Between-farm transmission routes of highly transmissible diseases in livestock: a literature study on the quantitative knowns and unknowns

[Routes van tussen-bedrijfstransmissie van zeer besmettelijke dierziekten: een literatuurstudie van de kwantitatieve kennis en kennislacunes]

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1. Samenvatting (summary in Dutch)

1.1 Vraagstelling

Dit rapport inventariseert de kwantitatieve kennis die beschikbaar is in de literatuur, alsmede de huidige kennislacunes, over de rol van specifieke transmissieroutes in de tussen-bedrijfstransmissie van bestrijdingsplichtige dierziekten in Nederland. Dit om na te gaan in hoeverre een kwantitatieve inschatting van de effecten van specifieke hygienemaatregelen (zowel in vredestijd als in crisis) en contact- en vervoersverboden (in crisistijd) mogelijk is. Op basis van zo'n kwantitatieve inschatting zou namelijk de (kosten)effectiviteit van maatregelenpakketten kunnen worden bestudeerd en mogelijk verbeterd. Daarnaast zou deze informatie ook meer houvast kunnen bieden om voor nieuwe dierhouderijsystemen risico's van tussen-bedrijfstransmissie in te schatten. Tenslotte zou deze kennis het draagvlak voor naleving van de maatregelen kunnen vergroten.

1.2 Achtergrond bij de vraagstelling

Het Ministerie van Landbouw, Natuur en Voedselkwaliteit (LNV) is verantwoordelijk voor de bestrijding van bestrijdingsplichtige dierziekten (voorheen lijst-A ziekten). In geval van uitbraken van deze ziekten is het van belang de besmettingsrisico's tussen bedrijven zo veel mogelijk te verlagen, uiteraard met inachtneming van andere maatschappelijke belangen. Instrumenten die daarbij worden ingezet, zoals vastgelegd in EU regelgeving en beleidsdraaiboeken van LNV, zijn bioveiligheidsmaatregelen (hygiënemaatregelen, contact- en vervoersrestricties, compartimentering), het ruimen en het vaccineren van dieren. De kwantitatieve effecten van de laatste twee typen maatregelen op de tussen-bedrijfstransmissierisico's in Nederland zijn voor drie belangrijke bestrijdingsplichtige dierziekten (KVP, MKZ en AI) wetenschappelijk vrij

goed bestudeerd onder meer met behulp van de epidemiologische gegevens van de epidemieën in 1997/1998 (KVP), 2001 (MKZ) en 2003 (AI) en van transmissie experimenten. Van zulk wetenschappelijk onderzoek is dan ook gebruik gemaakt bij de beleidsvorming ten aanzien van de toepassing van ruimings- en vaccinatiemaatregelen. Voor de meeste bioveiligheidsmaatregelen zijn er geen kwantitatieve gegevens beschikbaar van de mate waarin ze bijdragen aan het verlagen van besmettingsrisico's. Het nut van dergelijke inschattingen zou zijn dat op basis daarvan de (kosten)effectiviteit van zowel regelingen in vredestijd als crisis-maatregelenpakketten in beleidsdraaiboeken kan worden berekend en mogelijk verbeterd. Concrete bioveiligheidsmaatregelen zijn onder meer het veilig opslaan en/of verwerken van besmette mest, aanpassingen in houderijsystemen, bezoekersregelingen, en scheiding schone-vuile weg op het bedrijf. Om goede inschattingen te krijgen is inzicht nodig in de mate waarin specifieke transmissieroutes (zoals via bezoekers, werktuigen, transporten, en via de lucht) bijdragen aan het risico op transmissie tussen bedrijven. Dit inzicht zou in het bijzonder ook moeten worden nagestreefd voor situaties waar de bioveiligheidsmaatregelen worden toegepast in combinatie met noodvaccinatie.
Dit rapport inventariseert de kwantitatieve kennis die beschikbaar is in de literatuur over de rol van verschillende transmissieroutes, en identificeert de belangrijkste kennislacunes die opgevuld moeten worden om een goede kwantitatieve onderbouwing van bioveiligheidsmaatregelen mogelijk te maken. Inzicht in de kwantitatieve bijdragen van verschillende transmissieroutes kan ook van pas komen voor risicoanalyses ten aanzien van dierziektenverspreiding voor nieuwe dierhouderijsystemen.

