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| Moderator: | - If you need to, please feel free to listen by telephone, using the toll free number. During the presentation, we invite you to post questions by typing them in the box on the left of your screen.  I’d now like to introduce Dr. Lynora Saxinger from the University of Alberta. She’s going to be presenting on antimicrobial stewardship programs in hospitals. |
| Dr. Saxinger: | Hi there. I hope my audio is working okay. Does that sound alright? |
| Moderator: | It sounds good to me. |
| Dr. Saxinger: | My voice might not because I myself have a bit of a viral issue going on right now, and I’m hoping my voice holds out for the duration of my presentation. As mentioned, I have an interest in antimicrobial stewardship. I’m an infectious disease doc. And I’ve been trying to be involved with a lot of efforts, trying to engage people across the country in hospital antimicrobial stewardship. I am going to go over some principles of antibiotic stewardship because I recognize the [cut out], also recognizing that there’s a number of people with expertise that might be greater than mine, who might either be in on the call or accessing it later. I’ve also tried to include some more recent materials in terms of the literature that’s been evolving on how you could measure, justify, and sustain hospital stewardship. I’m happy to send people references on request. I’ve given my email address on the first slide. I also have the references listed on this slide.  And the first thing that I often hear is, what the heck does “Antibiotic Stewardship” mean? And strangely, there’s not really a single set definition, but there are a variety of definitions that are in different publications. And I like this one best because it seems very clear: *good antimicrobial stewardship is a practice that ensures the optimal selection, dose and duration of an antimicrobial therapy leading to the best clinical outcome for prevention or treatment of an infection while producing the fewest toxic effects and the lowest risk for subsequent resistance*.  So this is kind of the ‘Holy Grail’ of antibiotic therapy. And the stewardship model[?], when I was initially conceptualizing what this means, it’s not taking over prescribing, but it’s to help guide prescribers through the very large antibiotic menu that we have, and trying to make appropriate pairings of the patient situation and the antibiotic. And henceforth, when I say ASP, that means Antimicrobial Stewardship Programs, provide extra expertise in antibiotic use, and we pair that also with the prescriber’s knowledge of that patient for the best outcome, because we are aware that the individual looking after the patient has the most in-depth knowledge of that individual.  The other thing is that it is a multidisciplinary program. It takes a team. And usually, the team is a physician (often an I.D. physician), and a clinical pharmacist with infectious diseases training. When you look at the idea, say guidelines, which I reference in the next slide, that often and optimally should include an antimicrobial biologist and information system specialist and infectious control professional and hospital epidemiologist. And as a program, it’s usually directed or co-directed by I.D. and pharmacy, and the program part of it involves data tracking and analysis [cut]. So, it is in fact, an entity that has to be created within a hospital structure.  So these are the guidelines that really actually kick-started a lot of attention to stewardship. They came out in 2007, and the ensuing couple of years – few years now – every year we’ve seen increasing reports on outcomes from stewardship programs, a lot of workshops on how to do a Stewardship Program, and a lot of professional education and development, trying to get people involved in these types of initiatives.  And just to let people know, if they’re not familiar, the two core strategies that you can do if you’re trying to impact antimicrobial use in a hospital setting, well, and even community settings, are prospective audits with interventions and feedback, in which you use some kind of a cue to look at the antimicrobial use, and then go provide some unsolicited feedback.  The good news about that is, for example, if you’re using microbiology reporting, it means that you can intervene if it appears that a patient is not on the optimal therapy. And you intervene more or less in real time. The other thing that people often use as a trigger is use of certain broad-spectrum agents, and then you go and you see if the use of that agent appears to be warranted in that case, or if there’s an alternate suggestion maybe warranted.  The nice part about this is that if you have good relationships with your prescribers, and that you show that you’re a supportive influence, it allows a lot of educational dialogue, and I think it kind of elevates the practice and centres that have a good stewardship program.  The other option that some people propose is formulary restriction of pre-authorization, which basically comes down to, “*you can’t have that”* or “*you have to get permission to have that*.” Obviously, that has a lot more difficult sell job. And it often involves a lot of calls to whoever’s being the gate-keeper for the broader-spectrum antimicrobials. But in terms of getting immediate impact, it probably is the most direct way. It can be difficult to carry out. So I conceptualize this as being the good antibiotic fairies coming by to help you out with your problems, or the antibiotic police. And to be honest, both elements can have elements of both. I can put it that way.  Staying in my conceptual mode, the other thing that I want to point out is that you have your host at risk, your patient, and community antibiotic use, and in my mind that includes veterinary and agricultural use, is by far a major driver, and far away is hospital use. And when you look at where you have the host, the pathogen, and then their genetic determinants of resistance coming together, that is where you find resistance developing. And the approach to controlling that can be an infection control approach, where you try to impact where the pathogen and the host interact, and hospital and community and veterinary and agricultural stewardship, where you’re trying to impact the host at risk’s exposure to antibiotics.  