life stage.”
* “*I. ricinus* locates its host through an ambush strategy, termed questing, with the tick climbing to a prominent location on vegetation and waiting for the host to pass. To aid the tick, it has sense or Haller's organ, on the tarsus of the first pair of legs that detects changes in temperature and CO2.”

## Chapter 4 – Blood feeding as a life choice…

* IN DB
* “The [Ixodidae](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ixodidae) can be attached to the host for an extended period, in some instances, for over a week. In addition to the insertion of the hypostome and chelicerae, hard ticks produce a [salivary excretion](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/salivary-excretion), appropriately termed cement that binds the tick to the surface of the host ([Suppan et al., 2018](https://www.sciencedirect.com/science/article/pii/B9780323911481000113" \l "bib54)). In addition, this seals the wound and prevents excessive bleeding. The Argasidae do not produce this substance.”

## Driving forces for changes in geographical distribution of *Ixodes ricinus* ticks in Europe

* (Medlock et al, 2013)
* “The distribution of *I. ricinus* is known to be changing in Europe, both at extremes of altitude and latitude, as well as within its prior range. The reasons for these changes are manifold, and this paper aims to review the driving forces for changes in the geographical distribution of this tick species in Europe.”
* Ticks that spread a virus via co-feeding must also perform transstadial transmission, where the pathogen survives in the tick during the moulting process.
* “All the major continents are affected by a range of tick-borne diseases although in Europe and North America, human tick-borne disease is more commonly reported whereas in the remaining continents, it is the impact of tick-borne diseases on livestock, mainly large ruminants that are the focus of research directed at prevention and control.”

## The concept of state

- (Diekman, heesterbeek)

- Structured population models can allow for us to reflect the different states that different parts of a population can be in. They refer to h-states as the sex, age or otherwise type of host. From these, we can define Next-Generation Matrices. A NGM has elements of the expected number or proportion of new cases that have a particular h-state at the time of infection.

- Finding the dominant eigenvalue of that matrix, which is the spectral radius of the matrix. This is “As it is by definition the long-term average per generation multiplication number, we feel confident to denote it as R0”

## The Basic Reproduction Number for Complex Disease Systems: Defining R0 for Tick-Borne Infections

- (Hartemink et al)

- 2008

- “Deriving for natural systems of infectious agents R0 among wildlife is complicated. The reason is the high level of heterogeneity that is of epidemiological importance: differences between individual host species and host individuals cause differences in susceptibility, infectivity, and contacts, and such differences can also exist for a single individual in different stages of its life history. Apart from being generally multispecies systems, there are also (as a rule) multiple transmission routes for the infectious agent.”

# On pathogens affecting I. ricinus and I. trianguliceps

## The Eurasian shrew and vole tick *Ixodes trianguliceps*: geographical distribution, climate preference, and pathogens detected

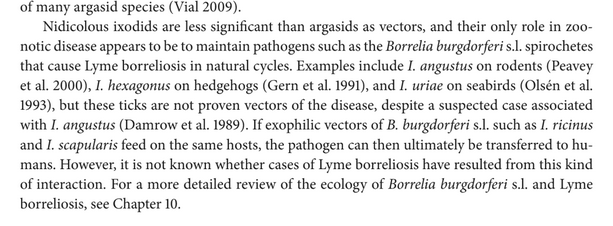
* (Rubel and Kahl, 2023)
* I. trianguliceps is a proven vector of Babesia microti.
* Possible vector of TBE, although no current study has found that TBE is in I. trianguliceps. Also, finding the pathogen inside a tick is not proof of vector competence.
* Possible vector for Borrelia burgdorferi (bacteria)->Lyme borreliosis (disease).

## Management Options for *Ixodes ricinus*-Associated Pathogens: A Review of Prevention Strategies

* (Černý et al, 2020)
* I. Ricinus is a known vector for the bacteria that spread Lyme disease, TBE.

## Biology of ticks, volume 2

- Gray 2014



# Pathogens transmitted by Ixodes ricinus

- Gray 2024

- “The way [ixodid ticks](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ixodidae) feed makes them particularly efficient as vectors of pathogens. They lack [digestive enzymes](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/digestive-enzyme), with blood meal digestion taking place intracellularly, so that the midgut is a relatively benign environment for microbes. Furthermore, they take large bloodmeals and feed for long periods compared to other [haematophagous arthropods](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/hematophagous-arthropods), providing much time for transmission of pathogens.”

# These are the most important articles that cited the article of interest, which refer to the Lloyd-Smith article.

## Antimicrobial Resistance in the Global Health Network: Known Unknowns and Challenges for Efficient Responses in the 21st Century

* IN DB
* References to talk about SuperSpreading, not significant
* Won’t read

## A practical guide to mathematical methods for estimating infectious disease outbreak risks

* IN DB
* Gives detailed information on calculating the probability of transmission chain extinction by using PGF, fixed point theorem

## Stochasticity and heterogeneity in host–vector models

* IN DB
* PGF method with branching process, for multiple individual types.
* Host vector models assumed to be those that are transmitted between vector and host, so not relevant.

## Infectious diseases and social distancing in nature

* IN DB
* Animals sometimes exhibit changes to their behaviour when infected with a disease. The notion of social distancing can be seen in animals.

