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Uncelebrated impacts of Nobel Prize-winning avermectins

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Abstract:
This year's Nobel Prize in Physiology and Medicine goes to scientists that have revolutionized the treatment of parasitic diseases in the world's poorest populations through the discovery of the avermectin drugs. However, the enormous impact these discoveries have in the world's developed as well as developing regions through parasite control in animals is underestimated. Roundworm infections are a highly significant problem in livestock production around the world and efficacious treatment –through avermectins- contributes significantly to efficient production methods and food security. In companion animals, these same drugs are widely used for preventing the establishment of major zoonotic pathogens, thus reducing the disease risk for humans. There are also undesired consequences of intensive reliance on avermectins, the most important arguably being selection for resistant worm populations. Now that avermectins are applied at unprecedented scales on whole human populations, exchange of knowledge on best practice between veterinary and human medicine may improve the wellbeing of millions of people.

Main Text:
The 2015 Nobel Prize in Physiology and Medicine goes to scientists, who have revolutionized the treatment of parasitic diseases.[1] After decades of global neglect, parasitic infections and the major problems they pose to global health are receiving the attention they deserve. This is corroborated by the renewed emphasis on these 'neglected tropical diseases' by the World Health Organization (WHO), the major focus that eradication of these diseases represents within the objectives of the Bill & Melinda Gates Foundation and now – the cherry on the cake - the Nobel Prize in Medicine. As mentioned in the official press release of the Nobel Prize Committee, "parasitic diseases affect the world's poorest populations and represent a huge barrier to improving human health and wellbeing".
In the communications however, little to nothing is mentioned on the enormous impact the discoveries, recognized by the award, have also had in the so-called developed and more temperate regions, including Europe and the U.S.A. through parasite control in animals.[2]
The drug – avermectin, a macrocyclic lactone - which William C. Campbell and Satoshi Ōmura discovered back in 1976 was, in fact, first used to control roundworm and other parasitic infections in livestock and companion animals.[3] Unlike in humans, where only one derivative of this class of drug is currently available (ivermectin) and where this drug is typically given orally, in animal health, six other macrocyclic lactones have been developed and are today routinely applied in different formulations (i.e. oral, injection and topical treatment).[4] These molecules have rapidly revolutionized parasite control in animals. For the first time, a single substance class that was safe, efficacious and easy to use against the majority of important endo- and ectoparasites of all livestock and companion animals was available.
Roundworm infections are a common and important problem in livestock production around the world. They usually do not provoke a risk for human health but impact on the production efficiency of the livestock sector. Current global trends including more outdoor ranging farm systems and increasing farm sizes as well as climate change are increasing the risk of parasitic disease.[5] Since their first commercialization in 1981, veterinary science has developed strategic approaches to use these drugs in such way that they improved animal health and welfare and reduced the associated economic losses. As a result, clinical disease due to roundworm infections has become rare and this is considered as one of the success stories in animal health. Their strategic use

improves the production efficiency of meat, milk and animal fibre products and reduces green house gas emissions from livestock production by around 10% (Fig. 1).[6] Although difficult to assess, this prevents economic losses which are likely to run into billions of dollars annually.

Less considered is that in the world's developing regions, livestock parasites also profoundly affect human health. In subsistence economies, livestock plays a fundamental role in the production of food and generation of income. There have been recent calls for the need and opportunity to reduce poverty by greater investment in animal health.[7]

Also in companion animals ivermectin and related drugs have become critical in preventing the establishment of major zoonotic pathogens such as ascarid and filarial worms, thus reducing the disease risk for humans.[8]

Veterinary science has also encountered the downsides of intensive use of these drugs. Reliance on the avermectins has selected resistant worm populations that are no longer killed and are now a real threat to sustainable livestock farming.[9] Usage may also lead to leakage of bioactive residues in the environment which can reduce biodiversity by killing susceptible micro-fauna such as dung beetles.[10] Consequently, current research is developing more sustainable, yet economically viable control methods based on a "diagnosis before treatment" philosophy and adopting selective anthelmintic treatment solutions.[11]

The extensive experience that veterinary scientists have acquired with the macrocyclic lactone drugs is welcomed by the public health community now that the drugs are distributed on an unprecedented scale and applied in mass treatment delivery to whole human populations.[12] This exchange of knowledge across disciplines, and learning the appropriate lessons from livestock, has helped to foresee the problems and may improve the health and wellbeing of millions of people.

The impact on society of these unique drugs is thus not only through the direct reduction of parasitic diseases in humans, but also through the reduction of these diseases in companion animals and livestock. Future benefits should be reinforced by a One Health approach uniting veterinary and human medicine.[13]

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Reference and Notes:

1 Owens B. 2015 Nobel Prize goes to antiparasitic drug discoverers. *Lancet* 2015; **386**: 1433.

2 Burki T. Honouring pioneers of treatments for malaria and nematode infections. *Lancet Infect Dis* 2015; **15**: 1382.

3 Campbell WC. History of avermectin and ivermectin, with notes on the history of other macrocyclic lactone antiparasitic agents. *Curr Pharm Biotechnol* 2012; **13**: 853—65.

4 Vercruysse J, Rew RS Eds. Macrocyclic Lactones in Antiparasitic Therapy *CAB International*, Oxfordshire, 2002.

5 Morgan ER, Charlier J, Hendrickx G et al. Global Change and Helminth Infections in Grazing Ruminants: Impacts, Trends and Sustainable Solutions. *Agriculture* 2013; **3**: 484-502.

6 Kenyon F, Dick JM, Smith RI, Coulter DG, McBean D, Skuce P. Reduction in Greenhouse Gas Emissions Associated with Worm Control in Lambs. *Agriculture* 2013; **3**: 271—84.
7 Perry B, Sones K. Science for development. Poverty reduction through animal health. *Science* 2007; **315**: 333—34.
8 Lee AC, Montgomery SP, Theis JH, Blagburn BL, Eberhard ML. Public health issues concerning the widespread distribution of canine heartworm disease. *Trends Parasitol* 2010; **26**: 168—73.
9 Kaplan RM, Vidyashankar AN. An inconvenient truth: global worming and anthelmintic resistance. *Vet Parasitol* 2012; **186**: 70-78.
10 Lumaret JP, Errouissi F. Use of anthelmintics in herbivores and evaluation of risks for the non target fauna of pastures. *Vet Res* 2002; **33**: 547—62.
11 Charlier J, Morgan ER, Rinaldi L et al. Practices to optimise gastrointestinal nematode control on sheep, goat and cattle farms in Europe using targeted (selective) treatments. *Vet Rec* 2014*;* **175**: 250—55.
12 Vercruysse J, Levecke B, Prichard R. Human soil-transmitted helminths: implications of mass drug administration. *Curr Opin Infect Dis* 2012; **25**: 703—8.
13 Zinsstag J, Schelling E, Wyss K, Mahamat MB. Potential of cooperation between human and animal health to strengthen health systems. *Lancet* 2005; **366**: 2142—45.

Fig 1. Illustration of a roundworm infection, impacting the productivity of a dairy cow.