So I’m going to step back into a clinical scenario. I’m not sure if this is a primarily clinical audience, so forgive me if you’re not. But, people have a certain approach to antibiotics that usually is very patient centered appropriately. And in this case, we have an 83 year old man who was admitted from home with fever, delirium, hypotension, responsive to fluids, a history of BPH which is prosthetic disease, and dysuria. So he had some symptoms relatable to his urinary tract. And he recently had a community acquired pneumonia that he’d mostly recovered from. And his creatine was 96, and his white count was 14, with a predominant neutrophils imbalance.  So when we think about that, you guys can actually type in your answers if you want, but if you don’t want, that’s okay too.  Antibiotic treatment – what do we think about? Many people would think about something like a third-generation cephalosporin. People who go for pattern recognition of UTI would maybe go for cipro IV or cipro PO. Ampicillin/gentamicin might be considered a reasonable option. And the imipenem pip-tazo might also be considered a reasonable option, depending on how sick you feel this gentleman is. And someone bravely typed in what they thought they would give. Anyone else want to throw in what they would give, just for discussion sake? There’s no down side, because the right answer is a moving target.  He doesn’t eat? Well he does now. He just got a Foley.  So actually, this is fairly representative of the people who typed in, what people say. I notice no one picked cipro. Thank you. When I give this to a general audience, many times they do. But a lot of times, the model used is - you think about efficacy for that patient, you think about safety for that patient. Sometimes people will go so far as to think about cost, but that’s actually quite rare in prescribers. And then, the next step is thinking about resistance.  So when I looked at his case, I thought, he’s got about a 60% chance with *E. coli* and 10% each chance at something like *Klebsiella* and *Proteus* – I want to cover those. And so I looked at our own local antibiogram, using our own data from our lab, and discovered that, my predicted efficacy for these agents are as listed there, based on that proportion of isolates. And to be honest, I think a lot of people kind of do this in their head in a generalized way, but not in this much detail. And then the safety issue, obviously the big outlier there is gentamicin.  And then the next question is, do you have a responsibility even to consider cost? And many prescribers find this an issue of some debate, but it’s one of the things that we use in stewardship as a lever to get stewardship programs going. So I think we in fact do have a responsibility to cover cost. And finally, what if one of the antibiotics is more or less likely to promote resistance? So you’re no longer thinking about this gentleman, you’re thinking about future patients. Do we have a responsibility to consider that?  Which brings me to the central problem of antibiotic stewardship, which is: antibiotics are good, but we must restrict their use.  So we’re balancing what all people see in hospitals, which is we shorten the duration of a bacterial infection related illness, and we can provide life-saving benefits for people with severe disease. But then, what you’re balancing that off is a change in the ecology in the patient, a change in the ecology of the community, and possible side effects.  So antibiotics, because of the resistance story, and because of the ecology, are actually societal drugs. An antihypertensive drug affects the person who takes it, but you can carry an antimicrobial resistant bacteria to other people. And the volume of use is far in excess of most other classes of drugs in terms of things that can impact on the whole community. 50 to 75% of hospitalized patients receive antimicrobials in different surveys, and most surveys of appropriateness suggest that 50 to 99% [cut off]. poor prescriber who’s looking at everything else, has to consider interpretation of tests, MIC’s, BAL’s, guidelines, resistance patterns, drug interactions, side effects, and a lot of other decisions about duration and route of therapy, and considerations about resistant organisms, such as VRE and the development of Cluster difficile.  So, the goals of stewardship are mainly three-fold. And I put resistance in the middle, because I think ultimately, that’s a very valid goal of stewardship: reduce resistance. Patient safety, I think is another huge goal, and the controlling cost part of it is, I think, plays a role in allowing us to accomplish our first two goals.  So in the hospital setting, antibiotics comprise the top therapeutic class in most budgets, basically. And, as I mentioned, in other studies, 30 to 60% of all hospitalized patients get an antimicrobial drug at least once during their stay. And so, hospitals are a “Target Rich” environment for improving antibiotic use.  Now I’m going to get into a little bit more nitty-gritty about some stewardship issues. And one of them seems kind of obvious, which is, you have to measure what you’re using and be able to look at the impact of that, and try to correlate it with your resistance pattern. And it’s actually harder than it seems it should be. Expenditures have to be indexed to compare between drugs in the same hospital, and between hospitals. And hospitals vary in their activities and case-mix. So ultimately, although my read of the entire field is that we’re moving towards ‘benchmarking’ antimicrobial use across hospitals, when you have hospitals with very different practices and different case-mixes, that can become very, very difficult. And the main point of doing all that is to identify the proportion of use that can be targeted for interventions.  