'One Health', from science to policy: examples from the Israeli experience

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Summary

The concept of 'One Health' aims to help bring about the integration of animal, human and environmental health for the mutual benefit of all. This multidisciplinary approach is of great importance in a variety of fields, from enhancement of breakthroughs in biomedical research, to epidemiological studies and public health policy decision-making. We demonstrate the strength embedded in this approach by using three case studies from Israel. We first describe successful scientific collaboration between physicians, veterinarians and microbiologists in two original research projects aimed at unravelling the link between *Mycobacterium avium paratuberculosis* and Crohn's disease as well as understanding the virulence of enterohaemorrhagic *Escherichia coli*. Next, fruitful collaboration between veterinarians and physicians led to the development of a post-exposure prophylaxis regime of tick-borne relapsing fever in humans, together with the detection of animal infection by *Borrelia persica*. We conclude with an example of a joint avian influenza outbreak investigation that demonstrates just how essential collaboration is between veterinarians and physicians from different organisations, not only across professions but also across state and political borders. The benefits gained by applying the 'One Health' concept in these three examples should encourage further collaboration between veterinarians and physicians.

Keywords

Animal, Decision-making, Epidemiology, Human, Medicine, One Health, Science, Veterinary.

"Una sola salute", dalla scienza alla regolamentazione: alcuni esempi dell'esperienza israeliana

Riassunto

Il concetto di "Una sola salute" punta all'integrazione della salute animale, umana ed ambientale per un beneficio reciproco. Questo approccio multidisciplinare è di estrema importanza in numerosi ambiti, dalle scoperte rivoluzionarie della ricerca biomedica agli studi epidemiologici, alle decisioni sulla salute pubblica. Vengono presentati tre case study*, relativi a Israele, che dimostrano l'efficacia di questo approccio. Il primo* case study *descrive una collaborazione scientifica tra medici, veterinari e microbiologi per due progetti di ricerca originali, rispettivamente sul legame tra il Map (*Mycobacterium avium paratuberculosis*) e la malattia di Crohn e sulla virulenza dell'*Escherichia coli *enteroemorragico. Il secondo* case study *delinea l'esito positivo della collaborazione tra medici e veterinari che ha portato allo sviluppo di un regime profilattico post-esposizione per la febbre recidivante da puntura di zecca nell'uomo, oltre al rilevamento dell'infezione da* Borrelia persica *negli animali. Il terzo* case

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study *riporta l'indagine congiunta sull'insorgenza dell'epidemia di influenza aviaria per sottolineare l'importanza della collaborazione tra medici e veterinari di differenti organizzazioni, non solo a livello interprofessionale. I benefici derivanti dall'applicazione del concetto "Una sola salute" in questi tre casi dovrebbero incoraggiare medici e veterinari ad approfondire la collaborazione.*

Parole chiave
Animale, Epidemiologia, Medicina, Processo decisionale, Scienza, Umano, Una sola salute, Veterinario.

Introduction

Since the domestication of animals, the human-animal relationship has undergone many transformations. Domesticated animals came to form an important natural resource for a variety of goods from food, clothing and fibres to laboratory testing that, although renewable, required careful maintenance. On the other hand, an important dimension of this changing relationship was the increased opportunities for infectious disease transmission. These changes carry a profound implication for veterinary medicine. As Joanna Swabe analysed in her book entitled *Animals, disease and human society: human-animal relations and the rise of veterinary medicine*, on the one hand, the role of veterinary medicine has became much more complicated and, on the other hand more habitual, than just the clinical one of treating injured animals: 'veterinary heroics, such as saving dying or injured animals, played a fairly limited role in daily veterinary practice, whereas tasks such as inoculation, parasite control, blood testing and neutering took up most of the average veterinarian's time' (28). Thus, veterinary medicine in many ways became an integral component of the rising industries related to animals and their products. It also became an important element of maintaining the health of the public.