## Daily longitudinal sampling of SARS-CoV-2 infection reveals substantial heterogeneity in infectiousness

* IN DB
* Evidence of PGF and branching method being effective, since populations have heterogeneity

## COVID-19 Superspreading Suggests Mitigation by Social Network Modulation

* IN DB
* Diagram shows that the pandemic survives by spreading from one superspreader to the next
* Whereas the Lloyd-Smith et al article suggested identifying the superspreaders, this paper suggests a reduction in mean connectivity

## Overdispersion in COVID-19 increases the effectiveness of limiting nonrepetitive contacts for transmission control

* IN DB
* To explore over-dispersion in a disease network, researchers used an agent-based simulation.
* THIS COULD BE A USEFUL IDEA FOR THE COINCIDENT COAGGREGATION DATA
* “Agent-based models, which set up a network of individual agents that interact according to defined rules, are well suited to exploring the impact of mitigation in the presence of superspreading.”
* “We varied the dispersion parameter *k* in the interval [0.05, 1.0] and found that as it increased, the effect of preventing random contacts gradually diminished ([Fig. 3](https://pmc.ncbi.nlm.nih.gov/articles/PMC8040586/" \l "fig03)).”

## Individual variation in susceptibility or exposure to SARS-CoV-2 lowers the herd immunity threshold

* IN DB
* Talks about the Kermack–McKendrick approach in 1927, which are the origin of the SIR approach
* Generally, talks about the limitations of SIR models… they have shortcomings.

## Impact of mobility restriction in COVID-19 superspreading events using agent-based model

* IN DB
* “Superspreading had special attention in SARS outbreaks in Singapore and China in 2003, since they helped in understanding transmission dynamics [[13](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref013)]. In Singapore, five people caused more than half of the 205 cases (and 163 cases led to zero secondary transmission)[[14](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref014)]. In 2015, in Korea, only 5 cases of MERS originated 154 secondary cases (166 cases led to zero secondary infections)[[13](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref013), [15](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref015)]. For COVID-19, one of the most emblematic cases of superspreading at the beginning of the pandemic was the “Patient 31”, who was linked to a cluster with more than 5.000 cases in Daegu, South Korea [[16](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref016)].”
* To model SSEs, some authors usually tag these individuals before the simulations starts, by attributing some characteristics that differentiate superspreaders from other individuals [[8](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref008), [11](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref011), [15](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref015), [17](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref017), [18](https://pmc.ncbi.nlm.nih.gov/articles/PMC7971565/" \l "pone.0248708.ref018)]”
  + But, in coincident coaggregation, SSEs are individual vertebrates that have many ticks on them. An agent-based simulation would need to tag the hosts, not the ticks themselves.
  + To add to the complexity, vertebrates move around and the ticks will drop off when they wish to, which implies that there will be some movement of the tick population.
* They use cellular-automata to model the behaviours of individuals.
* Individuals move through states as in an SIR model.
  + Will this be relevant to ticks? Would the time spent in coincident coaggregation mean that a tick passes through those stages before it drops off?
* They then model the network as a graph to measure centrality

## Superspreading events in the transmission dynamics of SARS-CoV-2: Opportunities for interventions and control

* IN DB
* “Here, we describe the different types of SSEs, how they influence transmission, empirical evidence for their role in the COVID-19 pandemic, and give recommendations for control of SARS-CoV-2”
* The article highlights the issues with using R\_0 to describe the spread of a disease, which hides the stochastic nature of the virus.
* Gives multiple examples of SSEs.

## The effect of superspreading on epidemic outbreak size distributions

* IN DB
* (Garske and Rhodes, 2008)
* Uses a stochastic model “to demonstrate the potentially considerable effect that heterogeneity of transmission will have on epidemic outbreak size distributions.”
* Relates to measles in urban centres.
* “These observations have led to the formulation of the 80/20 rule, according to which in many diseases more than 80% of transmissions are causes by the most infectious 20% of cases ([Woolhouse et al., 1997](https://www.sciencedirect.com/science/article/pii/S0022519308001124?via%3Dihub" \l "bib26)).”
* “Some situations like sexually transmitted diseases and livestock diseases (spread by animal movements between farms) are appropriately described by network models ([Kiss et al., 2006](https://www.sciencedirect.com/science/article/pii/S0022519308001124?via%3Dihub" \l "bib14); [Truscott et al., 2007](https://www.sciencedirect.com/science/article/pii/S0022519308001124?via%3Dihub" \l "bib25)).” This means that superspreaders give the disease to other superspreaders.

## Theory versus Data: How to Calculate R0?

* IN DB
* Shows that some models produce different R0, and it can be misleading. It is not always a threshold parameter.

## Heterogeneity in pathogen transmission: mechanisms and methodology

* NOT IN DB, https://doi.org/10.1111/1365-2435.12645
* “The number of secondary infections produced by an infected individual is a function of three components: an individual's infectiousness, the rate at which it contacts susceptible individuals and the duration of infection. Individual-level variation can emerge in each of these components through a combination of behavioural and physiological mechanisms.”
* “Two primary pathways give rise to heterogeneity in *V* (Fig. A): variation in number of contacts and variation in the likelihood of transmitting an infection given contact.
* An animal (in our case a tick) might be a super-spreader because it comes into contact with many other ticks. But, a tick might also be a “super-sheader”, meaning it is more infectious. There is heterogeneity in each of these factors, and each combine to make the individual reproductive number v, meaning we can expect to have multiple sources of heterogeneity.