So, looking at that, one relatively recent reference from our own poll showed that about a third of inter-hospital antibiotic consumption was explainable by a multi-variable model. And they used 87 antibiotics in 130 hospitals, and their mean total rate of antibacterial use was a fairly impressive 789 days of therapy per 1 000 patient-days. And the model that they found to explain about a third of the variability, was the number of hospital beds, the number of ICU beds, numbers of surgeries, and the numbers of pneumonia, bacteraemia, and urinary tract infection cases per 1 000 discharges, which meant that the other part of the variability between hospitals would have to be ascribed to prescriber variation, which would suggest that there’s some opportunity there to modify that use. And there’s other data sets that suggest that you can explain more of the variability by using different models, by the way, but that was a North-American example.  Then we have to decide what we’re actually going to measure, and many hospitals, the easiest thing to get is actually how much money was spent on a drug and how many vials you bought. And then, the most common practices that’s done in the European CDC, and basically world-wide for antimicrobial utilization is using the World Health Organization Defined Daily Doses to divide the number of vials by the assumed daily dose, and then you get your DDD number so you can compare drugs and compare between hospitals. And that’s an okay comparison for some of those purposes, but the administered dose is often dissimilar from the recommended DDD conversion provided by the World Health Organization.  It can be very difficult to really compare between drugs. It can be difficult to get an idea of the actual volume used, because you might be under-estimating the use, or over-estimating the use if the DDD is different from the actual dose given. And there’s been some talks that really we might want to move towards using data on therapy as well, if that data is attainable. So when we’re looking at hospital information systems, trying to gear things so that we can collect at least DDD’s, and probably DOT’s as well, would be a really worthwhile goal as things are changing.  So, show me the evidence. Stewardship programs have been around for a long time, and many people have well-established programs, and they show outcomes that are actually pretty compelling, especially, and most easily, for cost savings, but also for patient safety. Resistance changes can be more difficult, but the best data on resistance impact is for *C .diff* rates and VRE and ESBL’s.  And I’ll give you some of the references for that. So there’s data, among other things, that show unnecessary use, even in an ICU setting or our highest-risk patients, our sickest patients. And 30% of antibiotic days were deemed unnecessary in one study, including quite a lot of treatment of contamination colonization. And actually though, I’ll point your attention to the fact that the duration was longer than necessary in quite a large proportion of that.  And there is increasing studies being done on duration of therapy, and ICU patients, especially for ventilator-associated pneumonia, for example. And the evidence is quite compelling, and we should feel safe doing it, but this one physician basically said, “Failing to change our practice style to reflect the evidence because we feel comfortable with some other duration, ignores the harm we do to our patients when we overdue the antibiotics. And ‘physician comfort’ has never been and should never represent an endpoint in a clinical trial.” This person sounded a little ranty, but I actually appreciate that viewpoint because people do, when they’re looking at the patient in front of them, have an impulse to protect that patient and not necessarily recognize the potential harm in antimicrobials.  There is data showing that there is equivalent or better patient outcomes with a dedicated stewardship program assisting providers. To the tune of 82% versus 43% of patients on appropriate definitive therapy in a cluster randomized trial, which was educational in nature. Decreased *C. diff* with formulary changes and restrictions of broad spectrum agents, and improved renal dosing.  So, giving you kind of an example on antibiotic safety, we tend to have a very, very strong view in medicine that antibiotics are very, very safe and beneficial, but when you look at a situation such as an upper-respiratory tract infection such as I have myself right now, you would need to treat 400 patients with respiratory infections to prevent one complication such as pneumonia. And that includes high-risk patients with C.O.P.D. And if you look at the antibiotic risks, 5 – 25% could get *C. diff*; 2% may get a skin reaction, which occasionally can be severe; 1 in 5 000 can be anaphalax. And then there’s a whole host of things like QT prolongation, rabdomiolasisty, Steven’s Johnson Syndrome, nephrotoxicity. And antibiotics are responsible for 20% of ER visits for drug adverse events, and that’s a conservative estimate. And then, probably most of those antibiotics were not given necessarily for a compelling cause. And antibiotic risks for drugs like sulfa and clindamycin, basically is on par with the risks of drugs that we would usually consider fairly, you know – they’re good if they’re needed but you wouldn’t give it for no reason – insulin, warfarin and digoxin. Similar risks.  So what if we said like this: “For your infection, there is about a 1 in 400 chance that an antibiotic will prevent a serious complication, a 5 – 25% chance it will cause possibly severe diarrhea, and a 1 in 100 chance you will require a visit to the emergency room because of a bad reaction.” That seems maybe a little hard-hitting, but I think it’s an important point to remember. And some people would even argue that the resistance argument is outweighed by the individual risk to the patient when we’re talking about minimizing antibiotic unnecessary use.  So going to the ecologic argument for resistance, and I know that other speakers will be addressing this in a great deal more detail, use and resistance parallel each other in the hospitals as well as everywhere else. Care units with the highest use have the highest resistance rates. Antimicrobial resistant organisms are more prevalent in healthcare associated infections, rather than community associated infections. And patients with resistant organisms are more likely to have received prior antimicrobials, with resistant organisms increasing if people have been on antibiotics for longer.  