Historically, animals made a very strong contribution to the rise of modern medicine and to the development of public health. Since the second half of the 19th century, in both laboratory and field experiments, animals served for testing physiological theories, as well as for experiments involving new vaccines and disease causation theories (7, 19). At that time, sanitarians and public health physicians regarded the role of animals and veterinary knowledge as highly relevant to the advancement of public health. Animals and their products still existed in close proximity to humans, in a way that did not require too much innovation for understanding the importance of combining the knowledge about humans and animals (28). Among other things, complex reasons related to sociological changes and to dramatic transformations within medicine and public health alienated human medicine from veterinary medicine, influencing both scientific research and public health practices. The once obvious connection between human and veterinary medical knowledge became relatively neglected.

The concept of 'One Health' aims to revive the integration of animal, human and environmental health for the mutual benefit of all. Although commonly the 'One Health' concept is mentioned in the context of zoonotic diseases, the interdisciplinary approach presented by 'One Health' is far from being restrictive and is, in fact, multi-dimensional. This attitude is extremely important in a variety of fields, including enhancement of breakthroughs in biomedical research, epidemiological studies and public health policy decision-making. Combining different skills and ways of thinking acquired in the two disciplines can lead to a synergic process of brain storming and very valuable exchanges of ideas. In this paper we present three case studies that are based on our experience in Israel. These examples illustrate the strength of the 'One Health' concept and its implications from basic science to policy-making. We demonstrate the successful scientific collaboration between physicians, veterinarians and microbiologists through original research conducted in the Koret School of Veterinary Medicine (KSVM), Hebrew University, which was aimed at unravelling the link between *Mycobacterium avium paratuberculosis* (MAP) and Crohn's disease and at understanding the highly important disease associated with the

zoonotic agent enterohaemorrhagic *Escherichia coli* (EHEC). Next, we present the fruitful collaboration between veterinarians and physicians from the Israeli Defence Force that led to the development of a post-exposure prophylaxis regime of tick-borne relapsing fever in humans, together with the discovery of animal infection by *Borrelia persica*. We conclude with an example of a joint investigation of an avian influenza outbreak conducted by physicians and veterinarians from the ministries of health and agriculture, respectively. This example illustrates how the benefits of such collaboration lead to effective and proper decision-making.

Case 1
Humanised animal models for the study of infectious zoonotic diseases

In recent years, pathogens that are commonly found in domestic animals and in the food chain are emerging as global health problems. The study of virulence mechanisms and host-pathogen interactions of zoonotic and animal pathogens calls for cross-discipline collaborative efforts of scientists. A collaborative research partnership led by Nahum Shpigel, a former bovine practitioner and currently a veterinary microbiologist at the KSVM was established, together with Ilan Rosenshine, a molecular microbiologist from the Department of Molecular Genetics and Biotechnology, and Simcha Yagel, a gynaecologist from the Department of Obstetrics and Gynaecology of the Hadassah University Hospital, both at the Faculty of Medicine of The Hebrew University of Jerusalem.

The complex interactions between pathogens and body systems cannot be completely mimicked *in vitro* and therefore studying the pathogenesis of infectious diseases has relied extensively on the use of rodents and other animal models. Unfortunately, findings in these animal models cannot be extrapolated to the target species, namely humans. The research team successfully set up a highly challenging model of human and bovine intestinal graft in mice. Using this model, the team studied human Crohn's disease, a disease of unknown cause and haemorrhagic colitis caused by EHEC.

