Polygeia 2016 – One Health in Global Health

Executive Summary

The One Health concept acknowledges that human, animal and environmental health are intimately interlinked and interdependent. Global socioeconomic and ecologic transition is making this concept increasingly relevant to public health. With rising population sizes and urban densities, expanding economic growth, climate change and globalisation, there is rising demand for space, natural resources, food, water and infrastructure, driving intensification of agriculture, environmental degradation and expansion of the human-animal interface. This transition is posing unprecedented global health challenges, with human health being increasingly affected by that of the environment and the other animals we share it with. In recent years, we have more and more often been tragically reminded of the threat of emerging infectious diseases, the majority of which are now originating from animals[1]. Emergence and spread of antimicrobial resistance due to the misuse of drugs and spread of resistant bacteria and resistance genes represents a considerable public health concern[2]. Concurrently, globalisation and modern widespread movement of people, livestock and goods has resulted in 'globalisation' of infectious disease, with pathogens and vectors of infectious disease travelling further and faster than ever before around the globe; swelling population densities enhance the likelihood of epidemics. One of the main issues hampering the control of these emerging threats to global health is the limited interdisciplinary collaboration to mitigate these risks[3]. A One Health approach is needed, bringing together medical and veterinary professionals with environmental and social scientists, to share skills, technologies and conceptual frameworks in order to address these cross-cutting issues[3]. The global health community is beginning to embrace the One Health ethos. Germany's Federal Chancellor Angela Merkel called for a One Health approach to tackle the world's human and veterinary public health issues at the 68th World Health Assembly this year[4]. This was echoed by the leaders' declaration of the G7 summit in June 2015, stating they 'are strongly committed to the One Health approach, encompassing all areas – human, and animal health as well as agriculture and environment'[5]. This year's Polygeia One Health team has researched two diseases which could effectively be tackled through a One Health approach.

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[1] Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P (2008) **Global trends in emerging infectious diseases.** Nature, 451, pp.990-993.

[2] Garcia-Alvarez L, Dawson S, Cookson B and Hawkey P (2012) **Working across the veterinary and human health sectors.** J Antimicrob Chemother; 67 Suppl 1: i37–i49

[3] Mbugi EV, Kayunze KA, Katale BZ, Kendall S, Good L, Kibik GS, Keyyu JD, Godfrey-Faussett P, Van Helden P, Matee MI (2012) **One Health' infectious diseases surveillance in Tanzania: are we all on board the same flight?** Onderstepoort J Vet Res. 79(2):500.

[4] Angela Merkel opening speech, 68th World Health Assembly 2015, http://www.who.int/mediacentre/events/2015/wha68/speeches/en/

[5] Leaders' Declaration G7 Summit, 7–8 June 2015, https://www.bundesregierung.de/Content/EN/_Anlagen/G7/2015-06-08-g7-abschluss-eng_en.pdf?__blob=publicationFile&v=3

The first paper focuses on the control of Middle Eastern Respiratory Syndrome (MERS), particularly with the aim of reducing camel to human transmission in the Kingdom of Saudi Arabia (KSA). MERS was brought to global attention this year when its capacity for international spread lead to a devastating outbreak in the Republic of Korea. Camels are a likely reservoir for human infection with the causative agent, MERS-Coronavirus (MERS-CoV), and given its ability to effectively transmit between people, reducing initial infection of humans by camels could be a productive approach to protecting human populations from MERS. Lacking understanding of the zoonotic transmission pathways of MERS-CoV and poor compliance to hygiene measures are challenges currently hampering the control of MERS in the KSA. The proposals broadly aim to reduce human exposure to MERS-CoV in camels and reduce the burden of MERS-CoV in camels. In particular, novel strategies should engage positively with communities and camel farmers, taking into account traditional camel husbandry, mobilising the key stakeholders and introducing more substantial and efficient surveillance and regulation of MERS-CoV in livestock.

