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What is the proportional contribution of cattle-to-cattle, badger-to-cattle, and deer-to-cattle TB transmission to bovine TB in Ireland?

TB Scientific Working Group
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1 Background

1. Tuberculosis (TB) is a multi-host disease affecting humans, domesticated and wild animals including cattle species [1]. It is a contagious disease spread both by direct contact but also by indirect means. While the usual route of infection is by inhalation, oral infection also occurs. TB is exacerbated in all species by the impact of malnourishment, poor sanitation, poorly ventilated housing, close contact and overcrowding.

2. The primary causal agent of TB in cattle, *Mycobacterium bovis*, is a member of the *Mycobacterium tuberculosis* complex (MTBC). This complex also includes *Mycobacterium tuberculosis*, the main causal agent of TB in humans. Members of the complex are closely related species in their genetic make-up. While the different members of the complex have a predilection for specific species, they also have the ability to transmit to other species, e.g. *M. bovis* can infect humans and *M. tuberculosis* sometimes infects cattle.

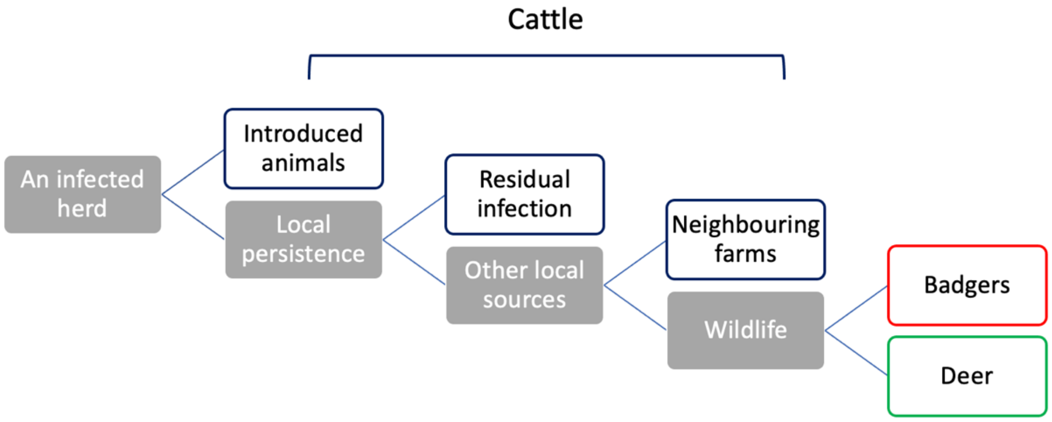
3. Progression of infection is protracted from initial exposure to clinical signs, taking months or even years. However, observations of clinical signs become uncommon once an eradication programme, including live animal testing and removal of those infected, commences.

4. The complex epidemiology of TB in cattle is well recognised, with the role of wildlife in transmitting infection to cattle acknowledged as an impediment to eradication [2–4]. However, a detailed understanding of inter-host transmission dynamics and their relative importance has been a recognised major knowledge gap. This has been mainly due to the slowly evolving nature of *M. bovis* and the lack of practical, cost-effective methods to discriminate between isolates. In cattle, it is also hindered by the frequency of skin testing where disclosure of a reactor does not necessarily reveal the precise timing and location of the infection event. It only points to an historic transmission of infection that could have occurred in a time frame ranging from weeks to years previously.

2 Evidence, in general, that cattle-to-cattle, badger-to-cattle and deer-to-cattle transmission each plays a role in the transmission of TB to cattle in Ireland

5. It is important to consider this question within the framework of recognised sources of TB infection in an Irish context [4]. As highlighted in the figure below, these include:
   - <u>From cattle</u>, either:
     - introduced infection,
     - residual infection (that is, infected animals that test negative to current diagnostic tests), or

  - infected cattle in neighbouring farms.
- <u>From badgers</u>
- <u>From deer</u>



