Responsible Use of Antibiotics on Sheep Farms

Application at Farm Level

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Introduction

There is global concern over rising levels of antibiotic resistance amongst commensal and pathogenic bacteria in human and animal populations. It is now considered that unless urgent action is taken by the medical and veterinary professions, we will enter a post- antibiotic era where bacterial diseases which were readily treatable with antibiotics will once again kill. Consequently, the use of antibiotics in both the human and animal health industries has come under intense scrutiny. Long held ideas and accepted behavioural norms have rightly been challenged. Progress in the agricultural industries has developed apace with the development of the Responsible Use of Medicine in Agriculture (RUMA) Target Task Force in December 2016 and the Department for Environment, Food and Rural Affairs (DEFRA) call for the implementation of sector-specific targets on antibiotic use.

Examination of antibiotic use in the sheep sector led by The RUMA Target Report [1], the Sheep Veterinary Society (SVS) [2] and supported by recent research [3] have identified that the areas of concern for the veterinary profession with regards to prescribing practices for sheep surround three specific disease management issues:-

i. Whole flock prophylactic antibiotic treatments for control of infectious lameness.
ii. Whole flock prophylactic antibiotic treatments for prevention of enzootic abortion.
iii. Whole flock prophylactic treatment of lambs against neonatal bacterial infections.

Responsible use of antibiotics in livestock is an ethical issue as we must at all times balance and justify our decisions in light of our primary consideration as a profession to uphold animal welfare. Current thinking on responsible antibiotic use in livestock

is that whilst treatment of individual sick animals with appropriate antibiotic therapy is **always** justifiable, metaphylactic treatment of groups of animals **can** be justifiable, prophylactic treatment of whole flocks or lamb crops is **rarely** justifiable (BOX1&2). There are many more tools available to us to manage these bacterial diseases aside from antibiotics, including; biosecurity, vaccination, hygiene measures, nutrition and other management actions. The responsibility lies with us as veterinary professionals to work closely with our clients to encourage their uptake and reduce dependence on prophylactic antibiotic strategies.

BOX 1: British Veterinary Association (BVA) Position on Use of Antibiotics in Food Producing Animals

1. BVA recognises antimicrobial resistance (AMR) as an issue of critical importance to society as a whole and is committed to providing leadership on this issue. Our overall aspiration is to reduce the use of antibiotics in animals under our care alongside improving the health and welfare of those animals, particularly through disease prevention strategies.
2. It is not possible to raise animals in sterile conditions; infections in animals are a reality and antibiotics will remain vital to treat bacterial infections in individual animals and in groups of animals managed within the same environment. Metaphylaxis will continue to be necessary in the face of disease outbreaks in groups of animals in order to minimise disease spread. Oral antibiotic treatments are effective and efficient methods of medicine delivery in some populations of terrestrial and aquatic animals.
3. BVA does not support the habitual use of prophylactic antibiotics. Animal husbandry systems reliant on such use must be interrogated and action plans developed to limit repeat disease occurrence and investigate alternative strategies for disease control, which may in turn impact upon the cost of food.
4. BVA opposes the introduction of arbitrary, non-evidence based target setting; such targets, to reduce antibiotic use, risk restricting vets' ability to treat animal diseases, which could have serious public health and animal welfare implications. However, we support the use of evidence-based targets to reduce antibiotic usage in

animal agriculture, which are likely to form part of the solution to address AMR globally.

BOX 2: Sheep Veterinary Society (SVS) Policy on Responsible Use of Antimicrobials in Sheep (2017)

1. It is essential that veterinary surgeons comply with the current veterinary medicines regulations regarding the prescribing of antibiotics and regulated by the Veterinary Medicines Directorate (VMD).
2. In addition veterinary surgeons should ensure they are prescribing in accordance with BVA guidance on responsible use of antibiotics.
3. Veterinary surgeons should engage with continuing professional development (CPD) on antimicrobial resistance and responsible antibiotic use.
4. **All** antibiotics should be prescribed responsibly, following current professional guidelines. However, in addition, the European Medicines Agency and the VMD consider special attention be paid to prescribing antibiotics according to the categorisation below:-

European Medicines Agency (EMA) Antimicrobial Expert Group (AMEG) Classification of WHO Critically Important Antimicrobial (CIAs) based on degree of risk to humans due to antimicrobial resistance development following use in animals