The second paper explores policy recommendations to combat antimicrobial resistant tuberculosis (AMR TB), with a particular focus on the Karakalpakstan region of Uzbekistan. Two decades ago, WHO declared TB a global emergency, and an estimated 2 billion people are infected today. With the rise of AMR TB, globalization and enhanced mobility of people and escalation of the immunosuppressive HIV/AIDS pandemic, TB represents a truly global threat to public health. The disease remains one of poor and marginalized populations, presenting a barrier to control through waning resources and political interest. In Karakalpakstan, widespread environmental degradation of the Aral Sea basin has hampered economic and social development in the region, with severe effects on public health. The proposals aim to tackle this issue, suggesting collaboration of the relevant national and international stakeholders and appropriate economic allocations for control of TB. There is a particular focus on the need for renewed efforts in research and development of new treatments and diagnostics, and improving delivery and access to these. The need for a strategy to tackle the severe environmental degradation in the region is also addressed, and an over-arching theme is necessity for appropriate community engagement and psychosocial support. Crucially these efforts would require the interdisciplinary collaboration of multiple professions.

Crucially, in the spirit of One Health, both discussions highlight the need for the interdisciplinary collaboration of multiple professions in order to tackle these pressing global health issues. The diseases in question may seem like local problems at first glance, but in fact have severe implications for global health in today's fast-paced, highly mobile and densely populated world. International collaboration coupled with respect and appreciation for local values, traditions and views is therefore paramount.

Of Camels and people: MERS-Coronavirus in the Kingdom of Saudi Arabia and beyond

Kaz Strycharczyk

Working statement of intent: To eliminate camel-to-human transmission of MERS-CoV in the Kingdom of Saudi Arabia using farm-based interventions as part of a multi-discipline strategy to (i) reduce exposure to farmers working with camels, and (ii) reduce the prevalence of MERS-CoV in the domestic camel population

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BACKGROUND

(i) MERS (Middle East Respiratory Syndrome)[6]

- An acute respiratory infection with symptoms including fever, respiratory distress, cough. Rare instances of gastrointestinal and renal symptoms. Miscarriage also implicated[7].
- Risk factors include cancer, immunosuppression, chronic pulmonary/cardiac/renal disease, diabetes. Rarely affects individuals younger than twenty years old.
- In the period 2012 - 7th July 2015 1368 lab confirmed cases reported to WHO. 26 countries affected. 75% cases in Saudi Arabia (followed by Republic of Korea, followed by United Arab Emirates).

(ii) MERS-Corona Virus (MERS-CoV)

- A novel coronavirus discovered in 2012[8].
- Coronaviruses are +ssRNA enveloped viruses with unusually large (26-32kb) genomes for RNA viruses.
- Other diseases caused by coronaviruses include Severe Acute Respiratory Syndrome and the common cold.
- Reservoirs in bats and domestic dromedary camels[9] (but not other livestock).

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[6] "Middle East Respiratory Syndrome (MERS) | Features | CDC." 2013. 26 Aug. 2015 <http://www.cdc.gov/features/novelcoronavirus/>

[7] Payne, Daniel C et al. "Stillbirth during infection with Middle East respiratory syndrome coronavirus." *Journal of Infectious Diseases* (2014): jiu068.

[8] Lu, Guangwen, and Di Liu. "SARS-like virus in the Middle East: a truly bat-related coronavirus causing human diseases." *Protein & cell* 3.11 (2012): 803-805.

SUMMARY

Middle East Respiratory Syndrome (MERS) poses a significant risk health in the Kingdom of Saudi Arabia (KSA) and beyond. Camels have widespread seroconversion to MERS-Coronavirus (MERS-CoV) and are a likely reservoir of infection for humans working with or around them. As MERS-CoV also exhibits effective human-human transmission, especially in a nosocomial context, reducing initial human infection by livestock seems a productive approach to reducing overall number of MERS cases in humans both within KSA and internationally. This entails: (i) reducing human exposure to the MERS-CoV burden in their camels, and (ii) reducing this burden in camels. Current hygiene measures are failing to contain MERS and this is likely due to poor compliance, at least in part.

Attempts to provide evidence-based advice is being hampered by a lack of specific data, especially on transmission - but we should be making educated guesses, especially given the seriousness of the threat. A precautionary principle[10] should be employed until further research elucidates some of the many 'known unknowns' relating to MERS-CoV in camels.

These measures may be divided into those taken in the short term, and those in the long term. Short term measures will need to focus on reducing exposure of humans to infected camels, while in the longer term the disease burden should be reduced. Novel strategies should frame MERS to camel farmers in an alternative light, mobilise all stakeholders, and introduce more substantial surveillance and regulation.