1.3. Modelraamwerk voor een kwantitatief perspectief op tussen-bedrijfstransmissie

Voor het nadenken over verschillende routes voor overdracht van een infectie (transmissie) tussen bedrijven is het handig om onderscheid te maken tussen directe transmissie (via diertransport) en indirecte transmissie (anders dan via diertransport). Een modelvoorstelling van indirecte transmissie tussen een infectieus bedrijf en een vatbaar bedrijf kan grafisch eenvoudig worden weergegeven als in Diagram 1. We beschouwen elke mogelijke transmissieroute daarin als een aaneenschakeling van drie processen:

1. Infectieus materiaal uitgescheiden door dieren op het geïnfecteerde bedrijf verlaat het bedrijf op een route-specifieke wijze.
2. Het materiaal wordt vervolgens op een route-specifieke wijze getransporteerd naar een (nog) niet geïnfecteerd en vatbaar bedrijf of de directe omgeving daarvan; de in het materiaal aanwezige ziektekiem overleeft dit transport in een zekere mate.
3. Eén of meer dieren op het vatbare bedrijf worden route-specifiek blootgesteld aan een zodanige dosis van het getransporteerde materiaal dat infectie optreedt.

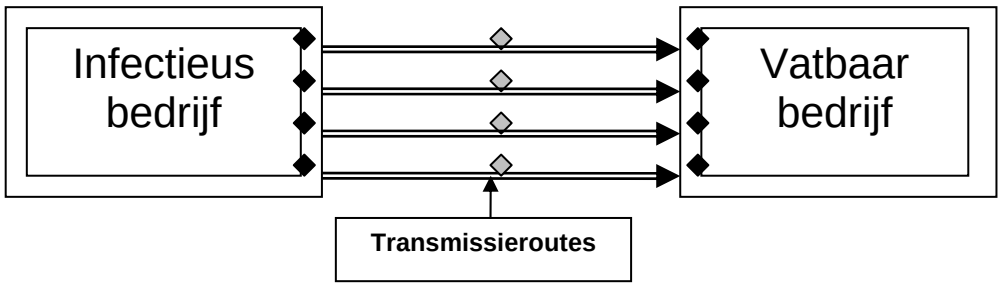

Diagram 1. Schematische voorstelling van (indirecte) transmissie tussen bedrijven. Zwarte ruitjes: plaatsen waar bioveiligheidsmaatregelen kunnen aangrijpen gericht op de processen 1 en 2. Grijze ruitjes: plaatsen waar bioveiligheidsmaatregelen gericht op proces 2 kunnen aangrijpen.

Zouden de frequentie van het optreden van proces 1 en de "succeskansen" van processen 2 en 3 bekend zijn voor alle mogelijke specifieke transmissieroutes, dan zou het mogelijk zijn het relatieve risico van verschillende routes te berekenen. Vervolgens zou het mogelijk zijn aan te geven wat het maximale effect zou kunnen zijn van specifieke bioveiligheidsmaatregelen. Namelijk door na te gaan op welke processen (en dus welke transmissieroute) de specifieke maatregel ingrijpt (zie ook Diagram 1). Is een schatting mogelijk van de mate waarin een dergelijke maatregel de frequentie of succeskans van een van de processen reduceert, dan kan ook het verwachte effect ervan worden bepaald.
In het literatuuronderzoek hebben we ons gericht op het inventariseren van de aanwezige kwantitatieve kennis ten aanzien van verschillende routes van transmissie tussen bedrijven van bestrijdingsplichtige dierziekten, en ten aanzien van bestrijdingsmaatregelen daartegen anders dan ruimen of vaccineren. Daarbij geeft de boven beschreven modelvoorstelling met frequenties, succeskansen en kansreducties een perspectief op het soort kwantitatieve informatie waarnaar we op zoek zijn.