I edited this, but there is some data also showing that you can also impact endemic risk in what I would call “hospital flora”. So this was an ASP that was run by ID staff, where they basically made people approve broad spectrum antimicrobials which previously had been very, very commonly used in the centre. This is relatively old data, but it did show that their *Pseudomonas* isolates changed their susceptibility pattern fairly dramatically in the period of time before the intervention, and then during the period of time after the intervention. And the time period span there is about a year and a half.  When you look at the impact of stewardship programs overall, 24% reduction in prescribing, and because I’m assuming that wasn’t associated with any higher death rate, that that would likely be prescribing that was not necessary for patient care. Inappropriate use reduced, so inappropriate use 42 versus 20%. MRSA infection reduction, not colonization but infection. And resistant gram negative reduction being shown for ESBL *E. coli* and *K. pneumonia*, and cephalexin-borne resistant *Acinetobacters*.  So better outcomes, decreased resistance, is sounding pretty good. And cost saving - Most studies have shown that most programs can relatively easily achieve $100 000 - $300 000 in savings per year, usually in US dollars, in individual hospitals.  But there’s a cautionary tale shared by a colleague at the recent IDSA meeting, who had success-, made a great business for a stewardship program, got funding for it, and then the first year they saved $1.25 million US. And that was with instituting IV to PO conversions, antifungal restrictions, and a program of narrowing therapy after 72hours with culture results. And when the administration received those results, they basically expected that same saving to happen every year for the ensuing time. And then when that didn’t materialize, because a lot of these were kind of one time, big hitting interventions, they didn’t actually expand the funding for the program. So I think you have to be careful how you frame what your expected results are.  And at the end of the day, cost saving is nice but people saving is really much, much better. Not just the patients in front of us, but our grandchildren should benefit from proper infection therapeutics.  So where this is going – there’s an increasing push for stewardship programs in hospitals, from professional societies, from accrediting bodies (this is starting to be looked at), from patient safety groups. And so, in terms of catch-up, we’re sort of analogous to the early days of infection control in many ways. We have to work out our [metrics]. We have to keep on collecting outcome data. We have to further develop our intra- supportive community of practice and stewardship, with doctors, pharmacists, and other professionals with an interest in stewardship. And I think another thing I should add overtly is that the link between hospital and community and veterinary agriculture use, has to be constantly acknowledged and communicated about so that we can try to correlate changes in these different areas. We should share resources that are useful for getting administrative support for stewardship programs.  The group that I’m chairing right now with AMMI Canada, which is the Association of Medical Microbiology and Infectious Diseases Canada. The antimicrobial stewardship and resistance committee is going to be starting to work on educational toolkits for pharmacists and doctors, kind of simultaneously on stewardship in a train-the-trainer type of way, as well as for CME. And also continued advocacy for legislation and accreditation standards to help drive proper utilization.  So, I’m actually summing up, almost on time, and with my voice still working. Antibiotic Awareness Day and modern hospital medicine . . . we are entrusted with the care of very ill people, we have excellent tools, and one of the most important that we have is antibiotics. Many people would say that antibiotics have kind of defined the modern medical era; they were the intervention available commonly that could create such a dramatic response, and be so obviously life-saving. And if we do things incorrectly, we might be looking at a scenario that’s kind of a post-antibiotic era.  I’d remind you that the word “steward” comes from the old Anglo-Saxon word ‘Stigweard’, which actually means ‘the keeper of the hall’. So this was the person charged with keeping the hall, which was the community centre, in order. And to keep the hall for the future we have to use antibiotics wisely in all settings. And because hospitals are a place where the sickest congregate and where we have very defined group of prescribers, it is a very logical place to really focus some attention on appropriate antimicrobial use and stewardship.  And I think that is the end of my presentation. I think we were going to leave the questions till later, is that right? |
| Moderator: | That’s right. We did have one question about asking about the case example. |
| Dr.Saxinger: | Oh, actually, I didn’t go back to that because when I’ve done this in the past, I’ve looked at the overall polls. I would say that the clearly wrong answer is cipro. I would say that ceftriaxone is a very good answer for most settings. I would say that if you’re in a community that has a high rate of ESBL infections, in urinary infections, that that would definitely be a consideration to use a carbapenem. And to be honest, a lot of people are actually moving, now if someone is very, very ill, maybe this man wasn’t quite that ill, but to use a carbapenem initially, and then really focus your stewardship efforts on narrowing therapy when the results are back. Because this gentleman had a levofloxacin, probably, I mean the odds are he had levofloxacin for his community acquired pneumonia, everyone’s avoidance of quinolones was extra justified, because, of course that gentleman would be likely to have quinolone resistant isolates for 3 months at least, after his antimicrobial exposure. So I’d say ceftriaxone is, and the carbapenems, would be my top two choices for that gentleman. |
| Moderator: | Great. Thank you very much Dr. Saxinger! We appreciate your presentation. All presentations, including this, will be posted online by the end of next week. I also invite you to post questions in the Q & A section of the webcast.  Now, Dr. Scott McEwen. He is a professor of the Department of Population Medicine, at the Ontario Veterinary College University of Guelph. |