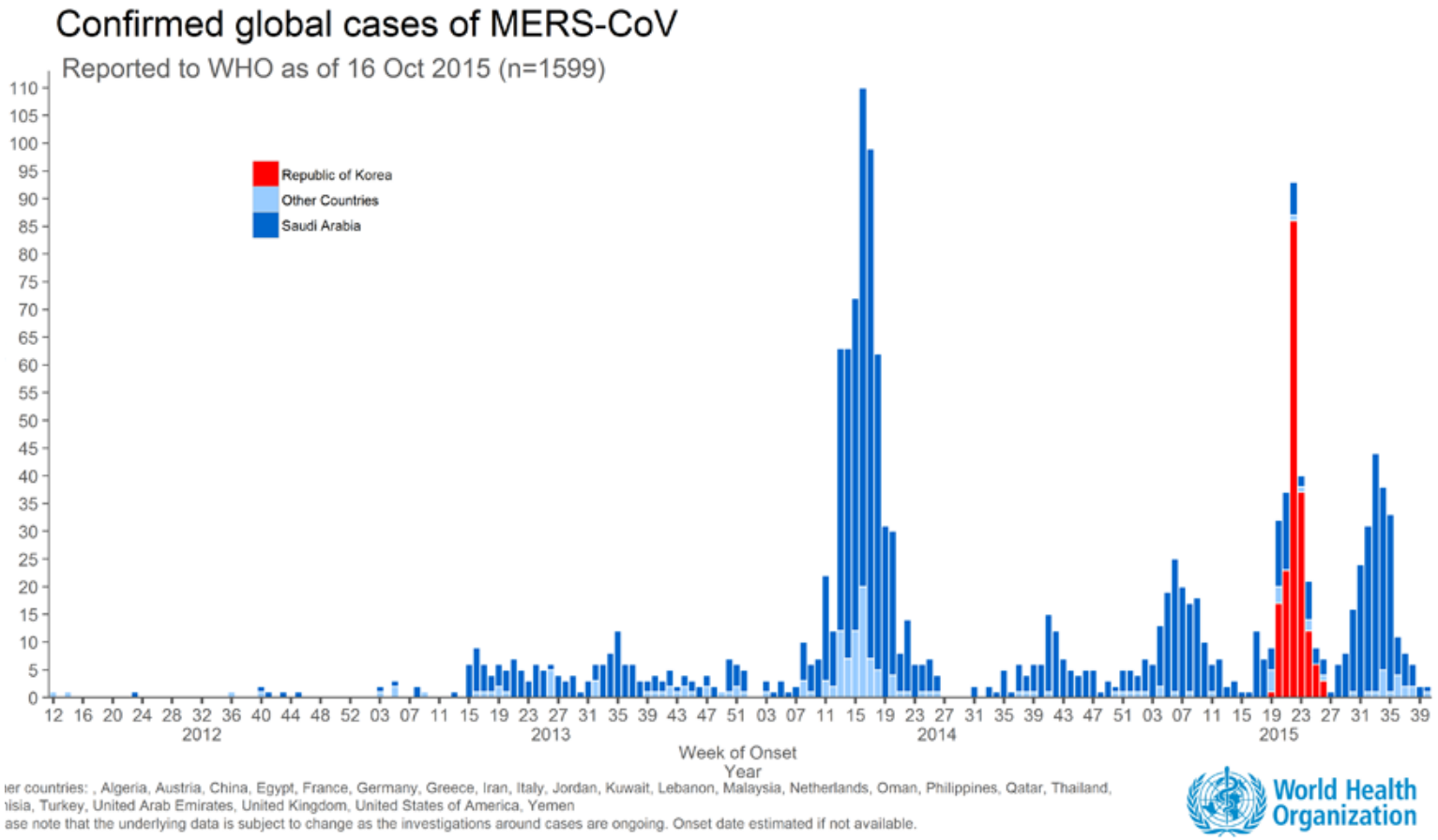
It is clear that MERS-CoV infection in camels is not exactly analogous to other diseases controlled or eliminated in the developed world, and that any effective regime will need to register the nuances of camel husbandry and movement. Uncertainty relating to natural history and transmission of the virus may also undermine confidence in control measures.