# Articles related to tick co-aggregation

## Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens

* FOUND VIA DETAILED SEARCH
* IN DB
* (Ferreri et al, 2014)
* Tried to fit ticks per host with three distributions, including Negative Binomial, but also Poisson-LogNormal and the Power-Law distribution…
* QUESTION: ARE THESE OFFSPRING DISTRIBUTIONS FOR A BRANCHING PROCESS ANALYSIS?
* PL distribution fits well.
* IS THIS CONCERNING COINCIDENT COAGGREGATION
* Tail of distribution changes with seasonal variation in host abundance.
* Strong heterogeneity in number of ticks on mice: few mice have many many ticks: 20% of hosts feed 80% of larvae and nymphs
* In the case of TBEv, the virus is short-lived in the rodent vertebrate, and trans-ovarial transmission is rare.
* Aggregation and correlation of tick stages increases R\_0
* NB distribution has been successfully used to describe tick distribution on hosts
* “a Poisson-LogNormal (PoiLN) mixed model has been successfully used to describe tick distribution on red grouse chicks”
* “while Bisanzio and collaborators [[30]](https://pmc.ncbi.nlm.nih.gov/articles/PMC4230730/" \l "pcbi.1003931-Bisanzio1) showed the first evidence that the distribution heterogeneity of ticks on hosts seemed to be better described by a power-law (PL) than a negative binomial distribution.”
* This paper showed PL distribution is best to describe the right tail of tick distributions on hosts, compared to NB or PoiLN.
* Minimum transmission probability for pathogen to spread, epidemic threshold, is driven by first and second moments of distribution
* “In particular, Pastor-Satorras et al. [[50]](https://pmc.ncbi.nlm.nih.gov/articles/PMC4230730/" \l "pcbi.1003931-PastorSatorras2) demonstrated that the larger the heterogeneity, the lower the epidemic threshold for the pathogen to spread, with an interesting behaviour in infinite size network showing a zero epidemic threshold”
* Has data in paper
* Describes methods of fitting distributions
* A necessary condition for an effective non-systemic transmission of a pathogen is the coincidence of the larval and nymphal aggregation distributions on hosts
* “… our first step was to examine the association between the number of larvae and that of nymphs on each host using Spearman's rank-correlation coefficient”
  + More interested in monotonic relations of variables than linear relations
  + A positive SCC would indicate an increase in nymphs per mouse is associated with an increase in larvae per mouse. This is indicative of coincidence of distributions. SCC of 0 would indicate independent distributions
* They simulate the spread via a monte-carlo simulation

## Epidemic dynamics in finite size scale-free networks

* CITED BY **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* (*Pastor-Satorras R, Vespignani A, 2002)*
* IN DB
* Shows that if a network exhibits more heterogeneity, then the threshold for a pathogen to become endemic is lower.
* QUESTION: IS TICK BURDEN DATA THOUGHT TO BE SCALE FREE?

## Patterns of macroparasite abundance and aggregation in wildlife populations: a quantitative review

* NOT YET IN DB, DOI: 10.1017/s0031182000075855
* (Shaw et al, 1995)
* shows that aggregation can be modelled using the negative binomial distribiton
* “Dispersion pattern of parasites between hosts. As described in a previous section, the ratio of variance in worm burden to the mean parasite burden can be used to indicate the dispersion pattern of parasites between hosts. From the 269 host-parasite systems in the database all but one have s\*\*2/x significantly greater than unity, indicating significant aggregation compared to a Poisson distribution. This result provides very strong support for the notion that parasites are in general aggregated in their hosts.”

## Patterns of macroparasite aggregation in wildlife host populations

* CITED BY **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* IN DB
* (Shaw et al, 1998)
* 49 distributions of wildlife host-parasite systems analysed. NB distribution found to be good in 90% of cases.
* “This general use may bring about the situation where parasite burdens are de facto assumed to fit the NBD.”
* This is about parasites, not concerning ticks, it seems

## MULTIPLE CAUSES OF VARIABLE TICK BURDENS ON SMALL-MAMMAL HOSTS

* CITED BY **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* IN DB
* (Brunner and Ostfeld, 2008)
* There is a complex relationship in a system of mice and chipmunks
  + Chipmunks draw larval ticks away from mice
  + Mice draw nymphs away from chipmunks
  + Densities of vertebrate populations important for understanding coincident co-aggregration
* 80:20 rule cited
* “Those hosts responsible for feeding most ticks are both highly likely to be infected, and to subsequently infect many naı¨ve ticks”
* The paper posed these questions:
  + Densities of host-seeking ticks
  + Host densities
  + Individual correlates
  + Varying aggregation
  + Super-spreading individuals
    - “Lastly, we wanted to know whether those individuals  
      that feed more nymphs than expected also feed more  
      larvae than expected. If so, the same individuals most  
      likely to be heavily inoculated by infected nymphs are  
      also most likely to feed a large number of uninfected  
      larvae.”
* “Even after accounting for this strong seasonality, however, we found substantial interindividual heterogeneity in tick burdens. Moreover, no one group or factor adequately predicted tick burdens on mice and chipmunks”

## The importance of the aggregation of ticks on small mammal hosts for the establishment and persistence of tick-borne pathogens: an investigation using the R(0) model