Category	Risk to Public Health	Antimicrobial Included	Advice on Use
A. Authorised CIA			
1	Low/limited risk to public health	Narrow spectrum Penicillins, Macrolides, Tetracycline	General principles of responsible use to be applied
2	Higher risk to public health	Fluoroquinolones, systemic 3rd and 4th generation Cephalosporins,	Restricted to use where there are no alternatives or response to

		(Aminogylcosides, broad spectrum Pencillins) Colistin	alternatives expected to be poor

5. Veterinary surgeons should work to reduce the total amount of antibiotics used on farms by encouraging uptake by farmers of alternate methods of disease control wherever possible. These include biosecurity, vaccination, improved farm hygiene and other management actions. Currently, areas where veterinary surgeons may be able to make the most impact to reduce the use of antibiotics on sheep farms are:-
    iv. Blanket treatment of lambs against neonatal bacterial infections
    v. Whole flock antibiotic treatments for lameness
    vi. Whole flock antibiotic treatments for enzootic abortion.
6. All sheep farms should have a health plan written in conjunction with their veterinary surgeon and reviewed at least annually. A review of preventative health strategies and antimicrobial use should be included in the health plan.

To support and encourage the profession in this endeavour, the Sheep Veterinary Society, alongside other planned activities, has produced "Good Practice Guidelines" [4] which detail their view on responsible antibiotic use for these diseases and it is these Guidelines that form the basis of this article.

Quite simply, the primary recommendations are that, in order to replace, refine and reduce antibiotics in these target areas, vets and sheep farmers should work to *plan* ahead, *prevent* disease and *protect* their flocks.

Lameness

Lameness in sheep is a common and serious welfare problem for many sheep flocks. In the analysis of data from 24 flocks served by one practice, two-thirds of the total antibiotic prescribed was primarily for sheep lameness (fig 1) [3]. In the UK lameness

is largely due to bacterial infectious causes e.g. scald, footrot and contagious ovine digital dermatitis (CODD) (Figure 2 a,b,c)).

It should be noted that it is entirely appropriate to promptly treat all sheep that are *clinically affected* with one of these bacterial infections with an antibiotic injection[5, 6]. Indeed, it may also be entirely appropriate to isolate and treat whole groups of clinically affected sheep in a flock. However whole flock treatments with antibiotics, and antibiotic foot bathing are not considered appropriate strategies (see below). Therefore the important challenge for lameness in sheep flocks is to *reduce* the number of new clinical cases of lameness that need antibiotic treatment.

BOX 3: "The Five Point Plan" [7]

THE FIVE POINT PLAN
1. Cull badly or repeatedly affected animals
2. Quarantine incoming animals
3. Treat clinical cases promptly
4. Avoid propagation of infection on farm
5. Vaccinate against foot rot biannually

Plan

The "Five Point Plan" (fig 3) [7] is the current sheep industry accepted standard for lameness control. It usefully summarises the tools which are available for lameness control on sheep flocks. Some or all of these can be applied on an individual farm basis following detailed veterinary investigation and formation of a farm specific plan. This should include:-

- Diagnosis of the causes of lameness in a flock.
- Assessment of farm specific risk factors. For example, seasonal trends, hygiene, housing, handling areas and field management.
- Design and application of farm specific disease control measures.

Reassuringly, research evidence shows that a reduction in new cases of lameness is fully achievable if the current tools available for lameness control are fully considered and applied by vets and farmers when tackling lameness in their flocks [7-9]. For further information, colleagues are referred to two recent articles for reviews of the current evidence base for management of footrot [5] and CODD [6] in sheep.

Prevent

The primary source of Dichelobacter and treponemes are from infected sheep though they will survive on pasture to some degree. Reducing the bacterial challenge on farm and thereby preventing sheep coming into contact with agents causing lameness can be through attention to the following areas:-

- Optimise hygiene of buildings, and handling areas by keeping as clean and dry as possible and use appropriate disinfection. For high sheep-traffic areas outside, such as gateways and around troughs, it may be appropriate to use lime or hard core.
- Ensure good hygiene of equipment that contacts sheep feet by cleaning and disinfecting hoof knives and gloves/hands between sheep.
- Biosecurity. Effective quarantine procedures are absolutely essential in preventing the incursion of types of *Dichelobacter* or treponemes that are novel to the flock.
- Reduce the numbers of infected sheep in the flock by isolation, prompt treatment or culling of clinical cases.