[9] Hemida, MG et al. "Middle East Respiratory Syndrome (MERS) coronavirus seroprevalence in domestic livestock in Saudi Arabia, 2010 to 2013." *Euro surveillance: bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin* 18.50 (2012): 20659-20659.

[10] "The Precautionary Principle | Precautionary Principle." 2008. 23 Sep. 2015 <http://www.precautionaryprinciple.eu/>

WHY IS MERS-COV A PROBLEM?

Between the first case in 2012 and 7th July 2015, there have been 1368 laboratory-confirmed cases of MERS, with a mortality of about 36%. For reference, there have been 8096 SARS cases since its emergence, with a mortality of just under 10%. While the SARS outbreak was more violent and shocking when it occurred, it was brought to a swift halt by the appropriate control measures. The failure to do the same with MERS has meant cases continue to stack up, and the number of fatalities is approaching the number killed by SARS (as of 11th September 2015, 544 people have died due to MERS, versus the 774 killed by SARS).



(WHO)

The ongoing presence of MERS-CoV in Saudi Arabia is not only a hazard to the residents of that country - a large, stable state in a region of current and historical volatility - but to the rest of the world's population. The scenario of export and subsequent flare up is no longer a hypothetical one; as of May 2015 the Republic of Korea suffered an outbreak of 185 cases. The virus has eventually been eliminated, but not before thirty-six South Koreans perished[11]. The predisposition of people suffering with conditions such as diabetes, immunosuppressive disorders and cancer to MERS means that many 'developed' countries provide a substantial pool of highly susceptible individuals. Given MERS-CoV has better survival than SARS-CoV in a typical hospital environment[12] and proven ability for effective nosocomial spread[13], the capacity of MERS-CoV to cause a pandemic should not be underestimated.

WHAT STEPS HAVE BEEN TAKEN SO FAR?

Justifiably alarmed by the 2015 outbreak, the Saudi Ministry of Health took some action. It also recommended that elderly, chronically ill or pregnant Muslims avoided the Hajj in 2013, and restricted the number of pilgrims[14]. From May 2014 the ministry Command & Control Center started to distribute media including brochures, posters (see Fig.2), infographics and videos to encourage Saudis to reduce their exposure to MERS-Cov[15]. Of these a number related to camel-to-human spread, and recommended: avoiding close contact with camels, especially those that are ill; wearing personal protective equipment (a face mask, gloves and long-sleeved surgical gown); boiling camel milk before consumption; and thoroughly cooking camel meat and liver before consumption. They also distributed information regarding the nature of the virus, good personal hygiene in the workplace, and how to recognise the symptoms of MERS.

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[11] "Middle East respiratory syndrome coronavirus (MERS-CoV)." 2015. 22 Oct. 2015 <http://www.who.int/csr/don/21-july-2015-mers-korea/en/>

[12] Van Doremalen, N, T Bushmaker, and VJ Munster. "Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions." *Euro Surveill* 18.38 (2013): 20590.

[13] Chowell, Gerardo et al. "Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study." *BMC medicine* 13.1 (2015): 210.

[14] "Hajj pilgrimage could cause deadly Mers virus ... - Daily Mail." 17 Sep. 2015 <http://www.dailymail.co.uk/news/article-2454273/Revealed-How-Hajj-pilgrimage-cause-outbreak-deadly-Mers-virus-million-gather-Islamic-event-hundreds-camels-slaughtered-possible-cause-disease.html>

[15] "Coronavirus (MERS-CoV) - Awareness Publications ..." 17 Sep. 2015 <http://www.moh.gov.sa/en/ccc/publicationsawareness/corona>

Figure 2: A Saudi Ministry of Health poster giving advice on hygiene around camel (www.moh.gov.sa/CCC)

However, many of these recommendations were ignored or derided by the people they were aiming to protect[16]. In light of this response, efforts to control MERS transmission appear to have stalled, at least in KSA. Domestic and international MERS outbreaks continue[17] [18].

Issues concerning compliance with animal or public health measures are not limited to Saudi camel keepers, and here may be exacerbated by a misunderstanding of the role of the camel in Arab culture.