| Dr. McEwen: | Well, thanks very much, and welcome ladies and gentlemen. I’m assuming for this presentation that most of the attendants are human health care professionals of some type or other. There may be some veterinarians here. If there are, this is going to be not much of specific or new interest. I’m going to take sort of a 30 000 foot view of antimicrobial use in animal populations and what effects that has on human health, and what can be done about it.  So those are the sort of major themes of my presentation today. Antibiotics have been used in animals almost since they were first discovered decades ago, both for therapy and for other purposes. For example, somebody found out by accident that if you fed the left-over mycelia from antibiotic production systems to animals, they grew a lot faster and put on weight a lot more quickly, so that was an early basis of growth promotion.  But first of all, one of the most important motives, I guess, for antibiotic use in animals is just as we heard a few minutes ago from Lynora, around treatment of sick people in hospital situations or in the community. And that’s for therapy of clinical bacterial infections. And in this slide, we got an old Rockwell picture of a veterinarian looking at a dog with you know, a young boy’s dog, in a veterinary hospital. And this happened every day in Canada and other countries, and this sort of companion animal application of antibiotics is probably most similar to what we see in people.  So we have community-level practice situations, we have some things that are analogous to human hospitals in veterinary medicine and larger veterinary clinics, and some of the same sort of dynamics of resistant problems as well as the types of patients that are being treated.  So you also have individual animal treatment on the farm in livestock, and the picture below is a dairy cow and someone is injecting an antibiotic preparation into the mammary gland of this cow, presumably for mastitis treatment. And that’s, you know, the most common requirement for antibiotic use in dairy cattle. And so it’s something that’s quite different than we see in people, but it’s still individual animal administration. And that happens in a variety of species.  But the majority of antibiotics by volume are administered to groups, and this is, you know, quite different than the situation we’ve just heard about in people. And it’s something that happens in large part because of the way the animal, food animals are housed and raised in society. We have some food animals which are raised extensively, as we call it. So out on pasture, you see, cattle out on range, that kind of thing, receive comparatively few antibiotics.  But lots of food animals are raised in confinement conditions. We have pictures on the screen here of some pigs in confinement and some poultry. And so animals typically are raised in groups, and for the practical purposes, it’s often only possible to administer antibiotics at the group level. So you can’t imagine, for example, in a broiler barn with ten thousand birds present, to try to go in and pick out the sick individual birds to treat them. You sort of cause more problems than you fix. So we have antibiotics administered at the group level sometimes in water, in feed, and by other means. So this group level treatment is often administered for therapy. And the example would be broiler chickens that have *E. coli* infection – that could be a variety of different things in birds - and so we might administer a flock level treatment, perhaps in water or some other means to cure the infection in those birds. Clinically affected, as well as some others that may be incubating the disease.  Sometimes the administration is given for more prophylactic purposes. For example, you may be surprised to learn that in the poultry industry, it’s sometimes at the hatchery level before the chicks actually go out to the broiler barn. They’re administered an injection with an antibiotic, and I’ll have a bit more information on that later. So that’s injection for prophylactic purposes to prevent later *E. coli* or other infections in those broilers.  And the third type of application, which is the most controversial, is administration of antibiotics for what we call “growth promotion”, or sub-therapeutic – some people use that term - purposes. So that’s the one that’s received a lot of attention over the years because it seems, intuitively, to be less, I guess, ethically warranted. You’re not you know, explicitly treating sick animals. You’re administering an antibiotic here to enhance growth, your increase of efficiency of feed conversion sort of thing. So that may be a little bit more questionable in some people’s minds. So I’m going to leave you with this important concept of group level treatment for different purposes, which has a profound effect on how we try to manage antibiotic use to limit resistance.  Okay, well, people often talk about how much antibiotic is used in the animal sector compared with the human health sector, and one of the problems we’ve got in North America, as well as most countries outside of Europe, is that we really don’t have a good measure of quantities of drugs used in the various fields of animal production or in companion animal medicine. And I’ll show you a bit of data later on from Denmark, but in North America, we’re left to provide indirect estimates of use.  And this slide is showing one group’s attempt to do this in the United States, and this received a lot of attention a few years ago and a lot of controversy. This group estimated, through a variety of indirect means, the quantity in terms of weight – which is you know a very gross estimate – of antimicrobial use in food animal production for non-therapeutic purposes. Their definition was sort of that prophylactic growth promotion use that we talked about a minute ago. And then compare it with the quantity of drugs that’s used in human, you can see that the quantity in livestock somewhat dwarfs that in human medicine. But of course, this sort of begs the question of, you know, how comparable are these data? And there are issues around that.  