Protect

Protection of the flock can be achieved through

- Breeding lameness-resilient sheep and the culling of persistently lame sheep - two practices which require meticulous flock record-keeping.
- Vaccination against footrot. This tool is often the most immediately useful to the practitioner wanting to make a clinical impact. As with all vaccinations, the footrot vaccine is not a panacea, it cannot be relied upon in isolation.

However, research [10], clinical experience and countless farmer testimonies suggest that footrot vaccination has a significant role to play in reducing a flock lameness issue to manageable proportions.

The RUMA Targets aim to see an increase in the uptake of the Five Point Plan on sheep farmers and, as a quantifiable proxy of this, aim to see an annual 5% increase in the sales of footrot vaccine over the next five years [1].

Which antibiotic to use for clinical cases of footrot and CODD?

Oxytetracycline is the most commonly used antibiotic for footrot and is generally effective for *Dichielobacter.* There are no licensed treatments for CODD, however, amoxycillin and tilmicosin have proven efficacy *in vivo* and *in vitro* for CODD treatment [8, 10]. The recent authorisation for both tulathromycin (Draxxin; Zoetis) and gamithromycin (Zactran; Merial Animal Health) specifically for the treatment of footrot in sheep has led to their widespread (but unauthorised) use against CODD with the particular advantage of their duration of action. This is currently acceptable within the EMA definition of high priority critical important antibiotics though it would not be surprising if the goalposts were moved in the future.

Inappropriate Antibiotic Use

Two practices which have been widely used by some practitioners in recent years in the control of CODD and footrot, are whole-flock antibiotic treatments and foot bathing in antibiotic solutions. Whole-flock antibiotic treatment has been shown not to be sufficiently effective to justify its high use of antibiotics [8] and cannot be advocated. However whole-**group** treatment of infected sheep following careful segregation of lame sheep can be beneficial and should be considered.

The lack of published evidence to support the benefit of antibiotic foot bathing, together with its use of high volumes of unauthorised products and insufficient guidance as to effective dose or appropriate disposal, means that this practice cannot be considered as an appropriate or responsible use of antibiotics.

Enzootic Abortion

Abortions and stillbirths cause significant losses to UK sheep flocks with 30% of total lamb losses attributed to the period between scanning and lambing (fig 4) [11].

Enzootic Abortion of Ewes (EAE, caused by *Chlamydia abortus*) is the most commonly diagnosed cause in the UK (35% of all ovine abortion 2012-2018; GB Sheep Disease Surveillance). Effective vaccines are available against EAE and should be used as the first line in protecting at risk flocks. Whole flock, prophylactic antibiotics are not considered necessary nor appropriate for control of EAE in sheep flocks

Plan

Replacement ewes are the primary source of infection in EAE naïve flocks. If it is necessary to buy in replacements an effective biosecurity plan is required.

- Source replacements from EAE accredited free flocks
- Alternatively, animals should be sourced from as few flocks as possible, from flocks with a known disease history and flock vaccination strategy should be designed and implemented.

In addition, ewes from different sources should not be mixed for the first time whilst they are pregnant and purchased ewes should be kept separate from the home flock until after their first lambing.

Diagnosis of the cause of abortion is essential for ongoing control and to this end, aborted material should be taken for laboratory diagnosis and aborted ewes clearly identified so that serology can be undertaken.

Prevent

An aborting ewe is the primary source of infection for *Chlamydia abortus.* Therefore to reduce the infection load for infectious aborting agents from any aborting ewe

- Isolate ewe from the rest of the flock as soon as possible.
- All aborted material should immediately be removed, destroyed or sent for laboratory investigation.
- Clean, disinfect, remove or destroy contaminated bedding.
- Ewe lambs intended to be kept within the breeding flock should not be fostered on to ewes that either aborted or produced dead lambs.
- All human personnel should also be protected from aborting ewes and it is not advisable for pregnant women to be involved with either ewes or lambs around lambing time.

Protect

Vaccination strategies.