OCCUPATIONAL HYGIENE OPPORTUNITIES IN MERS-COV CONTROL

There is clearly still a place for good workplace and personal hygiene. It is relatively cheap and easy to understand. Although the evidence remains equivocal, recent work in Qatar[19] has shown a clear correlation of presence of neutralising antibodies to MERS with contact with dromedaries, suggesting an occupational risk. The relatively poor viability[20] of MERS-CoV in Saudi field conditions means it should be susceptible to hygiene measures. Finally, it would bring greater protection from a host of other pathogens found in a farm environment.

The obvious obstacle is compliance. There appears to be significant friction between Saudi camel-keepers and the government, and some have even read the guidance from officials as an attack on camel keeping[21]. Many camels are kept by rural and nomadic communities also, who may not have consistent access to disinfectant or face masks. The effectiveness of the measures encouraged is also uncertain, due to the corresponding gaps in our understanding of MERS-CoV transmission.

To avoid seeming overcautious, the state could also accept some level of risk and be more selective about who requires personal protective equipment (PPE) and when. This could involve campaigns targeting at-risk groups - the immunocompromised, chronically sick, pregnant, elderly etc - or seasonal peaks of MERS cases.

Compliance is likely to remain an issue. Identification of Key Opinion Leaders[22] in the camel-keeping community may help. These KOLs would be likely to hold greater respect than

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[16] "Saudi Arabia: Farmers flout Mers warning by kissing ... - BBC." 2014. 22 Oct. 2015 <http://www.bbc.co.uk/news/blogs-news-from-elsewhere-27393045>

[17] "(MERS-CoV) – Republic of Korea." 2015. 23 Sep. 2015 <http://www.who.int/csr/don/03-july-2015-mers-korea/en/>

[18] "(MERS-CoV) – Saudi Arabia." 2015. 29 Sep. 2015 <http://www.who.int/csr/don/17-september-2015-mers-saudi-arabia/en/>

[19] Reusken, Chantal BEM. "Occupational Exposure to Dromedaries and Risk for MERS-CoV Infection, Qatar, 2013–2014."

[20] Van Doremalen, N, T Bushmaker, and VJ Munster. "Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions." *Euro Surveill* 18.38 (2013): 20590.

[21] "Saudi Arabia: Farmers flout Mers warning by kissing ... - BBC." 2014. 23 Sep. 2015 <http://www.bbc.co.uk/news/blogs-news-from-elsewhere-27393045>

[22] "Opinion leadership - Wikipedia, the free encyclopedia." 2011. 23 Sep. 2015 <https://en.wikipedia.org/wiki/Opinion_leadership>

government officials in Riyadh by the nature of their expertise and social networks. They could even be used to organise seminars, and issue media to camel keepers.

***Action**: Access to hygiene information and material to all individuals having close contact with camels should be surveyed. Any shortfall should be remedied by the distribution of these cheap but effective measures. Markets may be an effective focus for distribution.*

***Action**: Identify and mobilise KOLs to act as alternative channels for communicating official guidelines.*

***Action**: Commision relevant further research (see below) to ensure all policy is evidence-based and not unduly restrictive.*

CAMEL HUSBANDRY OPPORTUNITIES FOR MERS-COV CONTROL

A modest understanding of camel husbandry and biology may be instructive in understanding the (in)effectiveness of steps to control transmission of MERS. A full description of their place in the Arab world is beyond the scope of this document, but a brief account is given in Annex 1.

A MERS assay is available in camels, and we are able to distinguish between animals shedding virus and animals that have seroconverted. Certain populations of camels, at certain times of the year, may be more or less likely to transmit MERS-CoV to their keepers. Calves have been shown to be at higher risk of shedding virus[23]**.** The calving season then provides a sudden increase in susceptible hosts that are then more likely to shed virus. There is an association between MERS cases and the calving season[24], with peaks observed around the traditional weaning period[25]**.**

Some authors have suggested prolonging the suckling period[26]. This could have two benefits - firstly to maintain passive immunity for longer, and thus help protect against MERS-CoV. Longer weaning would also reduce human-calf contact, and so reduce the exposure of camel-keepers to this high-risk group. Since calves suffer other neonatal infections which include other coronaviruses and rotaviruses (which maternal antibodies would also protect