* CITED BY **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* IN DB
* (Harrison and Bennett, 2012)
* **FIND MORE ARTICLES ABOUT MODELLING AGGREGATION WITH NB, VIA RESEARCH RABBIT**
* “One transmission route involved is ‘co-feeding transmission’, where larvae become infected via feeding alongside infected nymphs. The aggregation of ticks on hosts leads to an increase in the number of larvae feeding alongside nymphs, increasing the transmission potential via this route.”
* **The transmission of pathogens from one tick to another, a pre-requisite for the establishment of cycles of infection, may occur via 3 pathways (see Randolph ([Reference Randolph1998](https://www.cambridge.org/core/journals/parasitology/article/importance-of-the-aggregation-of-ticks-on-small-mammal-hosts-for-the-establishment-and-persistence-of-tickborne-pathogens-an-investigation-using-the-r0-model/9D0A6D2A60D608A30D4758CB9C405F8B" \l "ref36)) for a review). Firstly, female ticks may transmit the pathogen to eggs via transovarial transmission. Secondly, nymphs may feed on, and infect, a host leading to a systemic infection; larval ticks may then acquire an infection by ingesting the blood of the infected host, maintain the infection transstadially, and infect an alternative host during a subsequent bloodmeal as a nymph. Thirdly, ticks may become infected by co-feeding, spatially or temporally, alongside infected ticks. This ‘co-feeding transmission’ does not require the host to have a systemic infection but instead pathogens are passed from one tick to another as they feed together.**
* “The relationship between the k-exponent of the negative binomial distribution and R0 was also defined”
* Cites 80:20 rule.
* Talks of the NB distribution being used to model the aggregated distribution
* “It has also been shown that increasing the diversity of vertebrate hosts in an ecosystem can reduce the risk of disease as only some hosts are competent for disease transmission and infective tick bites may be ‘wasted’ on non-transmission competent hosts, the so called ‘dilution effect’”
* Uses the NGM approach, and I think that’s to calculate R\_0
* **Cited by the (Johnstone-Robertson, 2020) paper,** which provides this description: “…theoretical burdens of larval and nymphal ticks on hosts were generated from either a [Poisson distribution](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/poisson-distribution) (such that all hosts had similar tick burdens); from a negative [binomial distribution](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/binomial-distribution) (which captures tick aggregation on hosts), but independently of each other (such that larval and nymphal burdens on individual mice were independent); or from a negative [binomial distribution](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/binomial-distribution), but arranged in such a way that the of mice with the highest larval burdens also accounted for of the nymphal tick population.”
* **METHODS:**
* Uses a NGM approach to measure the degree of aggregation of I Ricinus ticks on small mammal hosts affects the ability of pathogens to become established in small mammal cycles.
* Varied the k parameter of the NB distribution, so that the effect of aggregation could be observed. This establishes the relationship between k-exponent of the NB and the R\_0 to be defined.
* Increasing the diversty of hosts can reduce the risk of disease, as some hosts are not competent for transmission (via systemic transmition). This is the dilution effect.
* To generate data, they used the NB distribution:
  + Number of observations, or host population size
  + Size, or dispersion parameter, k-exponent of the NB distribution
  + Mu, or mean number of tick life stage
* Three methods of generating data:
  + Based on Randolph et al, starting with k=0.1 and increasing by 0.1 until 1.0
  + Poisson distributed
  + Coincident aggregated distribution, used data CONTINUE HERE… I’M COOKED

## Past and future perspectives on mathematical models of tick-borne pathogens

* CITES **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* IN DB
* (Norman et al, 2016)
* “In this paper, we review models of tick dynamics and summarize the main results.”
* “In general, the models of tick dynamics are used to determine when the peak in tick densities is likely to occur in the year and how that changes with environmental conditions.”
* “In the final section of the paper, we identify gaps in the current knowledge and future modelling approaches.”
* Focuses on *I. Ricinus* species of tick.

## Incorporating tick feeding behaviour into R0 for tick-borne pathogens

* CITES **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* IN DB
* (Johnstone-Robertson et al, 2020)
* “For [Borrelia burgdorferi](https://www.sciencedirect.com/topics/immunology-and-microbiology/borrelia-burgdorferi) and tick-borne encephalitis (TBE) virus, transmission of infection from one generation of ticks to another occurs when older nymphal ticks infect younger larval ticks feeding on the same host, either indirectly via [systemic infection](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/sepsis) of the vertebrate host or directly when feeding in close proximity.”
* Derives R\_0 and the tick type-reproduction number T, based on observation that larval and nymphal ticks tend to aggregate on the same minority of hosts.
* “For some of the most important tick-borne pathogens, e.g. [Borrelia burgdorferi](https://www.sciencedirect.com/topics/immunology-and-microbiology/borrelia-burgdorferi) (the causative agent of Lyme disease) and tick-borne encephalitis (TBE) virus, ticks acquire infection whilst taking their first blood meal from vertebrate hosts as larvae. Upon molting and emerging the following year as nymphs they feed a second time during which they can infect their vertebrate host (which in turn infects the next generation of larvae), as well as other ticks feeding at the same time, on the same host, and in close proximity. **Hence the two immature life-stages of a tick vector, termed larvae and nymphs, are responsible for maintaining the pathogens in nature.**”
* “Aggregation refers to when most ticks (of a given life-stage) feed on a small subset of vertebrate hosts. It is a very common feeding behaviour of macroparasites, with almost all species observing a distribution known as the 80/20 rule, whereby 80% of parasites are found on approximately 20% of the hosts”
* “When larvae and nymphs aggregate on the same subset of hosts they are said to co-aggregate”
* This paper uses the NGM approach to find analytic expressions of R0 and T, the type reproduction number
* “Co-feeding transmission refers to the horizontal (direct) transmission of a pathogen between ticks feeding on the same vertebrate host, at the same time, and in close proximity, without the involvement of a systemic infection in the host. This transmission route is particularly important for pathogens where the systemic infection of a host is cleared within a couple of days, e.g. TBE virus in Europe and some less prevalent strains of B. burgdorferi in the United States, but plays a smaller role in the emergence and maintenance of pathogens where host infection is lifelong, e.g. the predominant B. burgdorferi strains in Northeast United States”
  + QUESTIONS:
    - DOES THE SA MAMMAL IN THE KIELDER DATA EXPERIENCE LIFELONG INFECTION OF EITHER DISEASE THAT THE KIELDER DATA LOOKS AT?
    - IS TRANSOVARIAL TRANSMISSION IMPORTANT FOR THE KIELDER DATA? A: ASSUME NOT
* “if the majority of larvae and nymphs were to quest at the same time of year then co-feeding would play a larger role in the spread of tick-borne pathogens than if their questing behaviour did not overlap”
  + NOTE: THIS IS THE CASE FOR KIELDER DATA, SEE CHARTS
* The paper provides two useful NGM matrices, and for co-feeding transmission, the paper provides an R0 number
  + QUESTION: IS THIS A GOOD WAY TO FIND R0, WHAT ABOUT K? CAN WE FIX R0 IN THE MLE APPROACH AND JUST FIND K?
* Provides a reason for why R0 = k\_11 during co-feeding transmission, in the absence of systemic transmission
* The relative effect of coaggregation is given as \epsilon
* The paper uses a simulation to find R0
  + QUESTION: CAN WE SETUP THE KIELDER DATA TO DO SOMETHING SIMILAR… FIND R0. IF NOT, THEN CAN WE FIND R0 SOME OTHER WAY?