- Vaccination against enzootic abortion, is much more effective when administered before exposure to disease so in high risk flocks it is advisable as a precautionary measure. Flocks that are high risk for EAE to be introduced are those that buy in replacement ewes from flocks of unknown status. Even closed naïve flocks with close neighbours of unknown status with adjacent lambing fields, could also be considered as at risk and precautionary vaccination would be advisable.
- In the face of an outbreak of enzootic abortion, it is preferable to use an inactivated vaccine (eg Mydiavac; Benchmark) as soon as possible to reduce the spread of disease in the flock. In the year immediately following abortion due to Chlamydia, it is expected that either a live or an inactivated vaccine should be given to the whole flock by at least three weeks before the ewes are put to the ram (unless they were vaccinated in the face of the outbreak).

Inappropriate Antibiotic Use

There are areas of the country where there is evidence that certain farmers are still using prophylactic treatment of all ewes as a routine in late pregnancy to control EAE abortion. An unpublished questionnaire survey undertaken in 2015 suggested that this practice may be routine for 10% of sheep farmers [12].

Antibiotic treatment of ewes in late pregnancy, generally using a long-acting oxytetracycline, may help to reduce the number of ewes that abort but it does not reduce the shedding of Chlamydia, nor reduce the incidence of infected ewes within a flock. Neither is this a cost-effective approach when compared to vaccination over the medium to long term. It is not acceptable to use antibiotic to control abortion on an ongoing basis.

If it is not possible to use a dead vaccine in the immediate face of a new outbreak, it is acceptable to treat the affected group of ewes with injectable long-acting oxytetracycline. It is also acceptable to use this antibiotic treatment for later lambing ewes within the flock, when they reach the period between day 90 and day 126 of

that pregnancy or at the same stage for the affected group of ewes during their following pregnancy.

It is not acceptable to use routine antibiotic treatment in the period of late pregnancy as a control measure for abortion in general - i.e. in any flock **unless** in the face of an outbreak or if there has been a confirmed laboratory diagnosis of Chlamydia in the immediately preceding year.

Neonatal Lamb Bacterial Infections

Lamb morbidity and mortality due to the bacterial, infectious syndromes of "Watery Mouth Disease" (fig 5) and "Joint ill" (fig 6) are common on UK sheep farms. Over the past 30 years, on many farms we have come to rely on prophylactic use of antibiotics to whole crops of neonatal lambs for their control (fig 7). In 2015 there were 10.5 million doses of oral antibiotics (Orojet: Zoetis and Spectam:Ceva; figure 4) sold in the UK (CEESA International Sales Survey) and farmers report that veterinary surgeons in some regions will also prescribe antibiotic tablets to sheep flocks for prophylactic use in neonatal lambs. There are no antibiotic tablets licensed in food-producing animals so these antibiotic sales are not included in the UK Veterinary Antibiotic Resistance and Sales Surveillance Report (VARSS) reports. As recently reminded in published letters, veterinary surgeons are in the privileged position of being allowed to prescribe medicines under the veterinary cascade, but the use of any unauthorised products must be fully justified and have clearly auditable clinical evidence [13].

It is clear therefore that routine whole lamb crop prophylactic use of antibiotics for the whole lamb crop for the whole lambing season, is no longer considered a sustainable nor acceptable solution in most cases. That said, as veterinary surgeons our first priority must always be to the welfare of animals under our care, and a change in disease control policy on a farm should **never** be implemented without farm specific risk assessment and management through the health planning process. This is particularly important at the high risk lambing period.

"Watery Mouth" and joint ill

Watery Mouth Disease (WMD) is an endotoxaemia of neonatal lambs (figure 5). The disease is characterised by dullness, depression, salivation from the mouth, with or without abdominal distention and is typically associated with *E coli* infection. Morbidity and mortality can be high in a flock and for many years disease control has strongly relied on prophylactic administration of oral antibiotics to the neonate. Non antibiotic control measures have centred around ensuring timely and adequate intakes of ewe colostrum to the new born lamb and establishing good ewe and environmental hygiene [14]. Treatment strategies include use of non-steroidal anti-endotoxic drugs, fluids and antibiotics.