1.4. Kwantitatieve kennis en kennislacunes betreffende tussen-bedrijfstransmissie

De overall tussen-bedrijfstransmissie is voor een aantal belangrijke bestrijdingsplichtige dierziekten voor de Nederlandse situatie redelijk tot goed gekwantificeerd met behulp van de epidemiologische gegevens van de epidemieën in 1997/1998 (KVP), 2001 (MKZ) en 2003 (AI). Echter een kwantitatieve beschrijving van de bijdragen van de verschillende (mogelijke) transmissieroutes en hun opbouw in termen van de eerder genoemde drie processen (zie paragraaf 1.3) is grotendeels afwezig. Voor KVP zijn de risico's van verschillende (getraceerde) routes het beste gekwantificeerd. Een probleem is echter dat voor een zeer groot aantal bedrijfsinfecties (vaak > 50%) nooit een specifieke route of contactmoment is vastgesteld. Dit geldt in het bijzonder voor de zogenaamde buurtinfecties, d.w.z. bedrijfsinfecties die tijdens de bestrijding optreden via niet-traceerbare routes. De beste kwantitatieve informatie en analyses ten aanzien van buurtinfecties en de hierbij horende risicofactoren zijn beschikbaar voor KVP, dankzij de gegevens verzameld tijdens de epidemie in 1997/1998. Andere informatie komt uit studies naar de invloed van omgevingscondities op de overleving of besmettelijkheid van verschillende ziektenkiemen en uit dose-response studies. Deze informatie is relevant voor het

inschatten van de succeskansen van de processen 2 en 3 voor verschillende specifieke routes.
De beschikbare kwantitatieve informatie en kennis in de literatuur alsmede de informatie- en kennislacunes worden in detail besproken in hoofdstuk 2 van dit rapport. De belangrijkste kennislacunes betreffen afwezigheid van kwantitatief inzicht in de onderliggende transmissieprocessen die aanleiding geven tot buurtinfecties.

1.5. Hoe zijn de geïdentificeerde kennislacunes te verkleinen?

De volgende richtingen van onderzoek kunnen behulpzaam zijn om de kennislacunes te verkleinen:

a) Experimenteel werk aan modelsystemen voor transmissie op afstand
b) Experimenteel werk dat deelprocessen van de transmissie (excretie, overleving, infectie) kwantitatief bestudeert
c) Wiskundig modelleringswerk dat beschikbare gegevens over verschillende deelprocessen en over transmissieroutes combineert om uit die combinatie extra informatie te verkrijgen
d) Veldonderzoek aan tussen-bedrijfstransmissie van (niet-bestrijdingsplichtige) endemische dierziekten

2. Individual routes of between-farm transmission: Which quantitative information is available and which is lacking from the literature?

2.1 Introduction

Highly transmissible diseases of livestock can transmit from farm to farm by a variety of routes. For the design of biosecurity-based intervention measures against epidemic spread of such diseases, it would be very helpful to have quantitative estimates available of the risk of transmission through these different routes, or of the relative contributions of these individual routes to the overall between-farm transmission observed during an epidemic. Here we give an overview of literature sources that offer quantitative estimates of this kind (notably the references [1-8]), identify important aspects on which the available quantitative information is lacking or very limited, and formulate recommendations as how to obtain more quantitative insight into these aspects in the future.
The Dutch Ministry of Agriculture, Nature and Food Quality is responsible for the control of highly-transmissible diseases in livestock (former list-A diseases). In case of outbreaks it is important to reduce the risks of transmission from farm to farm as much as possible, whilst taking into account other public interests. Instruments that are used, as laid down in EU statutory regulations and national contingency plans, include bio-security measures (such as hygiene protocols and transport bans), culling and vaccination of animals. The effects of the last two types of intervention measures on between-farm transmission risks in The Netherlands can be quantitatively studied with reasonable precision for the three important diseases Classical Swine Fever (CSF), Avian Influenza (AI) and Foot-and-Mouth Disease (FMD), using data from epidemics in 1997/1998 (CSF), 2001 (FMD) and 2003 (AI). Consequently, this type

of epidemiological analysis has been utilized to assess the effectivity of preventive culling and emergency vaccination strategies, and in this way inform Dutch contingency planning. We note that for an estimation of the effectivity of culling and vaccination strategies, in contrast to that of biosecurity measures, it is sufficient to only have a quantitative estimate of the *total* transmission intensity between infected and susceptible farms (instead of estimates of the separate contributions of individual underlying transmission routes).
For most of the many different bio-security measures at present no evidence-based quantitative estimate is available of how much they contribute to reducing transmission risks. The rationale for seeking such an estimate is that it would provide a scientific basis for studying and improving the (cost-)effectiveness of these different measures, both those applied in peace-time and those used for in crisis intervention. Specific bio-safety measures of relevance here are the safe storage, removal and disposal of manure, alterations to farm management systems, farm visitor protocols, and separation of areas for living from those for the farming activities on the farm. To obtain such estimates insight is required in how much specific individual transmission routes (such as via visitors, shared equipment, transports, and via the air) contribute to the overall between-farm transmission risk.