## Non-systemic transmission of tick-borne diseases: A network approach

* Read this

## Few vertebrate species dominate the *Borrelia burgdorferi* s.l. life cycle

* CITES **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**
* IN DB
* (Hofmeester et al, 2016)
* There’s a positive correlation between host body mass. Nymphal burderns of hosts
* “Our quantification method suggests that only a few host species, which are amongst the most widespread species in the environment (rodents, thrushes and deer), feed the majority of *I. ricinus* individuals and that rodents infect the majority of *I. ricinus* larvae with *B. burgdorferi* s.l.”
* Continues to talk the mammal reservoir population having a high density.
* Compiled data via a review of data.

## An eco-epidemiological modeling approach to investigate dilution effect in two different tick-borne pathosystems

* CITES **Pattern of Tick Aggregation on Mice: Larger Than Expected Distribution Tail Enhances the Spread of Tick-Borne Pathogens**

## Ticks are not Insects: Consequences of Contrasting Vector Biology for Transmission Potential

* (Randolph S, 1998)
* TO READ AND SUMMARISE

## Co-feeding transmission in Lyme disease pathogens

* (Voordouw M, 2014)
* IN DB
* TO READ AND SUMMARISE

## A Stochastic Tick-Borne Disease Model: Exploring the Probability of Pathogen Persistence

* SENT TO ME BY SIMON
* THIS IS AN INTERESTING PAPER, LOOK AT CITATIONS AND REFERENCES!
* (Maliyoni et al, 2017)
* Stochastic model and ODE model, but then uses a multitype GWBP sim.
  + Continuous time Markov chain
* Stochastic model is a Galton-Watson branching process
* Stochastic and ODE models are compared to determine the effect of randomness in tick-borne disease dynamics
* Probability of disease extinction calculated via branching process technique and also from numerical simulations of ODEs. Results are different
* Focuses on HME, spread by lone star, white-tailed deer reservoir population
* GIVES A GOOD BACKGROUND ON THE HISTORY OF USING SIMULATIONS TO UNDERSTAND TICK-BORNE DISEASES
* “Our goal in this study is to formulate and analyse a stochastic epidemic model for the transmission dynamics of a tick-borne disease, HME, in a single population using a continuous-time Markov chain (CTMC) model.”
* This model is based on the work by Gaff and Gross in 2007. The 2007 paper used non-negative integers; the model in this paper uses densities or proportions
* “the variability introduced in stochastic models may result in dynamics that differ from the predictions made by deterministic models”
* Deterministic model:
  + Deer: (T: susceptible, Y: infected, N: total = T + Y)
  + Tick: (S: susceptible, X: infected, V: total = S + X)
  + Ticks don’t recover and remain infected. Hosts recover with temp immunity
  + No disease-induced death, but both populations have density-dependent death
  + Uses the NGM approach to derive R\_0… is this a useful approach also? Wouldn’t it be better to fit the NegBinom distribution to that data instead?
* Stochastic model (not GWBP):
  + Represents the terms in the deterministic ODE model as state transitions.
    - EG deer birth is T+1, deer infection is T-1,Y+1 etc
  + Markovian system: next state only depends on this state.
* Quotes LLoyd 2007: “the persistence of an infection into a wholly susceptible population is not guaranteed by having R0 greater than one”. However, deterministic models always predict an outbreak.” NOT A QUOTE OF LLOYD-SMITH ET AL
* The paper applies a multiple GWbp to T,Y,S,X, and earlier in the paper, this said that intraspecies transmission was not possible. Then the stochastic approach.
* QUESTION: CAN WE USE THE GWbp APPROACH WITH MULTIPLE TYPES TO MODEL TRANSMISSION IN COFEEDING? 2 TICK SPECIES, TRANSMISSION BETWEEN THEM AND WITHIN SPECIES
* “If a disease emerges from one infectious group with R0 > 1 and if i infectives are introduced into a wholly susceptible population, then the probability of a major disease outbreak is approximated by 1 − (1/R0)^i while the probability of disease extinction is approximately (1/R0)^I”.
* THIS IS OUTSIDE THE SCOPE OF THE HONOURS PROJECT. THIS COULD BE FUTURE WORK IF I GET TIME… USE A MULTITYPE GWBP.

## A stochastic epidemic model for the dynamics of two pathogens in a single tick population

* Another article by Maliyoni etc.
* (Maliyoni et al, 2019)
* Whereas the previous article talks about a mutltitype GWBP for vector-host transmission, this one talks co-feeding transmission and transovarial transmission, as a multitype GWBP simulation, for one species of tick that can transmit multiple pathogens
* Their model represents ticks without reference to their life stage: any two ticks may transmit the pathogen. Rather, the ticks are represented by the pathogen they are infected with.
* The paper compares the probability of extinction, using a fixed-point methodology, and to the probability of extinction found by \_\_\_\_.

