Use of EMA's risk assessment Guideline – Danish experience

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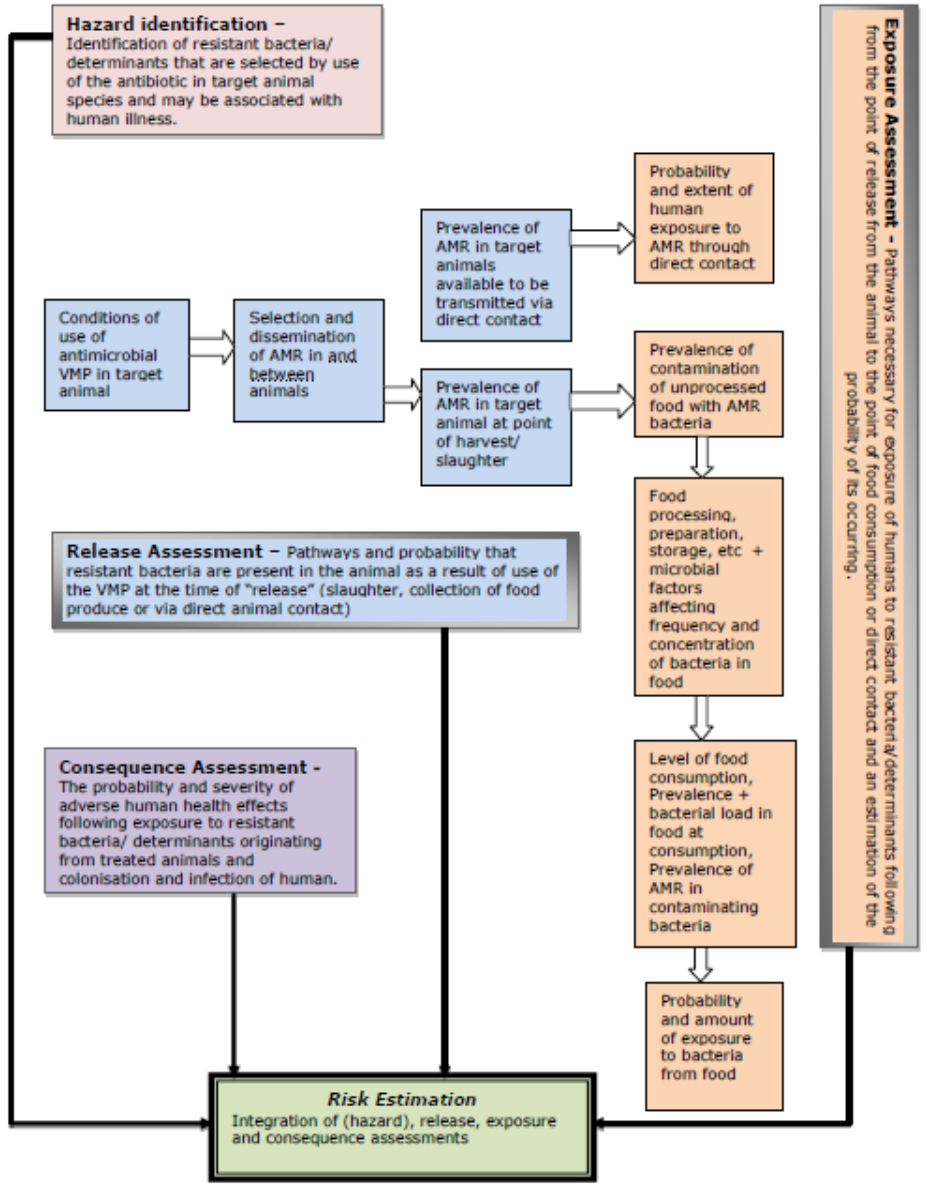


European Medicines Agency, London,
September 19, 2018

Tradition for AM treatment Guidelines in Denmark

Guidelines in place since 2005

- Qualitative approach, extensive use of expert opinion,
- Method: US FDA Guidance #152 to Industry
- Work undertaken in collaboration between academia, government, agency and industry
- Under the umbrella of the Danish Veterinary and Food Administration (DVFA)