Crohn's disease is a common inflammatory bowel disease, the cause of which is unknown and which affects approximately 1 in 1 000 individuals of European ancestry (5). MAP, a bacterium that is common in domestic animals and in the food chain was previously observed in the gut and blood of Crohn's disease patients (26), but causality was difficult to establish. MAP is the aetiological agent of severe gastroenteritis in ruminants, known as Johne's disease. The similarities between Crohn's disease and paratuberculosis (Johne's disease) in ruminants led researchers to suggest the possible association between the causative organism of Johne's disease and that of Crohn's disease (12, 13). MAP organisms have been found in dairy products, drinking water and meat products (8, 11). Infected animals were tracked as a constant source of environmental contamination. Isolation of MAP from breast milk, blood and intestinal tissue of Crohn's disease patients (as well as from healthy individuals) has raised the concern in that it indicated that it does play a role in the pathogenesis of the disease (23, 24). However, the MAP aetiology of Crohn's disease is highly controversial (22, 25) and Koch's postulates cannot be fully satisfied without infection studies in the human gut of genetically susceptible individuals. Using mice engrafted with human gut, the team showed for the first time that this bacterium invades the human gut epithelium inducing severe tissue damage and inflammation reminiscent of Crohn's disease (Fig. 1) (10). These observations implicate the role of this bacterium in Crohn's disease and offer a mouse model that will enable us to analyse its virulence mechanisms in the human gut.

EHEC is an emerging pathogen, causing outbreaks of food-borne gastroenteritis, manifested by bloody diarrhoea, which may progress to the potentially fatal haemolytic uremic syndrome. Cattle are the natural reservoirs of this important human pathogen and play a major role in the epidemiology of