## Modeling tick-borne disease: a metapopulation model

* CITED by Maliyoni et al, their model is based on the model in this paper

## Loop analysis for pathogens: niche partitioning in the transmission graph for pathogens of the North American tick *Ixodes scapularis*

* CITED BY JOHNSTONE-ROBERTSON AS SAYING: “

## Chapter 27 - Ticks (Ixodida)

* (Nicholson et al, 2019)
* IN DB
* Says that Trianguliceps is know to be nidicolous, while I Ricinus is non-nidicolous:
* “Typical habitat associations of non-nidicolous ixodid ticks include forests, meadows and other clearings, grasslands, savannahs, and semi-desert or desert areas. At one end of the spectrum are species that have very limited resistance to [desiccation](https://www.sciencedirect.com/topics/immunology-and-microbiology/desiccation) and occur in cool, moist forests (e.g., *I. scapularis* and *I. ricinus*).”
* “The apparent paucity of human *B. microti* infections in Europe may be attributable to the fact that *I. trianguliceps* is a nidicolous tick that seldom attaches to people.”
* **Given that Trianguliceps doesn’t attach to people, then a justification for focusing on I Ricinus is that it’s of a greater public health concern.**
* **Also see the final Bown et al paper, which says that most nymphs were Trianguliceps.**

## The generalist tick Ixodes ricinus and the specialist tick Ixodes trianguliceps on shrews and rodents in a northern forest ecosystem– a role of body size even among small hosts

* (Mysterud et al, 2015)
* “The generalist sheep tick *Ixodes ricinus* in Europe is the principal vector of several pathogens causing disease in humans and livestock. This includes the pathogenic genospecies from the *Borrelia burgdorferi* sensu lato complex causing Lyme borrelioses [[1](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR1)] and the virus causing tick-borne encephalitis (TBE) [[2](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR2)] in humans, *Anaplasma phagocytophilum* causing tick-borne fever in livestock [[3](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR3)] and the protozoan *Babesia divergens* causing babesiosis in cattle.”
* “Most parasites [[4](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR4)], including *Ixodes* ticks [[5](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR5)–[7](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR7)], are typically aggregated on certain species and individuals, and an important element in understanding the epidemiology of the tick-borne diseases is identifying which species and individuals are feeding most of the ticks.”
* “Specialized tick species can also play a role in the epidemiology by maintaining high infection levels in the reservoir hosts, even if they do not act as vectors of disease to humans or livestock. One such example is the nest-dwelling rodent specialist, *Ixodes trianguliceps* that do not act as direct vectors for pathogens causing human or livestock diseases (as they reside in burrows) [[11](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR11)]. It has been shown that *I. trianguliceps* may play a role in maintaining high infection levels in the reservoir hosts with regards to *Babesia microti* [[12](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR12)] and *Anaplasma phagocytophilum* [[13](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR13), [14](https://pmc.ncbi.nlm.nih.gov/articles/PMC4681159/" \l "CR14)].”

## The role of non-viraemic transmission on the persistence and dynamics of a tick borne virus – Louping ill in red grouse (*Lagopus lagopus scoticus*) and mountain hares (*Lepus timidus*)

* (Norman et al, 2003)
* IN DB
* Determistic model
* Louping ill virus carried by I. ricinus
* “The effect of non-viraemic transmission, if it occurs frequently enough, is to remove any dilution effect that does occur and to generally increase the probability that the virus can persist, particularly at low grouse carrying capacities. Indeed, if the non-viraemic transmission parameter and hare densities were both high enough it would be possible for the hares to sustain the virus in areas where grouse are unable to persist.

## Thresholds for disease persistence in models for tick-borne infections including non-viraemic transmission, extended feeding and tick aggregation

* (Rosa et al, 2003)
* IN DB
* Presents a general model for tick-borne infections.
* “…with non-viraemic transmission we see that the effect of non-viraemic transmission terms is to increase the basic reproduction number of the disease.”
* “For high enough values of the non-viraemic terms, the dilution effect completely disappears and the disease can persist in the absence of the viraemic host.”

## Long-term transmission dynamics of tick-borne diseases involving seasonal variation and co-feeding transmission

* TO READ

# ARTICLES RELATING TO SIMULATION

## BRANCHING PROCESSES

* Thorough descriptions of GWBP
* <https://reader.z-library.sk/read/bf739c3d99bae40a18cc71d6bd26158cb281c65108ea8e8b762d020c5f3b8b8a/17739222/efd8a3/encyclopedia-of-theoretical-ecology.html?client_key=1fFLi67gBrNRP1j1iPy1&extension=pdf&signature=a480cdacecb86f65280837974223a483980c2b2fb487f84e69c52b9fe48caa28&download_location=https%3A%2F%2Fz-library.sk%2Fdl%2F17739222%2F7b6041>

## Mathematical Statistics and Data Analysis

* This is very likely the parameterisation of the NB distribution that Lloyd et al used.
* P. 319
* <https://reader.z-library.gs/read/ca5b42bebc16eb04c7c485a2fa44b0188b8bebb771d4798a192658a8d1d1c72c/1176849/a13a69/mathematical-statistics-and-data-analysis-3ed-duxbury-advanced.html?client_key=1fFLi67gBrNRP1j1iPy1&extension=pdf&signature=626112fcca71b1750ca1c93e1296ca5d739a109a2c641b5f29b56842250d2925&download_location=https%3A%2F%2Fz-library.gs%2Fdl%2F1176849%2Fcae714>

# ARTICLES RELATING TO MOULTING SUCCESS

## Infection With Borrelia Afzelii Reduces Moulting Time of Lxodes Ricinus Ticks

* (Hurry et al, 2021)
* IN DB
* Concerns I Ricinus ticks
* “Of the 1739 engorged larvae monitored, the mean larva-to-nymph moulting success over 74 days was 91.9% (1598/1739), and the mean immature tick survival over 74 days was 84.5% (1470/1739).”
* Experiments conducted in a laboratory setting, with mice, where temperatures and humidities varied.