2.2 The quantitative importance of individual routes

The overall transmission rate between infected and susceptible farms has been estimated for a number of recent epidemics of CSF [2, 9], FMD [2, 9-13], and AI[14, 15], often as a function of the distance between the farms and sometimes also as a function of time.
If the overall distance-dependent transmission rate is characterized for a situation with movement restrictions and bio-security measures as required by EU regulations and national contingency plans, this is sufficient for the purpose of evaluating the effect of preventive culling and emergency vaccination. However to address the effectiveness of various bio-security measures, we do need to find out about the magnitude of the contributions (to the overall transmission) of the different routes. Also we would like to know as much as possible how the mechanisms of transmission via these routes are built up in terms of consecutive processes. Such knowledge could help us identify where in the chain of events that leads to transmission the best opportunities are present for additional or improved bio-security measures. First, it is helpful to make a distinction between direct transmission (via transport of animals) and indirect transmission (other than via transport of animals). A simple model representation disentangling the indirect transmission between an infectious and a susceptible farm is given in Figure 1 below. We consider every possible indirect transmission route as a sequence of three processes:

1. *Infectious material excreted by animals on the infected farm leaves the farm in a route-specific manner.*
2. *The material is subsequently transported in a route-specific manner to a different and still susceptible farm or its immediate surroundings; part of the viral load present in the material survives the transport*
3. *Animals on the susceptible farm are exposed in a route-specific manner to a dose sufficient to cause infection.*

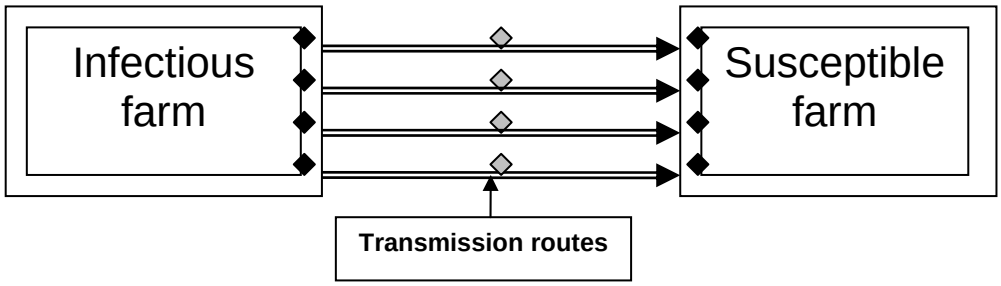

Figure 1. Schematic representation of (indirect) transmission routes between farms. Black diamonds symbolize opportunities for bio-security measures such as hygiene protocols suppressing the processes 1 and 3. Grey diamonds: opportunities for bio-security measures such as hygiene protocols and movement bans influencing process 2.

If the rates of process 1 and the probabilities of success for the processes 2 and 3 were known for all possible transmission routes, then it would be possible to calculate the relative risks of the individual routes. Subsequently, it would be possible to estimate the maximal effect of specific (improved) bio-security measures by working out which processes are affected by these measures or bans. If it is possible to estimate the extent to which a measure reduces the rate of probability of success of the relevant process, then also the expected effect of the measure can be calculated.
Clearly, a fully quantitative description as outlined above would require much quantitative and detailed data. Currently available data is not enabling us to come close in any way to obtaining sufficiently narrow and accurate parameter estimates for all the different possible routes and their underlying processes. However, as a starting point for further research, this literature study seeks to identify which pieces of information are available and which are not.

2.3 Information from epidemic data

We are interested in scientific papers that provide some kind of quantitative information related to routes of between-farm transmission for different highly transmissible diseases in livestock in the Netherlands and elsewhere. Obviously, data collected during epidemics is an important source of information, especially if the epidemic involved a large number of farms. Examples of such large epidemics are the 1997/1998 epidemics of CSF in the Netherlands [1, 2, 9, 16-20] and Belgium[4], the 2001 FMD epidemic in Great Britain [10-13, 21, 22], and the epidemics of AI in Italy in 1999/2000 [15, 23] and in The Netherlands in 2003 [3, 14, 24].
For Classical Swine Fever (CSF), the following papers obtain information by analyzing data from the 1997/1998 CSF epidemic in The Netherlands: [1, 2]. For Avian Influenza (AI), the following papers obtain quantitative information related to routes of between-farm transmission by analyzing data from the 2003 AI epidemic in The Netherlands and the 1999/2000 AI epidemic in Italy: [3, 23].