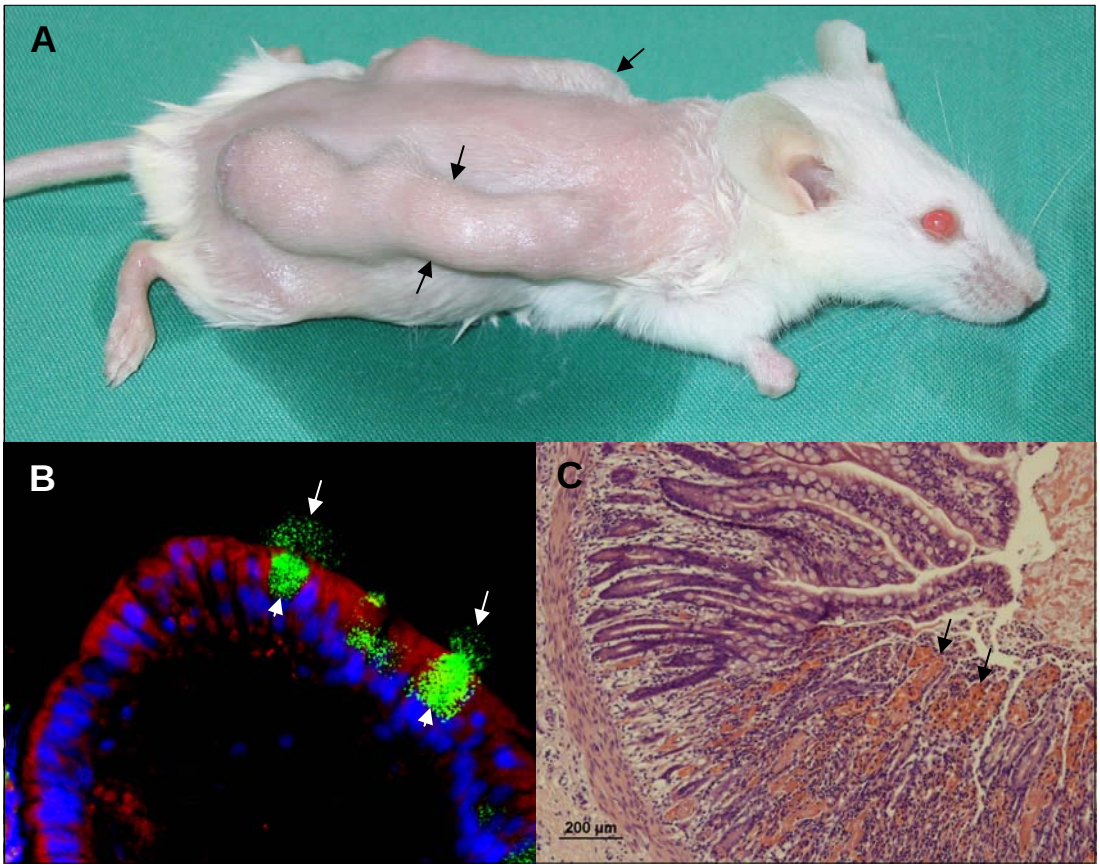

Figure 1
Mycobacterium avium paratuberculosis (MAP) infection of human foetal intestinal xenograft (arrows) 12 weeks after transplantation in SCID mice (A). MAP specifically invades human small intestinal epithelial goblet cells (B) and elicits inflammation (C). Representative microscopic images of tissue sections of human small intestinal xenografts in SCID mice 3 days after intraluminal challenge with 50 × 10^6 bacteria. As shown are H&E stained formalin-fixed section (C) and cryosections stained with anti-MAP antibody (green) (B) combined with DAPI (blue), and phalloidin-rhodamine (red) (B). MAP organisms adherent to mucus excreted by goblet cells are indicated by white arrows and numerous bacteria, which specifically invade goblet cells in the villus epithelium, are indicated by white arrow heads (B). Infection is associated with focal area of epithelial damage, haemorrhage and inflammation (arrows in *C*) characterised by murine macrophages and neutrophil infiltration. Original magnification ×100 (B), scale bar 200 µm (C)

Previously published in Golan *et al.* (10)

the disease (17). The humanised and bovinised mouse models enabled the study of virulence mechanisms of EHEC in the human and bovine gut. After infecting the bovine and human intestinal xenografts with EHEC, the pathogen maintains specific tropism to the colon and elicits the characteristic lesions and pathological changes which are dependent on the expression of its type 3 secretion system (T3SS) (N.Y. Shpigel, unpublished results). Using this animal model system, Shpigel and Rosenshine are currently trying to understand the molecular basis for this tissue tropism.

These two examples demonstrate the benefits of the new mouse model produced from this multidisciplinary collaboration established to understand the virulence mechanism and to

reveal disease pathogenesis. These will undoubtedly help to develop novel therapeutics and prophylactics.

Case 2
Relapsing fever

Tick-borne relapsing fever (TBRF) is an acute, febrile disease caused by various species of *Borrelia* (6) and transmitted by soft ticks. In Israel, the disease is caused by *Borrelia* spp. (14) which are closely related to other *Borrelia persica* associated with typical morbidity in Central Asia and in the Middle East (4). The vector of the disease in Israel is the soft tick *Ornithodoros tholozani*. This tick is primarily found in caves and small niches (3).

While there is a clear reduction in TBRF incidence in the civilian population in Israel, incidence in the army population is stable with some annual fluctuations (27). This is probably due to urbanisation and decreased contact of civilians with the transmitting ticks as opposed to the continuous contact with these ticks during field training by military trainees. The disease associated with relapsing fever appears 2 to 18 days after a tick bite which causes a frequently unnoticed red lesion measuring only a few millimetres in length (Fig. 2). Clinical signs are characterised by recurring episodes of fever and non-specific symptoms, such as headaches, myalgia and arthalgia (9). Symptoms usually last for a few days, followed by a period of remission lasting several days, followed by recurrence. Several relapses can occur without treatment. Although *Borrelia* are sensitive to a wide range of antibiotics, there is one major side-effect associated with this treatment, a phenomenon called the 'Jarisch-Herxheimer reaction' which occurs after antibiotic treatment and is characterised by sudden fever, rigors and hemodynamic instability and might be present in a significant proportion of treated patients (15, 16).