6. For each source, both direct contact and indirect environmental exposure are a potential risk: direct transmission may occur when there is close contact between animals; indirect transmission may occur via contact with infectious excreta such as faeces, urine or sputum in the environment.
7. There is a large body of evidence for direct transmission between cattle which indicates that transmission occurs readily but at a lower rate outdoors when compared with housed environments [5–9].
8. Traditionally there was a paucity of evidence to indicate indirect transmission resulting from environmental sources, even with heavily contaminated pastures [10,11]. This may be partly related to the difficulty in establishing the mechanisms under natural field conditions because of the lag in time between the exposure event, establishment of infection and detection of infection with the skin test. However, advancements in environmental sampling and isolation techniques enabled French researchers to find samples positive for the presence of MTBC and *M. bovis* strains in the environment of farms affected by TB [12]. The persistence of detection for months after the removal of diseased animals and the detection of MTBC positive signals in 10% of water samples from naturally occurring water sources is supportive of a potential role of water in the dissemination of MTBC in the environment and in animal contamination. In a review of the scientific literature, Allen et al. concluded that cattle and other species may contribute to the contamination of the environment and thus be a potential source of infection to any susceptible species which shares the same environment [13]. However, evidence of indirect transmission is still lacking and the significance of environmental contamination is still unclear. It is expected that the further application of new methodologies may provide more clarification to the role of indirect transmission of TB in the coming years.

9. Infected wildlife can play differing ‘epidemiological roles’ with respect to TB in cattle. Wildlife species can act as either:

   - *a spillover host,*

- *a maintenance (or reservoir) host* [allowing infection to self-sustain in that wildlife species], or
- *a maintenance host with spillback to cattle* [14,15].

A spillover host is likely of lesser concern for national TB eradication, whereas wildlife that act as a maintenance host with spillback to cattle, such as badgers in Ireland, pose substantial challenges. The ability of a species to act as a maintenance host will be dependent, among many factors, on that species being present at sufficient density to maintain TB independently without the need for another infection source of TB.

2.1 Evidence of cattle-to-cattle transmission

10. Cattle are a maintenance host for TB [16], with infection being sustained in cattle in the absence of any other susceptible species. Indeed, the origins of *M. bovis* are thought to be linked to the domestication of cattle in East Africa, with subsequent dispersal to different parts of the world driven by cattle movement [17,18]. Prior to the 1960s, TB eradication programmes were based solely on efforts to mitigate cattle-to-cattle transmission. This strategy proved highly effective in a number of settings [19], leading to successful eradication from each of the countries of northern Europe [20], from all but northern Australia [21], throughout US and Canada except in areas where wildlife reservoirs are implicated, specifically Hawaii [22], Michigan [23], Minnesota [22], and several national parks in Canada [22].

11. The cattle herd is the primary epidemiological unit in TB and this opinion focuses primarily on herd-to-herd transmission. Nonetheless, transmission of *M. bovis* between herds will be amplified by within-herd transmission which, by definition, describes transmission between individual animals.

12. Introduced TB-infected animals are recognized as a potential infectious source:

    - There is very substantial movement of cattle in Ireland. In 2016, there were 1.3 million movement events, this being all journeys travelled by vehicles (such as trailers) to transport cattle to marts, new herds, slaughter plants or export facilities [24].
    - Substantial cattle movement coupled with residual infection offers the potential for ongoing *'churn'* or the efficient cattle-to-cattle recycling of infection within the national population.
    - An estimated 6–8% of TB restrictions have been attributed to the recent introduction of an infected animal, based on data from 2003-04 [25] and 2012 [26]. In these studies, source attribution was determined after considering the past movement history (including potential for TB exposure) of animals identified as reactors at the start of a TB restriction. However, there are several reasons why these estimates must be interpreted with caution. On the one hand, 'potential for exposure' was assumed to lead to infection in these calculations, and if this is not always the case, risk has been overestimated. Conversely, the potential for latency (animals becoming infected following exposure but passing at least one test following introduction) was not considered at all, and risk has been underestimated if it is important. There is now an opportunity to re-evaluate the role of movement on TB restrictions in Ireland, using new methods to evaluate trading networks [27,28], and these are currently being applied.
    - Recent work from the UK [29] investigating an emergent *M. bovis* outbreak in an area of England with no previously known wildlife infections and where cattle TB was considered very low risk has demonstrated that this outbreak was due to the

single introduction of *M. bovis* with cattle from Northern Ireland that occurred at least 6-years prior to its discovery in badgers. Indeed, the introduction of *M. bovis,* may have occurred up to 16 years before first detection in a bovine – the introduced bovine case was never identified. Undoubtedly, the initial spread would have been from bovine-to-bovine and thence onwards to badgers. It is likely that multiple infected animals escaped detection at slaughter and skin test during the period prior to first detection of infection in a home-bred 7 month old bovine. By the time this first bovine was detected in 2014, multiple herds in multiple counties were already infected and the infection had spread into badgers. Further study indicated that most transmission had occurred within species with a lower number of inter-species transmissions but that there had been more cattle-to-badger than badger-to-cattle transmissions up to the time the study was completed.