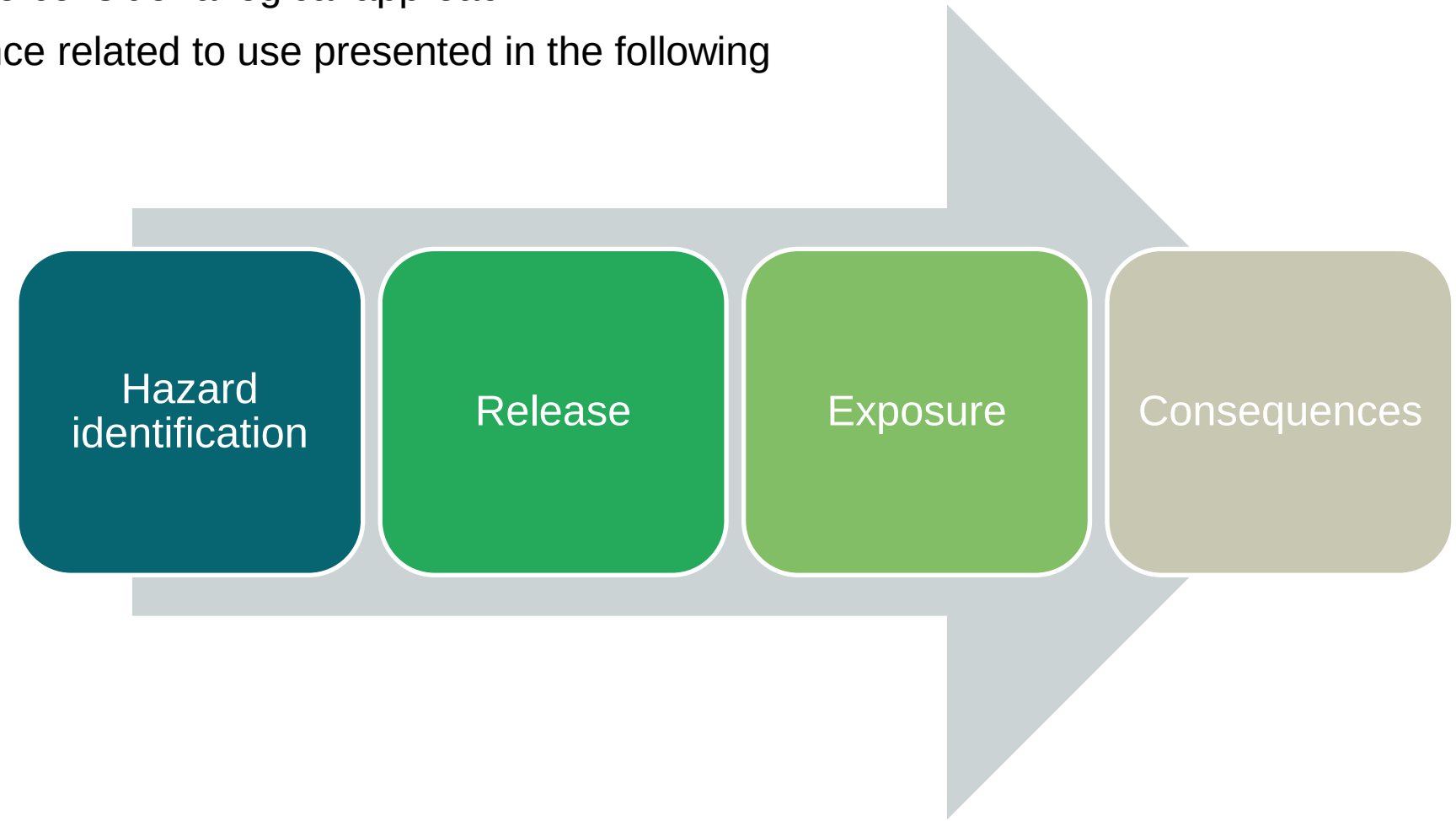
Update of treatment guidelines in 2016-17

- We wanted to use a better method

EMA’s Guideline to evaluate risk

Chosen among others because it follows OIE’s approach to risk assessment

- Which we consider a logical approach
- Experience related to use presented in the following



General approach – which data to use?