## Influence of temperature and relative humidity on the moulting success of Amblyomma limbatum and Aponomma hydrosauri (Acari: Ixodidae) larvae and nymphs

* (Chilton et al, 2000)
* IN DB
* Not concerning I Ricinus or I Trianguliceps
* “The moulting success of Ap. hydrosauri and Amb. limbatum was influenced by the temperature and relative humidity regime to which they were exposed. Ticks moulted within a certain temperature range.”
* It has a table of temperatures and relative humidity, that lists % of larvae that moulted to become nymphs.
* Not the same species, but are Ixodes

## What do we still need to know about Ixodes ricinus?

* (Gray et al, 2021)
* IN DB
* “The various tick-borne pathogens that are transmitted by *I. ricinus* survive the long periods between feeds sequestered in various specific tissues. For example, *B. burgdorferi* s.l. spirochaetes remain in the midgut during the digestion of the blood meal and moulting. Once the tick starts to feed again, they multiply rapidly in the newly engorged blood, cross the midgut barrier and enter the haemolymph and salivary glands.”
* “It is often assumed that cold weather tends to increase the mortality of overwintering *I. ricinus* populations, but this is simplistic and under normal conditions in northern Europe, the majority of the tick population overwinters successfully as unfed stages, with a smaller proportion overwintering as eggs, engorged larvae and engorged nymphs in developmental diapause. Field observations in Germany suggested that it was only when snow cover was absent at very low air temperatures (−15 °C or even colder) that tick populations were adversely affected ([Dautel et al., 2016](https://www.sciencedirect.com/science/article/pii/S1877959X21000352" \l "bib0130)). In Ireland it has been observed that under quasi-natural conditions, unfed larvae and nymphs showed high rates of survival at air temperatures of −10 °C without snow cover for a short period, whereas most engorged larvae and nymphs in developmental diapause perished ([Gray, 1981](https://www.sciencedirect.com/science/article/pii/S1877959X21000352" \l "bib0265)). The cold-hardiness of *I. ricinus* larvae has been investigated under laboratory conditions ([Dautel and Knülle, 1997](https://www.sciencedirect.com/science/article/pii/S1877959X21000352" \l "bib0125)), and it was found that although winter-acclimatized engorged larvae could survive −10 °C for several days, they were not resistant to freezing and high mortality was experienced when in contact with ice. At present it is not clear how such data can be extrapolated to the field.”

## Density-dependent acquired resistance to ticks in natural hosts, independent of concurrent infection with Babesia microti

* (Randolph, 1994)
* Regarding I Trianguliceps
* “Mortality from larvae to nymphs is markedly density-dependent, correlating most strongly with the numbers of feeding larvae upon which the mortality estimate is based (Fig. 3a). Stepwise multiple regression showed that the deviations from the density-dependent regression are negatively correlated with the rainfall of the month the larvae were feeding and thus entering their development phase (Table 2). The numbers of nymphs declined sharply in December/January of each year (Fig. 2a), for which no clear explanation consistent with the rest of the annual pattern has been found.”

## How an extreme weather spell in winter can influence vector tick abundance and tick-borne disease incidence

* (Dautel et al, 2016)
* Regarding I Ricinus
* Larvae, once fed on vertebrates, were placed in the field. They then moulted into nymphs. The researchers then conducted surveys to measure nymphal questing activity.
* There was significant variation in the percentage of questing nymphs at the different sites, depending on the year.
* “The decrease of tick activity in 2012 when compared to that in 2011 was most distinct at the locations Bielefeld and Giessen where there was almost no snow cover during the cold spell mentioned above. It was less distinct in Berlin and Regensburg where there was at least some snow cover. As snow cover acts as a temperature buffer, it might have protected the ticks in the subjacent leaf litter against the cold.”
* NOTE: KIELDER FOREST IS KNOWN TO SNOW

# ARTICLES RELATING TO THE KIELDER DATA

## Seasonal Dynamics of Anaplasma phagocytophila in a Rodent-Tick (Ixodes trianguliceps) System, United Kingdom

* CONCERNS TICK DATA, NOT KIELDER FOREST
* IN DB
* (Bown et al, 2003)
* Concerns the bacteria, Anaplasma phagocytophila
* Ixodes trianguliceps is the tick species, feeds almost exclusively on small mammals
* Bank voles and wood mice are the vertebrate populations
* “This study confirms that woodland rodents can maintain A. phagocytophila in Great Britain in the absence of other reservoir hosts and suggests that I. trianguliceps is a competent vector.”
* Appears to be the first paper where they talk about the data. I can expect later papers to reference this one.
* Suggests that infected ticks are the overwinter reservoir.
* “Distributions of larval, nymphal, and adult ticks were significantly different from normal and Poisson distributions (p<0.05), but none were significantly different from the negative binomial distribution (p>0.1)”
* “larvae were most abundant from August to December or January, with a shorter period of activity in early summer that varied in amplitude between years. Nymphs were most abundant from May to August with some activity continuing through autumn”.
* “Because of such short periods of infectivity, the occurrence of endemic cycles of TBEV depends on coincident seasonal activities of different I. Ricinus tick instars, coupled with aggregation of ticks of more than one instar on a small proportion of the rodent population (38). In our study, seasonal activities of larvae, nymphs, and adults were partly coincident, the distribution of ticks among rodents was highly aggregated, and larvae and nymphs co-fed on a small proportion of the population (particularly bank voles), conditions that may have enhanced transmission of short-lived A. phagocytophila infections. Such conditions may also promote co-feeding transmission of A. phagocytophila”