13. <u>Residual infection</u> in cattle is an important contributor to herd infection:

    - Residual infection refers to the presence of infected – but undetected – cattle. This is of particular concern at the time of TB derestriction, noting that residually infected animals can pose a future infection risk within the index herd or to livestock in neighbouring herds, or to - and within - herds to which the animal subsequently moves or to the local wildlife or to the local environment both within the farm but also in the general environment e.g. in slurry and 'broadcast' with slurry spreading [30,31].

    - Multiple studies from a range of countries have highlighted the contribution of residual infection to TB persistence in a herd or locality (including [4,21,32–34]. Further, difficulties in clearing infected herds, leading to herd TB recurrence, has been identified as a key challenge to TB eradication, both in Ireland [4] and New Zealand [34].

14. Infected cattle in neighbouring farms

    - Although the biosecurity risks are clear [35], there has been relatively little research on the relative importance of infection from <u>neighbouring herds</u>. TB prevalence in the locality is a recognized risk factor [36], however, this does not distinguish neighbouring cattle from 'other local sources'.

2.2 Evidence of badger-to-cattle transmission

15. The role of badgers in the epidemiology of TB in cattle has been subject to intensive investigations since *M. bovis* infection was first identified in badgers in Ireland in 1974 [37]. Infected badgers satisfy the criteria for a maintenance reservoir host for *M. bovis* in Ireland [14]. They are highly susceptible to infection and the social structure of badgers facilitates close interactions that lead to an increased risk of transmission. Infection with *M. bovis* is endemic in Irish badgers [38,39]; however, prevalence is not uniform throughout the country [40]. Badgers in areas with herd breakdowns have a higher prevalence of infection than the badger population at large [39]. Results from the Four Area Badger Removal Study in Ireland provided evidence of a positive effect of badger culling on incidence rates of tuberculosis in associated cattle herds [41]. These observations provide robust evidence that badgers play a key role in the epidemiology of tuberculosis in cattle.

16. Strain typing of *M. bovis*, whereby genetically related strains can be distinguished, has historically used a combination of multi-locus variable number of tandem repeats analysis (MLVA) and spoligotyping methods. These approaches have demonstrated that both

badgers and cattle share similar strains with geographic clustering across hosts indicative of interspecific transmission at a local scale, in Ireland [42–45] and in Northern Ireland [46–48]. *M. bovis* infections typically present as a series of geographically localised micro-epidemics [36,49]. While these strain typing techniques can be used to define *M. bovis* strain type home ranges [50,51], their lack of discriminatory power limits their ability to elucidate and quantify inter and intra species transmission dynamics.

17. The UK and Ireland have the highest average recorded density of badgers compared to any other country in Europe [52]. Moreover, badgers are distributed throughout the country. The density varies according to factors such as soil type, altitude, drainage and habitat composition. As regards soil type, badgers prefer sandy loamy soils for sett construction [2]. The density of both cattle and badgers and/or total density in the environment is considered to be a key risk factor for inter-species transmission [53]. Large-scale epidemiological studies in Ireland [54] and Northern Ireland [55] have found significant and positive associations between metrics of badger density and increased TB herd breakdown risk.

18. Transmission of *M. bovis* between badgers and cattle in Ireland is facilitated by the fact that badger setts are located predominantly in hedgerows and that cattle are kept on pasture for a large part of the year. Feed supplied to cattle may also be available to local wildlife, and this would put wildlife and cattle into closer contact than might otherwise be the case [56].

19. In summary, badgers are an important maintenance host for *M. bovis*, acting as a reservoir of infection with spillover of infection to cattle, on the island of Ireland [57], in Great Britain [58], and likely in parts of mainland Europe [59,60].