Evidence, suggests that *Streptococcus dysgalactiae* is the most common cause of joint ill (fig 6) in lambs under four weeks old in British sheep flocks [15]. *Erysipelothrix rhusiopathiae* is another agent that can cause septic arthritis in sheep, though typically this is in older lambs or adults and not in lambs less than one month of age, with a diagnosis on positive serology of affected cases Whilst in tick areas consideration should be given to *Staphylococcus aureus* associated with tick bites as the cause of infectious arthritis. Full consideration of the epidemiology and risk factors for these diseases is beyond the scope of this article, however there is an excellent recent review [16].

In general terms, for all forms of septic arthritis, early detection and treatment is essential and it is always appropriate to undertake diagnosis to identify the causative pathogen and antibiotic sensitivity profile – by arthrocentesis of affected joint for culture and sensitivity and/or post-mortem examination of untreated animals (fig 8). Ideally, multiple animals should be sampled to improve the chance of a diagnostic result. Clinical cases that are not treated promptly will respond poorly to antibiotic therapy. Culture and sensitivity results will inform the choice of antibiotic for treatment but it should be noted that oxytetracycline is seldom effective [17]. It is appropriate that severely lame lambs, that show insufficient clinical improvement within five days of treatment, are euthanized. Common control measures have involved whole lamb crop prophylactic administration of antibiotics.

However, recent research and clinical experience has emphasised the role of high environmental, equipment, and personal hygiene standards at lambing time and ensuring adequate and timely colostrum intakes.

A summary of the Plan, Protect, Prevent approach is shown in figure 9.

Plan

- Ewe nutrition. Appropriate nutritional management of pre- and post-lambing ewes is absolutely essential for ensuring lamb and ewe health. It ensures good lamb birth weight, lamb vigour, brown fat stores, ewe colostrum quality and quantity and influences ewe maternal behaviour. Therefore nutritional planning is necessary in any preventative health plan for neonatal lamb disease. This should include ewe body condition score as well as the quality, quantity, and accessibility to the diet. Readers are referred to the recent AHDB manual for an excellent guide to the topic [18].
- Housing should be planned to meet recommended stocking rates, group sizes and provision of suitable mothering pens [19].
- Neonatal lambs should be protected from stress by provision of adequate shelter from inclement weather.
- Husbandry tasks should be planned also to reduce stress. For example the need for tailing and castration should be scrutinised as well as the timing that they are undertaken (with recommendations of not before 24 hours old).
- Ewe lameness kept well controlled.
- Provision of sufficient competent staff to supervise the lambing period.

Prevent

To reduce the burden of pathogens the lambs are exposed to, ewe, equipment and environmental hygiene should be optimal. Their role in joint ill prevention, even in what appear to be farms with good standards of hygiene, has recently been highlighted.

- Ewes should be dagged or sheared pre-lambing
- When lambing assistance is required, clean gloves should be used for all ewes and hands and equipment regularly washed.

- The lambing environment, for both indoor and outdoor systems, should be sheltered and as hygienic as possible with appropriate stocking densities and lie-back area.
- Lambing pens should be dry, draft-free and cleanly bedded with appropriate cleansing and disinfection between occupants.
- Navels should be appropriately and effectively treated as promptly as possible after birth.
- Husbandry procedures such as stomach tubing, ear tagging, castration or tailing should be undertaken with close regard of hygiene. All equipment should be suitable cleansed and disinfected between individual animals.

Protect

The recent campaign "Colostrum is Gold" is designed to emphasise to farmers the critical role of ensuring adequate and timely colostrum intakes for the neonatal lamb. Current guidelines are

- 50ml/Kg BW as soon as possible after birth with a total of 200ml/kg within the first 24 hours.
- Where there is any doubt about effective passive transfer of colostral immunity, the situation should be monitored by testing blood samples from lambs under 5 days old (e.g. Zinc Sulphate turbidty (ZST) test or total protein).
- Vaccination of pregnant ewes against clostridial disease
- Vaccination for joint ill is possible if *Erysipelothrix rhusiopathiae* is confirmed to be the cause of the joint ill and following due consideration of the risks and responsibilities associated with the prescription of an unauthorised product [20].

Appropriate Antibiotic Use

- Treatment of joint ill and WMD cases. First line treatments should be planned ahead with the farmer and reviewed in the health plan. Treatment should be prompt, full courses should be given, and ideally based on culture and sensitivity analysis.