2.4 Contact-tracing data

For farms infected in the early stage of an epidemic there is usually a good chance that a plausible moment and route of infection can be determined by contact tracing. Such tracing data clearly presents information on the transmission rates along different specific routes. In addition, the infection prevalence on the farm at detection can be used to calculate an estimated time interval within which the infection might have entered the farm. This estimate can be used to check for consistency with the contact traced and possibly to exclude contacts traced to infectious farms as candidate infection cause if there are several such contacts traced on different moments in time.
The contact-tracing data available for the 1997/1998 CSF epidemic in The Netherlands perhaps provides the most powerful source of information on the quantitative importance of individual routes of between-farm transmission. In [2] these data have been analyzed, yielding estimates of transmission rates for the following specific individual routes: shipment of live pigs, lorries visiting an infected herd and subsequently a susceptible herd on the same day, persons in contact with pigs visiting an infected herd and subsequently a susceptible herd on the same day (combined with: shared equipment being used on an infected herd and subsequently on a susceptible herd on the same day), semen being transferred from an infected boar centre to a pig breeding herd, lorries that go to a susceptible herd after leaving an assembly point where pigs from an infected herd have been brought to be killed, and pick-up services from rendering plants picking up a dead pig on an infected farm and subsequently picking up a dead pig from a susceptible farm. The range of uncertainty in the estimated rates differs between the routes, and ranges from much less than one order of magnitude (pick-up service route) to several orders of magnitude (assembly-point route).

2.5 Neighborhood infections

The specific transmission routes considered in [2] and listed above derive from situations where contacts could be traced. All these contacts relate to movements and other type of contacts (via persons and shared equipment) that are banned shortly after the virus has been detected in the country. So these transmission routes are no longer relevant to the transmission dynamics after standard control measures have been installed, unless there is an illegal continuation of certain movements and contacts. However, usually in epidemics of highly-transmissible disease in livestock, new between-farm infections continue to occur after standard control measures have been installed, and for most of these infections no definite route can be traced. This has also (and dramatically) been the case in the 1997/1998 CSF epidemic in The Netherlands. In [2] these untraced contacts have been described by using geographic proximity as a risk factor. Indeed, the risk of transmission via an untraced route declines with distance for CSF [2, 4], and the same is true for AI [14] and FMD [10-13]. Because of this proximity effect these infections are often termed “neighborhood infections” [4, 17]. For an overview of hypothesized transmission routes that may underlie neighborhood CSF infections, see [25]. For an experimental confirmation of the possibility of CSF transmission via contacts with people, see [26]. Neighborhood infections are extremely important quantitatively, as they are responsible for the majority of farm infections observed in the largest epidemics in recent years (1997/1998 CSF epidemic in The Netherlands, 2001 FMD epidemic in Great Britain,

and 2003 AI epidemic in The Netherlands). Thus we observe that for the most important “class” of transmission events (i.e. neighborhood infections) the least direct information is available on the contributions of specific routes of transmission. The strategy must therefore be to try and combine the information that is there from the early stage of the epidemic with other sources of information. One of these sources of information arises from the study of farm-level risk factors for disease introduction.

2.6 Risk factors

Farm-level risk factors for disease introduction can shed quantitative light on the processes 2 and 3 in the model depicted in Figure 1. Factors associated with the introduction of CSF into pig farms infected via untraced routes in the 1997/1998 CSF epidemic in The Netherlands have been studied in [1]. In summary, seven risk factors were shown to be significantly associated with infection risk. Four of these factors were related to bio-security measures: whether the driver of a lorry transporting pigs for a welfare disposal scheme used his own boots instead of boots supplied by the farm, whether the lorry transporting pigs for the welfare disposal scheme was cleaned by the farmer outside the farm before it was allowed to enter, whether an aerosol produced during high-pressure cleaning of electrocution equipment used to depopulate a neighboring infected herd within 250 meters was carried by the wind onto the premises, and whether visitors could enter the pig units without wearing an overall and boots supplied by the farm. Comparison of the corresponding odds ratios suggests that the last two risk factor are quantitatively most important. Three more risk factors identified were the presence of commercial poultry in addition to pigs (possibly indicating enhanced contact risks between pig farms that also have poultry on the premises), whether the farmer had more than 30 years of experience in pig farming (possibly resulting in better bio-security practice), and the size class of the farm (with farms with 500-1000 animals or >7000 animals being more at risk than farms with <500 or 100-7000 animals). A study of farm-level risk factors in the 2003 AI epidemic in The Netherlands was carried out in [3]. Associations found in this study were less strong in comparison to those found in [1], and give less indications on the importance of specific transmission routes. From the broad perspective of respiratory diseases in swine, a literature review by Stärk [6] of environmental risk factors provides a wealth of references in which many different risk factors were identified. This overview may serve to identify possible risk factors and transmission pathways for highly-transmissible diseases and inspire further study. As noted by Stärk, despite the wealth of epidemiological studies, only limited information is available as to the quantitative importance of single risk factors.