2.3 Evidence of deer-to-cattle transmission

20. In some countries, there is evidence that wild deer act as a maintenance host, playing an important role in the epidemiology of TB in cattle [53].

21. In Ireland, data are sparse, and the epidemiological role played by wild deer (predominantly Sika (*Cervus nippon*) or Sika hybrids) is not certain.

    - Using occurrence data (that is, presence or absence in defined areas, based on confirmed deer sightings), Carden et al. found a considerable expansion in the range of several deer species in Ireland between 1978 and 2008 [61]. Based on hunting bag data from the National Parks and Wildlife Service, Kelly et al. found that there was an increase in the number of sika deer in many counties between 2000 and 2018, with the overall population increasing from 18,288 in 2000 to 72,423 in 2018 [53].
    - Based on available data (unpublished, except Doyle et al. (2018), TB prevalence in wild deer is very low in most areas of Ireland:
        - Based on the results of passive surveillance of deer – that is, wild deer that were shot and submitted to Regional Veterinary Laboratories for TB testing - from areas outside Co. Wicklow during the years 2016 and 2020 inclusive, 467 wild deer were tested and 10 (2.1%) were reported to have had TB (Parliamentary Question 14918 21).
        - Of 17 wild deer that were examined during a large outbreak of TB in north Co. Sligo in the period 2014-2016, none were found to be infected [62].
    - Higher TB prevalence has been observed in Co. Wicklow, particularly in recent years:

  - Tissues from 130 wild deer shot by hunters in County Wicklow, Ireland in 1983-1984 were examined for evidence of tuberculosis. Gross lesions were found in five deer [64].
  - Based on the results of passive surveillance of deer – that is, wild deer that were shot and submitted to Regional Veterinary Laboratories for TB testing – 35 (12.9%) of the 272 deer examined from Co. Wicklow during the years 2016 and 2020 were positive (Parliamentary Question 14918 21). The comparable figure in the rest of the country for the same period was (2.1%). Considerable caution is required in interpreting this type of passive surveillance data given the different surveillance methods and effort used across different counties. In deer infected with TB, the *M. bovis* is primarily located in the head and thorax [65,66]. It should be noted that it is often the case that only the head and the contents of the thoracic cavity (lungs) are submitted, so the full deer carcase is not always available to determine the overall distribution of infection.
  - An unpublished DAFM research study carried out in the Calary area of Wicklow in 2014 and 2015 found that 16% of deer had TB in that area. Sampling was random, using fresh full carcasses. This area had a high prevalence in cattle. The same (local) *M. bovis* strain was identified in cattle, badgers and deer.
  - A follow-up study by DAFM, from the same area, reported that 8.3% (10/121) of deer shot on farmland had TB, whereas 0% (0/32) of deer from a nearby control area (in the National Park) were infected. Sampling was non-random, utilising frozen heads and plucks
- In addition, there is further evidence that deer may be influencing the epidemiology of TB in cattle in Co. Wicklow:
  - Using whole genome sequencing on *M. bovis* isolates from cattle and deer from the Calary study, Crispell et al. found that cattle and deer share highly similar *M. bovis* strains, suggesting that transmission between these species is occurring in the area [67]. Further, the high level of diversity observed in the sampled deer population suggested that deer may be acting as a source of infection for local cattle populations. Within-species diversity is commonly used to evaluate the epidemiological role of species, with high diversity suggesting the species is acting as a source of infection [68]. However, conclusive evidence on the direction of transmission was not possible from the limited sample number.
  - In Co. Wicklow, when using hunting bag data from the National Parks and Wildlife Service to determine population levels of deer and allowing for deer aggregations in preferred habitats (e.g. pasture and woodland), higher levels of TB in cattle are associated with higher local densities of Sika deer. Further, densities of Sika deer in Co. Wicklow are now at regional densities comparable to deer populations in other countries where TB maintenance has been demonstrated [53]. Crispell et al. highlighted the fact that “County Wicklow represents one specific area in the Republic of Ireland with a high density of deer that has had consistently high bTB prevalence for over a decade, despite control operations in both cattle and badgers” [67] .

3 Issues in determining the relative contribution of the different transmission routes

22. In endemic situations, as in Ireland, where there are multiple sources involved and multiple control measures in place, it has proved very difficult to disentangle the relative contribution of different infection sources using current epidemiological methods [3,4]. In

addition, it is difficult to determine the extent to which indirect transmission of *M. bovis* occurs from each of these sources.