And this next slide is an attempt to sort of get to some of that issue about what types of antibiotics are we talking about. And these data here are from Ph.D. thesis of Kelly Carson, who, as part of her studies, recently tried to adapt the methodology around indirect measurement of use of antibiotics in agriculture, to the cattle production situation in Canada. And that is to estimate the quantities of antibiotic use in cattle for, again, for non-therapeutic or prophylactic/growth promotion uses. And this time the data are broken down by categories of importance to human health.  Health Canada has categorized these antibiotics into four levels. The first level, category I, are those deemed most important or essential for use in humans and includes drugs like fluroquinolones and third generation cephalosporins and some others. Category II contains some of the other drugs that are important for use in humans, but there are alternatives available - things like tetracyclines and so on. And all the way down to group four, which is the category of drugs that are used in animals but there’s no sort of counterpart for use in humans. And a prime example here is a class called ionophores, which are widely used for growth promotion purposes in animals but quite toxic in people.  So by breaking them down in these categories, you can see that there is still a large volume of use in cattle relative to humans. It tends to be at the right side of the equation, and the more in the higher quantities of human use, as you might expect, and in those categories that are more important to human health, so just this I think sort of peels the onion a bit more in terms of what is used in the various categories.  Alright, so what, so we have use in animals. What are some of the drivers for doing this? Well, of course, therapy is an important one, so the attempt to cure clinical bacterial infections in animals, pets, food animals, whatever. Nobody wants to see animals with clinical infections suffering, and so there are animal welfare considerations there, and so I think this category mostly would seem to have clear and well-defended benefits.  And then another one that’s there is to prevent bacterial disease from happening, as well as promoting growth. I sort of put these together because the most data around the world in the last few years suggest that probably the mechanisms by which growth promoting uses of antibiotics realized any benefits that they do (and there’s a lot of debate about whether they do much anymore), it’s probably mediated through a disease prophylaxis mechanisms. There are some people who argue that it does alter the distribution of nutrients, so then the god effect of commensal bacteria that aren’t disease-causing, and so on and so forth, but the evidence from big experiments that took place recently in Denmark indicate it’s probably prophylaxis.  So these laws also have a degree of animal welfare and so on, but there’s also an element of economic impact. Therapy does, for that matter. The attempt, the desire to reduce economic losses due to morbidity and mortality of bacterial diseases in livestock. And so for those people working in the livestock sector, that’s the farmers and veterinarians and allied, the feed companies and so on, that have a stake in antibiotic use from one sense or another, the economic aspects are quite important.  And at this stage, I probably should point out that the distribution mechanisms for antibiotics in agriculture and in companion animals, the systems are quite different than they are in human medicine. For example, many antibiotics are available over-the-counter, essentially the vast majority of feed drugs are available over-the-counter, without prescription, outside of the province of Québec which has a different system of, that’s prescription only.  And another thing that’s different is that the health care professional, in this case the veterinarian, is very often also the pharmacist and the dispenser of drugs. So sometimes they’re the source and in some cases they profit from the sale of antimicrobials, which is a very sort of controversial topic. If I really want to get vets mad, I start bringing up the issue of, how much money they make from selling antibiotics, what effects that has on prescribing practices. And so that’s something else that’s in the background in terms of an issue with respect to antibiotic use.  So we talked about antibiotic use in animals. Of course that’s going to have some selective pressure on resistance, as it does in the human field, and then we need to get into, I think, some discussion about the possible mechanisms of transfer resistance. Determinants and resistant organisms, from animals to people, is the emphasis of this talk is on public health. And this figure, we call it, someone’s called it ‘the confuso-gram’ around here, this particular one came from Health Canada a few years ago, you see adaptations in a variety of areas.  And I think the thing to sort of point out here, is that when we talk about transfer from animals to people, and we should think about transfer backwards as well, the main sort of route of transmission is through the food chain, in the case of food animals, not unexpectedly so.  Resistant bacteria that are selected on the farm can make their way to people probably most importantly through contamination of animal carcasses at the slaughter process. It’s hygienic but it’s not a sterile sort of environment. We get contamination with enteric bacteria at slaughter and on to meat, and then through a whole variety of mechanisms through food distribution, cross-contamination, and so on. Failure to properly cook and prepare foods. People get exposed to these foodborne bacteria, and if they’re susceptible, if they’re taking antibiotics or other reasons, if they’re immunocompromised, or in some cases even if they’re completely normal, they may suffer an infection that is made worse because it’s resistant. But that’s only one route.  These bacteria and genes can also come through direct contact with animals, and through the environment, through contamination of water-ways, through manure spread on land, through uptake by environmental bacteria where people may be exposed through recreational swimming for example. Consumption of well water that’s not treated. Or through a variety of other mechanisms.  