- Where there are farmers who are used to giving prophylactic antibiotic treatment to all lambs within a flock, it is suggested that vets should undertake risk assessment for different groups of lambs in the flock as shown in figure 10 with a rough worked example shown in figure 11. Good management and planning is the key to reducing the risk of disease and control measures should be discussed between the farmer and vet well ahead of lambing time, ideally at mid pregnancy, to give sufficient time to assess and implement new actions.
- Antibiotic treatments should be targeted only towards highest risk individuals, following a proactive flock health plan. Figure 12 gives suggested criteria for categorising the risk associated with lamb, ewe and environmental factors.
- Investigation of suspected treatment failure should be based on bacteriological culture and monitoring of the sensitivity of the pathogen to the antibiotic used on an individual farm. There are significant levels of resistance in *E coli* isolates from sheep, with higher levels in neonatal lambs (figure 13;[21]) This clearly emphasises the urgent need for farms to employ non-antibiotic preventative strategies and for vets to prescribe according to current professional guidance [22]

Inappropriate Use

- Whole-flock injectable or oral antibiotic treatment of lambs in order to prevent "Watery Mouth Disease" or "Joint-ill" is very rarely appropriate as a routine management action.
- Use of unlicensed medicines, unauthorised for use in food-producing animals, unless justified under the "cascade".
- Use of the high-priority critically important antibiotics (fluoroquinolones, systemic 3rd and 4th generation cephalosporins and colistin, as designated by the European Medicines Agency and the VMD) Box 2. These are already used at very low levels within the UK sheep industry [1]. Practitioners are urged to only use them in sheep under exceptional circumstances, where culture and sensitivity clearly indicate that there is no alternative appropriate antibiotic and follow appropriate licensing regulations.

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416 Implementation

417 Reduction, replacement and refinement of antibiotic use in sheep flocks should be
418 implemented by a whole veterinary practice, planned approached [23], and not left to
419 individual vets in the practice to address when the client appears at reception with a
420 “shopping list”! Otherwise the practice risks poor animal welfare and damage to
421 relationships with clients. It will require closer engagement with sheep farmer clients in
422 preventative medicine through activities such as flock health planning, regular farmer
423 meetings and vet/farmer clubs [24]. Practitioners should be encouraged to collate individual
424 flock usage for auditing purposes as well as to satisfy recently updated Red Tractor Farm
425 Assurance guidelines. Through improvement in preventative medicine uptake in sheep
426 flocks there is considerable potential to improve sheep flock health, welfare and economic
427 performance whilst addressing the global public and animal health challenge of emergent
428 antibiotic resistance.

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Figures

Figure 1 Proportion of antibiotic prescribed to 24 sheep-only farms of over 100 breeding ewes, between August 2015 and July 2016. 'Others' made up of lincomycin 4.7%, fluoroquinolones 0.5% and florfenicol 0.5%, with the remaining 0.9% consisting of cephalosporins, sulphonamides, trimethoprim and thiamphenicol (Davies et al 2017)

Figure 2 Infectious Foot Disease Lesions in Sheep
A Interdigital dermatitis (scald)
B Foot rot
C Contagious Ovine Digital Dermatitis (CODD

Figure 3 The Five Point Plan (Clements and Stoye 2014)

Figure 4 Indication of the proportion of lambs lost at different stages of development

Figure 5: Lamb with Watery Mouth Disease

Figure 6: Lamb with Joint Ill

Figure 7 Administering oral antibiotic to a neonatal lamb

Figure 8 Post mortem examination of lamb with joint ill (photo Phillipa Page)

Figure 9 An infographic describing the Plan, Prevent, Protect strategy with respect to controlling bacterial neonatal lamb diseases

Figure 10 Suggested flow chart of the steps to undertake risk assessment on groups of lambs within the flock with a sketched-out example (figure 11)

Figure 11 Example flock with rough detail of application of risk assessment

Figure 12 Suggested scoring system for assigning risk to lambs based on factors relating to the lamb, the ewe and the environment. Clearly it is not expected that this will be undertaken for every lamb but it can be used to indicated different risk groups (as identified in figure 10)

Figure 13 Total number and percentage of resistant isolates of *Escherichia coli* from sheep (by age category) in 2016 taken from VARSS report (VMD 2017)