23. Research to-date has mainly focused on individual infection sources, such as introduced cattle, residual infection or badgers. Further advances are expected in these areas, with recent advances including:

    - Improved methods to assess introduced cattle as a source of infection (network metrics, ongoing contact chains), see [27,28].
    - Improved understanding of residual infection, using advanced modelling methods [33].
    - A range of methods relevant to 'other infection sources', including approaches to herd fragmentation and spatial networks of land parcels. Further, *M. bovis* whole genome sequencing offers the potential to understand, discriminate and quantify local infection sources [67].

24. To-date, there has been only limited success in disentangling the various contributors to 'other local sources' (neighbouring cattle, badgers, deer), either using national data or during local investigations. Important progress was made by White et al. [69], who investigated the relative importance of 'neighbourhood' (other local sources and residual infection) on TB persistence, with the following attribution:

    - 15% to residual infection
    - 0-20% to spread from neighbouring farms
    - 19-39% to wildlife (i.e. badgers)

    This study was conducted on Irish data during a single period in time, 2001-2006, following the completion of the Four Area badger removal [41] and before the commencement of the national strategy of focused badger removal [70]. For this reason, these results cannot be readily extrapolated. As noted by White et al. [69], it would be useful to repeat the analysis in areas of the country where badger-to-cattle transmission is likely to have been reduced to low levels, such as within the areas of the Four Area project subjected to proactive badger removal. This would allow for a better estimation of true cattle-to-cattle (herd-to-herd) spread among directly contiguous herds.

25. In further work by Aznar et al. [71], the transmission among cattle, among badgers, and the interspecies transmission (cattle to badgers and badgers to cattle) in Ireland was quantified and disentangled by deriving new simple mathematical formulae based on estimations of the prevalence of TB in cattle herds and badgers and the number of cattle herds that were likely to be in contact with badgers and the number of badgers present in Ireland. The reproduction ratio, R, was used to summarise the dynamics of the infection between and within the cattle herd and badger populations. R was defined as the average number of new cases caused by one infectious individual in a non-necessarily completely susceptible population. An epidemic can only be sustained if R is greater than one. This approach allowed calculations of the relative contributions of cattle and badgers to the maintenance and transmission of the *M. bovis* infection. One of the main results from this work was the finding that the most plausible value for the reproduction ratio for cattle herd to cattle herd transmission in Ireland was below 1 and the maximum value was 1.07 (not far from 1). These values indicate that, although further controls in cattle would be required, cattle-to-cattle transmission is not the largest constraint to disease eradication. Indeed, the mean reproduction ratio for badger-to-badger transmission (R_{bb}= 0.77) was about twice of that of the cattle herd to cattle herd transmission (R_{cc}= 0.36). These estimates come with a number of points of caution. Specifically, the work currently only

considered a two-host system (cattle, badgers). The work was based on national averages (e.g. cattle herd and badger TB prevalence), therefore R would be expected to vary in different areas.

26. Analysis of data from England estimated that while the overall contribution of badgers to confirmed TB herd breakdowns was 52%, only 5.7% was directly attributed to badgers as a primary source of infection (with the difference reflecting the role of onward cattle-to-cattle transmission) [72]. However, these values had wide confidence intervals. In Northern Ireland, 21% of confirmed TB herd breakdowns have been attributed to a badger source by investigations carried out by DAERA veterinary officers [73]. In another study, approximately 40% of breakdowns were attributed to the presence of a contiguous herd that had a confirmed breakdown, and 40% to the presence of badgers [74]. Information from other countries on the relative contribution of different sources of infection should be treated with caution given differences in past TB history and variations in approaches to disease control and other factors.

27. As noted above (15), *M. bovis* strain typing has relied on MLVA and spoligotyping methods. In recent years, Whole Genome Sequencing (WGS) technologies and associated phylogenetic analytical frameworks are available and can be practically applied as a research tool for *M. bovis* disease investigations. Using such techniques, the available evidence so far has indicated that situations can vary considerably depending upon the geographical location/population demographics. In the Woodchester Park (England) situation, badger-to-cattle transmission occurred up to nine times more commonly than cattle-to-badger transmission indicating that wildlife can play a key role in maintaining livestock infections within this local area [75]. In contrast, analysis of data arising from a 100km^2 study area in Northern Ireland, indicated that with cattle-to-badger transmission being approximately three times more common than badger-to-cattle transmission and suggested that badger-to-badger transmission may not be a key determinant of disease persistence [48].