For these reasons, it was of the utmost importance to conduct a study that would lead to the establishment of a post-exposure prophylaxis regime for soldiers training in endemic areas. However, medical prophylaxis was not the only objective of this study. It was also necessary to clarify the 'whole picture' and to learn more about the epidemiology of the disease as well as to develop new methods for diagnosing relapsing fever. For this purpose, a team was set up, including human and veterinary epidemiologists as well as molecular microbiologists. The study design was a placebo-controlled randomised clinical trial which necessitated visiting various military compounds on the return of trainees from their field training (15). The volunteers were then followed to ensure prompt detection of any suggestive clinical signs of relapsing

Figure 2
Typical bite signs of *Ornithodoros tholozani*

fever; in addition, blood samples were taken to detect the agent. Along with this study a polymerase chain reaction (PCR) assay based on the glycerolphosphodiester phosphor-diesterase (GlpQ) gene was developed to ensure better detection of the disease and serological assays based on commercial assays for the detection of *Borrelia burgdorferi* were performed (14). To better understand the epidemiology of the disease, ticks were trapped in various geographic locations and analysed using a newly developed molecular assay for the detection of *B. persica*. To extend the scope of this work further, contact was

made with Gad Baneth from the KSVM who was assisted by Eyal Klement, a veterinary epidemiologist who took part in the design and implementation of the study. Interestingly, during the study period, a domestic cat, a marmoset monkey (*Callithrix geoffroyi*) and a dog were presented for veterinary care with presence of spirochetemia. These three animals suffered mainly from lethargy and anorexia and all had anaemia and thrombocytopenia. A large number of bacteria were detectable as single forms or in clusters of several spirochetes in the blood smears from all animals. The dog and cat improved within two days of antibiotic treatment but the monkey died one day after the beginning of therapy. The same PCR assay used during the human clinical trial was used to diagnose the agent in these three animals and sequencing indicated that infection was caused by *B. persica* or a closely related relapsing fever borreliae (2).

Thus, cooperation between veterinarians, physicians, epidemiologists and molecular microbiologists defined a wider and clearer picture of disease epidemiology and potential reservoirs, all in a joint endeavour to find ways to prevent this disease both in humans and in animals. Further studies combining this multidisciplinary expertise are warranted to elucidate the epidemiology of this interesting and disturbing disease.

Case 3
Avian influenza outbreaks in Israel, Jordan and the Palestinian authority – an example of national and cross-border 'One Health' collaboration

Avian influenza is considered as one of the most important threats to public health. Although there is no persistent human-to-human transmission, the high case fatality associated with human infection is of serious concern to health authorities. The greatest concern comes from the emergence of a human pandemic strain, through either reassortment of a highly pathogenic avian influenza (HPAI) strain with a human strain (antigenic shift) (30) or a set of sequential mutations in an avian strain. The emerging new virus may have high case fatality rates similar to that of H5N1 HPAI as well as effective human-to-human transmission (20). The 'Spanish flu' pandemic that occurred during the early 20th century caused a global mortality estimated at about 50 million people (29). Considering the case fatality of that pandemic which, according to current estimations roughly exceeded 2.5% (29) and taking into consideration the case fatality rate of HPAI which approximates 60% (21), the possibility of a H5N1 pandemic is a very grim forecast. This is the reason why, in Israel, H5N1 HPAI outbreaks, despite being almost solely a veterinary problem are handled by both veterinary and human epidemiologists and involve officers from both the ministries of health and agriculture. The outbreaks that occurred in Israel during the spring of 2006 serve as a perfect example for such collaboration both nationally and internationally (1, 18).

In March 2006, an outbreak of H5N1 HPAI occurred in nine commercial poultry farms in Israel. Six of these were turkey farms. An investigation of these outbreaks posed some major challenges that necessitated the collaboration of physicians and veterinarians; effective outbreak control and investigation could only be achieved by the expertise of veterinarians in both poultry medicine and public health who understood the unique interface from both the animal and human perspectives. Balicer *et al.* reported that, in this particular outbreak, the fact that all such professionals were assigned to regional outbreak containment at multiple foci, delayed the outbreak control and epidemiological investigation by about 10 days (1). They therefore suggested the precise allocation of professional veterinarians and the performance of joint investigations with human epidemiologists as a key factor in the containment of such outbreaks.