## Relative Importance of Ixodes ricinus and Ixodes trianguliceps as Vectors for Anaplasma phagocytophilum and Babesia microti in Field Vole (Microtus agrestis) Populations

* CONCERNS KIELDER FOREST, 8 sites, 4 fenced…
* QUESTION: HOW DOES THIS RELATE TO THE DATA?
* IN DB
* (Bown et al, 2008)
* I Ricinus was well-recognised across Europe in 2008, but this study looked into I Trianguliceps, too.
* This study assess both ticks’ role in transmission of Anaplasma phagocytophilum and Babesia microti
* Field voles are the vertebrates
* I Ricinus targets a number of vertebrate hosts, but rodents can be infested with specialised ticks (I Trianguliceps).
* I Ricinus and field voles:
  + Larval burdens varied significantly seasonally, peaking in May, June, and July.
  + At the individual level males carried larger numbers of ticks than females at all bodyweights greater than 10 g; furthermore, tick burden increased more rapidly with increasing body weight among male voles than females
* I trianguliceps and field voles:
  + As with I. ricinus, burden varied with season, with larval numbers peaking between April and June.
  + Again, there was an interaction at the individual level between tick burden and vole sex and body weight due to the fact that males of all but the lightest body weights hosted higher numbers of larvae than females.
  + However, in contrast to I. ricinus, the burden of I. trianguliceps larvae decreased with increased body weight for both sexes, with this decrease occurring more rapidly for females.
* In summary, fences erected at sites prohibited deer from entering, meaning that the I Ricinus anundance was reduced. However the pathogen persisted in the vole population, and the I Trianguliceps was not affected by the lack of deer. This indicates that I Trianguliceps is a more specialised species, in that it targets just smaller vertebrates. So, A phagocytophilum can be maintained in woodland where I Ricinus is not present, if I Trianguliceps is present (as it is the principal vector).

## Delineating Anaplasma phagocytophilum Ecotypes in Coexisting, Discrete Enzootic Cycles

* TALKS ABOUT KIELDER FOREST, 4 SITES AS IN DATA
* IN DB
* (Bown et al, 2009)
* “The tick-transmitted bacterium Anaplasma phagocytophilum is the causative agent of granulocytic anaplasmosis, an infection of medical and veterinary importance that is widely encountered across the temperate zones of the Northern Hemisphere”
* “We obtained compelling evidence to support the proposition that different subpopulations of A. phagocytophilum exploit different tick and mammal species and, as a result, occur in discrete enzootic cycles even though both vectors and hosts are sympatric.”
* QUESTION: CAN WE ASSUME IN OUR CASE THAT WE WILL USE A SINGLE SUBPOPULATION?

## The Common Shrew (Sorex araneus): A Neglected Host of Tick-Borne Infections?

* TALKS ABOUT KIELDER FOREST
* IN DB
* (Bown et al, 2011)
* At the time, relatively little was known about the role of shrews.
* Studies common shrews (Sorex Araneus) and field voles (Microtus Agrestis)
* Shrews face a heavier tick burden for larvae and nymphs, for the species I Ricinus and I Trianguliceps
* Nymphs collected from shrews were almost entirely I trianguliceps
* Findings suggest common shrews are a reservoir for tick-borne infections.
* “Ticks are considered to be second in importance only to mosquitoes as vectors of zoonotic and veterinary infections (Sonenshine 1991)”
* GLMM analyses on factors associated with tick infestation
  + I. trianguliceps larvae: “Both infestation with I. Ricinus larvae and nymphs (both species combined) were positively associated with increased levels of infestation with I. trianguliceps larvae (Table 2). Shrews carried significantly higher burdens of I. trianguliceps larvae.”
  + I. ricinus larvae: “Increased abundance of I. trianguliceps larvae and nymphs were both positively associated with increased burdens of I. ricinus larvae. Burdens were generally higher on shrews than on field voles, although this was dependent on season, reflecting that, for example, in May 2005, infestation levels were sometimes higher on field voles.”
  + Ixodes spp. Nymphs: “Increased burdens of nymphs were associated with the presence of both I. trianguliceps and I. ricinus larvae. The infestation levels were generally higher on shrews, but this was again dependent on season.”
* Shrews: 647 sampled:
  + 121 (18.7%) tested positive for A. phagocytophilum
  + 196 (30.3%) tested positive for Ba. Microti
  + 11.7% positive for both
* Field voles: 1505:
  + 96 (6.4%) tested positive for A phag.
  + 458 (30.4%) tested positive for Ba. Microti
  + 3.5 % positive for both
* QUESTION: THE DATA ON KIELDER FOREST MIXES TWO SPECIES OF TICKS. SHOULD WE TRY TO REDUCE THEIR NUMBERS IF WE ONLY LOOK AT I. TRI? THIS IS BECAUSE THESE TWO SPECIES MIGHT BE COMPETENT VECTORS FOR BOTH DISEASES, BUT NOT NECESSARILY THE SAME LEVEL OF COMPETENCE.