For hazard identification

- All evidence used - irrespective of origin outside the EU

For risk assessment (and exposure assessment)

- National data primarily
- Data from EU/comparative countries,
  - If no national data were available

Not really specified in the EMA Guideline

- Except from a mentioning of variability of risk factors within EU

Qualitative approach used

- Scale used for each risk element: Very low, low, medium and high
- Scale used for uncertainty: Low, medium and high

Included in the updated EMA Guideline

EMA Guideline: probability

- But it is prevalence/incidence we are using

Challenge - Hazard identification

Systematic approach to select relevant hazards needed

- To document, justify and communicate

Solved by developing a risk pathway

- One pathway drafted for each combination of kind of resistance and type of bacteria

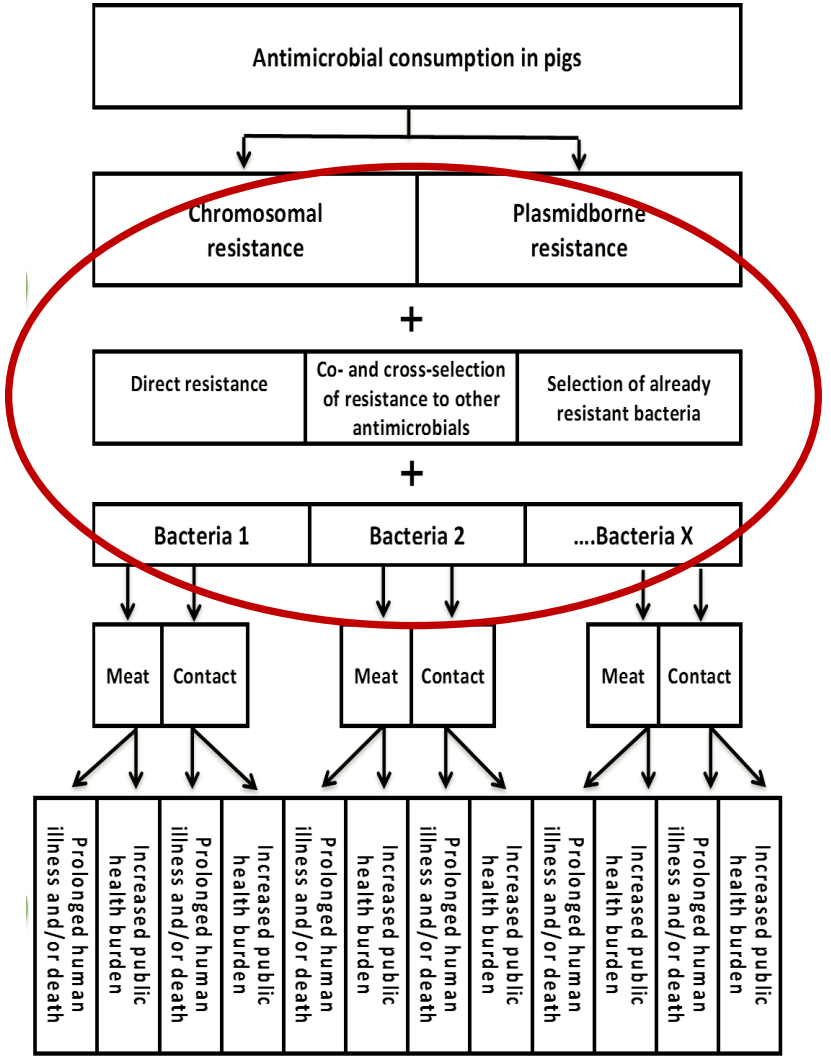
Revised EMA Guideline is more detailed on these issues

- Zoonotic pathogens: focus on those for which the concerned AM is a recognised treatment in humans in EU
  - This will help the users in identifying the hazards
  - And distinguish between a potential and a relevant hazard

Emergence or presence?