2.7 Quantitative information from experiments

An outstanding body of work based on generating and analyzing quantitative experimental data is that of Donaldson and coworkers on the air-borne spread of FMD [7, 27]. The parameters quantified in this work have been used to construct predictive models of airborne spread through viral plumes requiring detailed information on local meteorological conditions. For a small number of farms infected during the 2001 FMD epidemic in Great Britain, this model has been used to investigate the possibility of airborne spread [21, 28]. The type of result from these predictive models that is

most useful for our goal of obtaining insight in the relative quantitative importance of different routes, would be to exclude the possibility of airborne spread for a large number of outbreaks, thus reducing the number of possibilities. Apart from the air-borne route of transmission, the quantitative data on airborne excretion may be also relevant for the study of other routes (particularly for process 1 within the model in Figure 1). For a review, again by Stärk, on what is known (or better, was known up until 1999) about the air-borne transmission of diseases in pigs in general we refer to [5]. Recent work on quantifying CSF virus in air samples originating from infected pigs and in experimentally produced aerosols is reported in [8]. Furthermore, experimental work has been done on the survival of CSF virus at various temperatures in faeces and urine produced by experimentally infected pigs (Weesendorp et al., under review). Other relevant quantitative information is that from infection studies on dose-response relationships [29].

2.8 Learning from endemic infections?

In the above we have focused mostly on information available for the former list-A diseases CSF, FMD and (highly-pathogenic) AI, that are exotic to The Netherlands (i.e. The Netherlands is free from these diseases most of the time). On the one hand, understanding the between–farm transmission is most relevant for these exotic diseases due to the importance of maintaining freedom from disease. On the other hand, quantitative information on the between–farm transmission can only be gained directly during crises. The question therefore arises whether our quest for a better understanding of neighborhood transmission of exotic diseases can profit from studying the between-farm transmission of infections that are endemic to The Netherlands and/or other developed countries. To give an overview on the relevant literature for such diseases is beyond the scope of this review. We refer to [30], in which different routes for the colonization of broilers by Campylobacter are considered, as a possible starting point for literature study.

2.9 Conclusions: knowns and unknowns

In the literature only very limited quantitative insight is available into the relative importance of individual routes of between-farm transmission of highly-transmissible diseases in livestock. For movement and personnel contacts in the period of spread before the presence of the virus in the country has been detected, useful estimates of individual transmission routes have been obtained for CSF using the data of the 1997/1998 Dutch epidemic. For other diseases such as FMD, much less quantitative insight is available in this respect. In modeling work that nevertheless presents a quantitative modelling of specific individual routes of FMD transmission between farms such as [31], it appears that the values of many of the necessary parameters are based on informed guessing (expert opinion) [32, 33], and are therefore subject to very large uncertainties.

An important problem is that for a large number of farm infections, notably the neighborhood infections, a specific transmission routes was never traced. The best quantitative information on risk factors for neighborhood transmission is available for CSF, due to data gathered during and after the 1997/1998 epidemic in The

Netherlands. Other useful information derives from experimental studies of virus excretion and survival as well as infection dose-response studies.

2.10 Recommendations

Considering the many unknowns still present despite a significant amount of past research, it would be an illusion to think that one day there would be a complete quantitative understanding of the between-farm transmission studied in this review. Nevertheless, I believe that progress can be made, by gathering more quantitative data using experimental and field work and by combining such quantitative data in mechanistic models for individual transmission routes. The following different types of research, in no particular order, can play a role:

- Experimental work on model systems for transmission across a distance
- Experimental work quantitatively studying sub-processes underlying transmission (excretion, survival, exposure)
- Mathematical modelling work that combines available data on different sub-processes and routes to obtain further insight. The mathematical models to be developed could be more formalized and detailed extensions of the simple model of Figure 1.
- Field work on between-farm transmission of endemic infections

These different types of research should be directed also towards the transmission properties relating to farm populations subject to (emergency) vaccination.

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