One important ecological point that’s not demonstrated on this slide is the important global dimension to antibiotic resistance, which is an issue for people and human-derived resistant organisms. But also for animals. And that is exemplified by the global nature of our food supply. So we not only have local dissemination here ecologically, but also global.  What impacts do we have on human health? I’m conscious of the time so I won’t delve into this in depth. For the most part, the issues have for years been on foodborne enteric infections: *Salmonella* and *Campylobacter*, for which animals are known reservoirs and amplifiers of infections for people, through the food chain. From time to time we have other issues which pop up. Back in the 90s, VRE was a hot topic with respect to animals because in some countries (not Canada), a glycopeptide was used as a growth promoter, which probably had some impact on the epidemiology of [DRA?] in people. And more recently, we’ve got issues around extended spectrum beta-lactamases in enterobacteriaceae you see in animals that may have a role in people. MRSA is another one I’ll touch on here in a moment. But one point I’d like to emphasize is that while we have lots of evidence of the types of impact that may be present due to these organisms, we really don’t have a very good measure of the magnitude of the impact and burden of illness, which is very important information to have in terms of evaluating the overall health risk to people and what sort of intervention should flow from that.  In the interest of time, I think I’ll skip over this fairly quickly. MRSA has been around in animals for quite some time and was thought to be mainly an animal health problem until quite recently, when there was some bit of work in the Netherlands that showed a particular strain of MRSA that became endemic in the pig population. Then was picked up by pig farmers and pig vets, and other people started looking. So now we’re seeing in many countries of the world a particular strain that pops up in people on occasion but it’s not one of the more common strains that are important in the community or in hospitals and people. But there is some sort of linkage there. In some cases animals, horses and dogs in particular, appear to get MRSA from their handlers, from their owners. And some of these human-derived strains appear to become resonant in animal populations at least for a little while. So, the role of drug use in MRSA in animals is still being investigated. Probably had something to do with selection of resistance strains, but at this point, we don’t know that much about it.  One of the big topics that always comes up in this discussion is: so what do we do about this? I mean we’ve obviously got lots of use in animals. Some of it appears to be questionable in terms of legitimacy, although that really depends a lot on where you sit, whether you’re a human health advocate or an animal health advocate or a farmer trying to make a living. And so, we have lots of discussions and have over the years had many panels that have looked into this about what should be done. And it sort of boils down to a variety of options, none of which are particularly easy to do, and sometimes meet with a lot of resistance.  Some of these involve regulatory changes. That might be bringing in measures to ban the use of certain drugs, like for example growth promoters. Or restrict the use of antibiotics that are critically important to humans from animals. That’s talked about in some cases.  Another class of important interventions or rather, tools to help us decide what interventions to use, involve surveillance.  And another group that I’ll talk about briefly are voluntary measures.  So this is a graph that shows the quantity of antibiotic use in Denmark over time. And we use Danish data a lot because they have excellent monitoring programs, and they’ve also been very aggressive in both the human and animal sector in terms of doing things to try to reduce the impact of resistance on humans. And the main message I want to make here is that up until the late 1990s, a large proportion of the drugs used in livestock in animals in Denmark were growth promoters. And then the Danish industry, the Danish authorities took steps to stop that through a variety of means and then banned it. And what we saw happening was that with the ban, there was a dramatic reduction in growth promoting uses, as you’d expect, but there’s also some rise in the use of therapeutic drugs which is not accounted for by population increase of pigs and poultry. And, to make a long story short, this is, probably a result of an added expression of some clinical disease due to the loss of growth promoters that was then compensated for by increase in therapeutic drugs. So there was a net reduction use, but a bit of a change in terms of what particular drugs are actually used in Denmark. So that’s an example of the effect of a national level intervention on use.  There’s lots of other stuff to talk about in terms of its effect on resistance and so on. Some people talk about restricting, making restrictions based on class. Or, stop using those drugs - they’re clinically important to use in humans - in animals. This slide shows some information from a recent report, an international report on critically important drugs for use in humans and animals.  And the point I want to make here is that, if you can see it, is that there are some drugs which are deemed to be important only for humans, and are not used in, virtually any animals, and so it’s easy to restrict that use in animals. But there are others, at the top, which are outside the circle, which are used in those groups. And so, those proponents of animal health and human health think that they have rights to use these things because they’re valuable therapeutic agents. So you run up against these sorts of issues around trying to make those kinds of restrictions in terms of who would like to keep them.  I’ll try to do this fairly quickly so there’s time for questions, but one of the things that we can be, I think, proud about in Canada in terms of antimicrobial use, is that we have a very good surveillance program for at least enteric bacterial resistance in animals and people, in a program called, a Canadian created program for antimicrobial resistance surveillance, CIPARS, that’s run by the Public Health Agency. And this program monitors resistance in *Salmonella*, *E. coli*, and some other organisms, both from clinical isolates and people, as well as clinical isolates from animals and also isolates obtained from clinically normal animals at slaughter and from retail meat.  