- We looked at presence

} Not dealt with sufficiently in EMA Guideline



Hazard identification

Pleuromutilin use in Denmark:

- Extensively in Danish pigs - 10% of the total consumption
- Curently no human use of pleuromutilin, but new drug in pipeline (Lefamulin)
- Limited use of linezolid, a last line antibiotic in humans

Data available in DANMAP/ Vetstat registers

We identified the following as relevant hazards:

- Livestock-associated *Staphylococcus aureus* – through contact route
- Enterococci – through foodborne route or contact route

Fine that both routes are included in EMA Guideline

Anaerobe bacteria (e.g. *Clostridium*) described to carry relevant resistance genes

- But neither pleuromutilins nor linezolid are used for treatment in these cases
- No surveillance of resistance mechanisms in human anaerobe bacteria
  - Therefore not included in our risk assessment

Not mentioned by EMA Guideline how to handle this

Release assessment

Limited data show low prevalence of pleuromutilin-resistance in enterococci in Denmark

- According to Ute Sönksen, Statens Serum Institute, Denmark

Valuable to monitor resistance against pleuromutilins in selected human pathogens

- In line, relevant to monitor linezolid resistance
  - Because resistance mechanism for pleuromutilins and linezolid are often coupled

Outome of work: Recommendation for additional future DANMAP monitoring

Better data show high prevalence of pleuromutilin-resistance in LA-MRSA

We are aware that the situation may look different elsewhere in the world

- Risk assessments should be used using local data
  - And updated when new knowledge arises

Exposure assessment

Data available to describe general exposure of Danes to LA-MRSA through contact

Poor data available to describe food-borne transmission of pleuromutilin resistance

} Recommendation for additional future DANMAP monitoring

TABLE 3 | Number of carriers of MRSA CC398 in Denmark based on information from National statistics, relevant literature and expert opinion.

Group	No. of persons	Carrier proportion (%)	No. of carriers assuming all herds positive	No. of carriers assuming 69% positive herds[a]
Swine farmer/employee, full time	8,000[b]	74[c]	5,920	4,085
Farm employee, weekly work with swine	1,000[d]	74[e]	740	511
Swine veterinarians and advisors with daily contact to swine	200	74[e]	148	148
Craftsmen with weekly contact or less to swine	7,564[d]	11[f]	821	566
Swine transport workers	453[d]	22[g]	100	100
Abattoir workers	6,600[d]	4[h]	264	264
Household members to all persons listed above	26,199[b]	6[i]	1,511	1,073
Remaining society	5,600,000	0.10[j]	5,607	3,980
Sum of carriers		0.27	15,111	10,615

Very low proportion, but high number of persons

- Detrimental, if consequences of exposure had been high

Consequence assessment: *additional* risk related to resistance

Challenging to separate effect of various confounders from effect of resistance

- Despite extensive data collection in DK
- Valuable to register selected parameters in relation to disease course for humans undergoing hospital treatment
  - in a standardised way

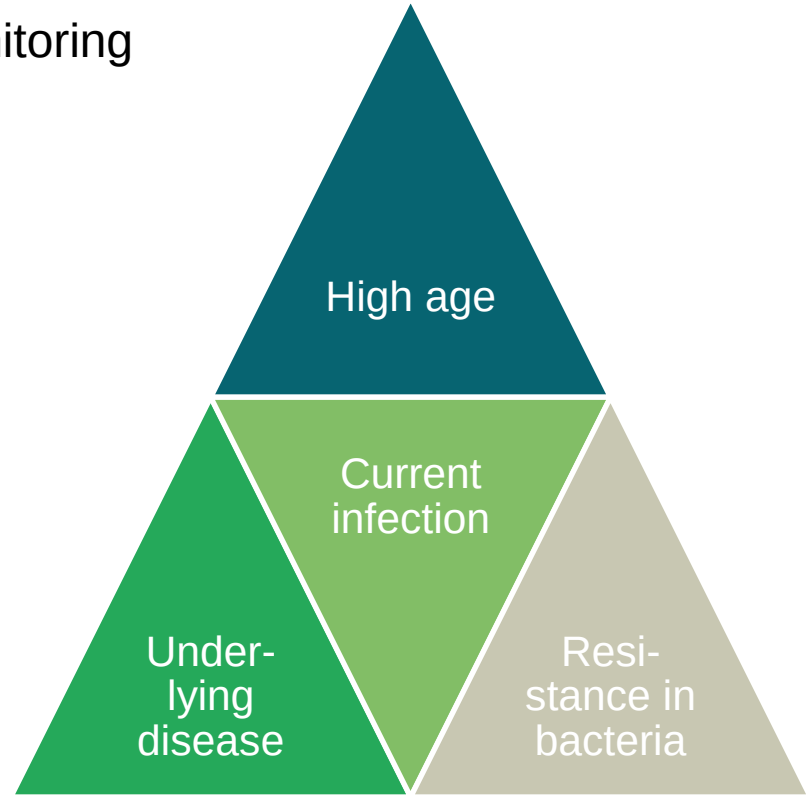
Recommendation for additional future DANMAP monitoring