Outbreak containment and efficient and prompt culling of birds in the defined zones

were of major importance from both the veterinary and human health points of view because of the profound psychological effects of such an outbreak on the public. For this reason, the importance of compensation for affected farms was understood and encouraged by both veterinarians and physicians. Physicians had also to decide what prophylactic treatment should be administered to veterinarians and other workers when handling affected birds to obtain their willingness to participate in outbreak containment. The importance of effective risk communication during such outbreaks cannot be overstated and, again, this was understood by both veterinarians and physicians who responded to questions associated with proper food handling and contact with animals (veterinarians) along with questions regarding prophylactic treatment and identification of typical symptoms in suspected human cases (physicians) (1).

This outbreak of HPAI in Israel serves as a perfect example for a situation in which physicians and veterinarians collaborate and combine their expertise for one aim and one health. In such outbreaks, there is also a need for collaboration between veterinary diagnostic laboratories and human medicine laboratories that need to share both materials and samples to enable the prompt diagnosis of the infecting agent, map its spread and promptly detect human infection.

Multiple outbreaks that took place simultaneously in the Palestinian authority, Jordan and Egypt have shown the importance of such multidisciplinary collaboration across borders; the agent that caused the outbreak in Gaza was identified by the Israeli veterinary services. The Israeli specialists despatched protocols for outbreak containment, delivered protective equipment and Oseltamivir to the Palestinian authority and exchanged information with both the Palestinians and the Jordanians. All of these joint activities were taken by both veterinarians and physicians from all three countries (18).

Conclusion

The 'One Health' initiative is presented as a direct response to increasing concerns on the global threat of emerging diseases and the significant threats such outbreaks pose to the health of humans and domesticated animals. These threats also have the potential to affect regional and global economies. In this article, we presented three case studies to illustrate the importance of combining veterinary and human biomedical theories and practice in a way that can serve the possibilities embedded in the 'one health' initiative. The partnership between physicians and veterinarians must include a wide range of disciplines so as to fulfil the potential in a multi-dimensional way, ranging from basic sciences, epidemiological studies and epidemiological investigation of potentially zoonotic outbreaks and their containment, to policy making. These case studies illustrate these different aspects. The humanised animal model developed in the KSVM is a good example of combining and exchanging thoughts and ideas from both disciplines to achieve a breakthrough for a better understanding of the aetiology and virulence of common diseases. The relapsing fever case shows the contribution of this collaboration to the understanding of a zoonotic disease, both in humans and in animals and to the representation of a wider and clearer epidemiological picture of the disease, thus improving both prevention and treatment. And finally, the HPAI outbreaks in Israel demonstrate the fruitful and necessary collaboration between veterinarians and physicians in the field, all of whom come from different institutes and organisations, not only across disciplinary and professional borders but also across state and political borders for one common mission associated with the concern for public health.

One of the major goals of the 'One Health' initiative is the integration of educational systems within and between human medical schools, veterinary medical schools and schools of public health. Indeed, in Israel a field epidemiology course was held recently, including veterinarians and physicians, as well

as nurses and laboratory workers, from Israel and the Palestinian Authority. The course is referred to as 'MEPIET' (Middle East Programme for Interventional Epidemiology Training) and can serve as a platform to implement the 'One Health' principles.

These are only a few examples of the positive experiences we have witnessed here in Israel through the implementation of the 'One Health' concept. Future directions to promote the initiative in Israel should also include cooperation in workshops, conferences and the establishment of allied health networks, as well as improved cross-disciplinary communication in professional journals.

Conflict of interest

None of the authors has any conflict of interest in this manuscript.

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