There is a lot of information on this slide and, I’m just going to focus in on a couple of bits, but I think it shows the value of having a surveillance system in place for this important issue that we’re talking about. Basically, what we’re showing with these various lines, are the proportion of isolates of *Salmonella* Heidelberg that are resistant to a drug called ceftiofur (which is a third generation cephalosporin) from people, clinical isolates of Heidelberg from people, as well as Heidelberg from retail chicken and from *E. coli* that are taken from chicken. And we see that we have fairly comparable trends in the resistance pattern to this drug. And this black line here shows an intervention that was taken, and that is a voluntary withdrawal of the use of ceftiofur for injecting eggs or day-old chicks and hatcheries, before they go out to commercial barns. And when they, the Québec hatcheries did this, there was a pretty dramatic decrease in the prevalence of resistance to this drug in Heidelberg, which, I think, shows the effect that the use of a prophylactic drug can have in a population of animals, and also shows some of the benefit that can happen with an intervention of this type.  Some of the other things that are being done in veterinary medicine – we have some stewardship programs or volunteer efforts to enhance prudent use. A lot of veterinary organizations have adopted these principles and some quality assurance programs in animal industries have tried to improve antibiotic use, or taken steps to ensure that drugs are used wisely on farms.  A few countries have therapeutic guidelines or formularies. But in general, there are questions around whether any of these things are having much effect on actual antibiotic use on farms. And one of the reasons for that, I think – people haven’t done the research for one thing – but in terms, my personal view is I’m somewhat sceptical that these things are actually doing very much.  And there’s a variety of reasons for that, but one important one I think, is that resistance does not seem to be a crisis in animal health. In veterinary medicine, there are resistance issues around animal pathogens, but it hasn’t reached this sort of level of perception of a crisis, that’s one thing.  Another thing is that most veterinarians and people in the agriculture sector really don’t believe that drug use in livestock populations has an effect or at least an important or measurable effect in people. So there’s not the same incentive to do things in order to improve public health, because nobody’s quite sure that it would actually do anything.  And then, the third important thing is that farmers and veterinarians would not receive any kind of financial benefit from doing, from making these kinds of interventions. So there isn’t a sort of, a natural incentive that’s driving people to seek stewardship programs.  So while I’m not totally pessimistic, I think that the situation is quite different in this sector, and we have a long way to go to improve understanding.  So I’ll try to wrap up a number of things fairly quickly. I just want to leave you with the message that antibiotics are considered quite important in animal health and welfare that both from a disease treatment point of view, and also from an economic production point of view. That may not sound that valid, but if you’re a farmer trying to make a living on slim profit margins, and you’ve seen your income decreasing every year for the last twenty years, it’s kind of hard to give up, you know, a little bit of margin you might have with treatment, with antimicrobials.  Resistance is an important food safety issue in my opinion and in the animal production industries. There’s lots that can be done to improve the situation. And it may be important in companion animal medicine, but a lot less research has been done there. The human health impacts, while they exist, are very difficult to measure. And so, the fact that we don’t have very good estimates of this does make it hard to convince people that things need to be done. And as I said before, in general, it’s my opinion it’s not perceived to be a problem. And when you don’t, people don’t think it’s a problem then it’s kind of hard to get them to try to fix it.  So I think that’s the end of my presentation. Thank you very much. |
| Moderator: | Great, thank you very much [].there was one which I think you touched on there . . . [] |
| Dr. McEwen: | Well, I do, and it’s an important point. And so one of the other – I mean, I didn’t talk about all the ways that we can reduce antibiotic use in agriculture, but – one important way to improve the general level of health and hygiene on the farm, and so that’s now I guess too, some of the things that are done in hospitals I guess to, for infection control. And so, I mean there’s lots of evidence out there that shows that if you reduce the amount of disease, then you reduce the need for treatment, and reduce then the amount of drug that’s used. And the sort of classic example is, had to do with fish-farming in Norway, where there was an important bacterial infection endemic in the salmon population that required antibiotic treatment, and then, a very efficacious vaccine was introduced that reduced the importance of this disease tremendously in the population of farmed salmon, and therefore the incentive for treatment to antibiotic use dropped precipitously. And you know, that happens sometimes and, but I think it sort of makes the point with good production systems, good management, good bio-security, as we call it in veterinary medicine, good infection control, that you can reduce the amount of disease, and therefore reduce the requirement to treat. |
| Moderator: | Thank you very much, Dr. McEwen. I’d also like to thank Dr. Saxinger. Both []. All of the webinars will be posted online at the end of next week. |
|  | **END OF RECORDING** |
|  | **TRANSCRIPTIONIST’S NOTES: Words in [brackets] are either unknown to me or I can’t quite make them out. Most of the [] in this transcription is however due to the cutting out of audio, where nothing can be heard for brief or long periods of time.** |