- EMA's view?

Revised EMA Guideline: impact also includes

- Increased disease severity
- Increased burden on healthcare services

Very good



Consequence assessment: MRSA as an example

TABLE 4 | Human cases of bacteremia and death in Denmark, distributed according to type of staphylococci, for the time period 2011 to mid-2016.

Kind of staphylococci	Year						30-day mortality (%)
	2011	2012	2013	2014	2015	2016[a]	
MSSA bacteremia	1,504	1,507	1,735	1,908	1,973	[b]	
MSSA deaths	347	337	408	425	452	[b]	23
Non-CC398 MRSA bacteremia	20	19	26	48	26	13	
Non-CC398 MRSA deaths	6	4	6	10	6	3	23
CC398 MRSA bacteremia	1	2	4	8	3	5	
CC398 MRSA deaths	0	1	2	2	1	0	26

In Denmark, same case-fatality rate observed for MRSA and MSSA

- Maybe attributable to the general healthcare service in Denmark + screening of risk-groups upon admittance to hospital

Consequence assessment: pragmatic approach

Revised EMA Guideline contains possibility of using ”pragmatic approach”

- Based upon AMEG categorisation and extent of use of AM class in human treatment in EU
- Helps in assessing consequences in absence of data

But does it always make sense?

- Figure in revised EMA Guideline suggests that consequences will be high for all AM listed as AMEG category 3
  - Even if use of AM in humans is very low

} Contradiction to original version of EMA Guideline

Case: Use of macrolides in pigs for treatment of disease

- Risk assessment has shown that this is not a risk for exposure of humans to macrolide-resistant Campylobacter (Alban et al. Prev Vet Med, 2008, 83, 115-129)
  - Campylobacter - we blaim it on the poultry

Risk estimate, context and limitations

EMA Guideline: Integration of release, exposure and consequences

- Presumably this means equal weight of each element
  - But consequences could be considered as the most important
  - And if there are no consequences, there is no risk

Total risk related to current use in Denmark estimated as low

- On-farm: Due to Yellow Card setting limits for use
- Hospitals: Due to effective healthcare services, screening procedures and infection control measures

Fine that revised EMA Guideline specifies that risk management measures implemented to keep risk low may be taken into account

But what if the use of pleuromutilins will increase?

- That could lead to higher prevalence of resistance determinants

=> We conclude that new evaluation is needed

Valuable if EMA Guideline could specify, when an assessment should be repeated

Conclusion

EMA Guideline useful, comprehensive but demanding

- Requires detailed data, skilled personel, and a lot of time
- Revised version looks better than the first version

Can be used to identify where additional monitoring is needed

- In our case: pleuromutilin and linezolid resistance in selected human pathogens
- More standardised data on outcome of human treatment – incl. treatment failure
  - To assess human consequences (who/where/why)

} Valuable if EMA could specify which data to collect

EMA Guidelines helps to separate a potential hazard from a risk

- If there are no negative consequences, then there is no risk

Epilogue

Our work – and the process - will be presented at International Symposium of Veterinary Epidemiology and Economics, Chiang Mai, Thailand, 12-16 November 2018