28. To-date, there has been limited success in simultaneously considering all infection sources. Expertise and methods to do this are now available (Madden et al., submitted), and will be applied in the near future.

    - Epidemiological models have the potential to assist in determining relative importance of different infectious sources. As yet, there has been no such modelling of TB in Ireland, in contrast to BVD [76], IBR (Brock, in preparation) and Johne's disease [77]. It is expected that these methods will soon be adapted to TB.

4 Conclusions on the proportional contribution of cattle-to-cattle, badger-to-cattle, and deer-to-cattle TB transmission to bovine TB in Ireland

29. Currently, because of the localised nature of the disease and the complex interactions between the different sources, it is not possible to give a precise breakdown at national level of the proportional contribution of cattle-to-cattle, badger-to-cattle, and deer-to-cattle TB transmission to bovine TB in Ireland. Research to-date indicates that TB occurs in local epidemics with each instance being context-dependent, driven by local host population demographics as well as animal husbandry factors.

30. However, some general conclusions can be made as to their relative contributions to the occurrence of TB in cattle herds in Ireland:

    - There is strong evidence that the cattle-to-cattle transmission pathways contributes to TB in cattle in Ireland. Cattle herds can be subjected to movement restrictions resulting from cattle-to-cattle transmission by a variety of ways, including purchases, residual infection and transmission from a neighbouring herd. Taking into consideration all potential routes, cattle-to-cattle transmission is likely to constitute a dominant route of transmission for cattle herds. In addition, cattle-to-cattle transmission between herds will be compounded by within-herd transmission.

- There is strong evidence that badger-to-cattle transmission pathways contributes to TB in cattle in Ireland. While the precise contribution of badgers to breakdowns in cattle herds is not clear, it is likely to be significant. It must be recognized that infection from this source can be compounded by dissemination of the infection within and between cattle herds by cattle-to-cattle transmission. Therefore, even if such inter-species infection events are uncommon, they can have significant consequences for the eradication of TB in Ireland.
- Apart from Co. Wicklow, there is currently no evidence to support deer acting as a maintenance host for TB, i.e. a host in which the infection is self-sustaining. It is more likely that they act as a spillover host, i.e. a host in which infection occasionally occurs as a result of transmission from a maintenance host such as cattle or badgers. There is strong evidence that the deer-to-cattle transmission pathway contributes to TB in cattle in Co. Wicklow but evidence that this pathway contributes to TB in cattle is lacking for other parts of the country. In TB hot-spot areas of Co. Wicklow, deer may be playing an important epidemiological role in transmission of infection. However, the relative contribution of infected deer to local TB epidemiology (establishment and spread) in these areas, compared with cattle and badgers is currently uncertain.

31. Based on international experience, eradication efforts will only be successful if all relevant sources are addressed, including:

    - All cattle sources that substantially contribute to herd infection, and
    - All wildlife that are maintenance hosts, and particularly those with spillback to cattle.

    Indeed, in complex systems such as *M. bovis* infection in animal populations, it is extremely unlikely that eradication can be achieved unless all factors contributing to persistence and spread are addressed. This has been a key lesson from the successful Australian TB eradication programme [21], and from experiences in several other countries, including New Zealand [78] and the USA [79]. The need to tackle all sources of transmission is not a new concept or suggestion. In 1958, Francis, an English veterinarian who emigrated to Australia where he advised the Australian Bovine TB Eradication programme, when speaking of the difficulties in the final stages of eradication of TB, recommended that TB had to be dealt with in all species to achieve complete success. This advice is as relevant today as it was in 1958.

5 Recommendation

32. The TB Eradication Programme should address, at both national and local levels, all relevant sources of transmission of TB to cattle. Current relevant sources include:

    - All cattle sources that substantially contribute to herd infection, and
    - All wildlife that are maintenance hosts, and particularly those with spillback to cattle.

    This situation may change over time and should be kept under review.

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