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[23] Wernery, U et al. "Acute middle East respiratory syndrome coronavirus infection in livestock dromedaries, dubai, 2014." *Emerging infectious diseases* 21.6 (2015): 1019-1022.
[24] Hemida, Maged G et al. "MERS coronavirus in dromedary camel herd, Saudi Arabia." *Emerg Infect Dis* 20.7 (2014): 1231-4.
[25] RISK, UR. "07-01-2015-RRA-635562330562668486 (Birgitta ... - ECDC." 2015. <http://ecdc.europa.eu/en/publications/Publications/RRA-MERS-CoV-thirteenth-update.pdf>
[26] Hemida, MG. "Dromedary Camels and the Transmission of Middle East ..." 2015. <http://onlinelibrary.wiley.com/doi/10.1111/tbed.12401/abstract>

against) there would also be likely benefits to camel health and productivity. Camel keepers might also be more responsive to campaigns that are framed to protect camels, rather than separate camel and owner.

***Action**: Distribute official recommendations outlining the benefits to camel health and public health of (i) a sufficient dose of colostrum for neonatal camels, and (ii) later weaning in older calves. As above, there may be better uptake if the initiative is industry-led, so KOLs should be used to communicate guidelines.*

MOVEMENT OF CAMELS IN SAUDI ARABIA AND OPPORTUNITIES TO CONTROL MERS-COV

There is significant intranational and international trade in camels[27]. Moreover, no one is sure of the exact prevalence or distribution of MERS-CoV in camels across KSA.

One of the most common and effective food animal disease strategies used in Europe, North America, and Australasia is the use of test-cull-compensate programmes. The severity of culling can be modified depending on disease, as it was with the 2001 Foot and Mouth Disease (FMD) outbreak in the United Kingdom when 'firebreak culling[28]' was introduced in some areas. Control programmes for different diseases can also be successfully combined, as was the case for bovine tuberculosis and brucellosis in Australia[29]. Farmers may also improve their compliance with biosecurity and hygiene measures if they risk valuable livestock being culled through non-compliance. However while such programmes have been part of successful control programmes, they are not always sufficient. The stubborn persistence and spread of bovine tuberculosis in British cattle[30] has not been halted by testing and culling. Moreover, the statutory requirement to test and surrender stock for compulsory slaughter may fuel animosity between authorities and livestock keepers. Given the unusual niche in Arab culture camels occupy - part livestock, part performance animal, part companion - it seems reasonable to expect a greater degree of resistance or anger than would be seen in similar schemes for other livestock. Finally, programmes like this require infrastructure, skilled manpower, and effective administration; a

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[27] Hemida, MG et al. "Dromedary Camels and the Transmission of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)." *Transboundary and emerging diseases* (2015).
[28] "Disease control protocol - GOV.UK." 2015. 23 Sep. 2015 <https://www.gov.uk/government/publications/foot-and-mouth-disease-control-strategy-for-great-britain/disease-control-protocol>
[29] "Bovine tuberculosis eradication in Australia - OIE." 2011. 23 Sep. 2015 <http://www.oie.int/doc/ged/D8570.PDF>
[30] "Figures to May 2015 - Gov.uk." 2015. 23 Sep. 2015 <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/459209/bovinetb-statsnotice-12aug15.pdf>

project on this scale would be relatively expensive and beyond anything the Ministry of Agriculture has done before.

In an intensive situation, where camels are housed and separated from neighbouring or migration camel herds, a MERS-CoV free herd should be relatively easy to establish as the virus does not persist well in the field environment[31]. Such herds could even be state-sponsored.

Unregulated movement poses a major threat to individual herd biosecurity. Nomadic farmers may also find it more difficult or be more unwilling to submit their animals for routine testing, leading to more compliance and goodwill issues. As a result, it may be prudent to make any herd health schemes that are introduced voluntary, or restrict compulsory surveillance to camel herds that are easy to test (intensive, contained herds) or pose a high risk (urban or peri-urban animals). Farms with camels of a high value (e.g. racing camels) may be more keen to have animals tested and have their herds certificated as MERS-free.

A common adjunct to elimination schemes is the use of pre-sale testing of livestock. Testing for MERS before sale would allow farmers purchasing camels to confirm MERS-free status for bought-in animals and maintain their own herd status. This has been an important part of successful eradication scheme against other diseases[32], and as for the test-cull-compensate measure it could easily incorporate other relevant diseases of camels. It has the advantage of being a relatively simple and quick. There is some inconvenience caused to the vendor by this testing however, in addition to cost if this is not borne by the state. This may hinder compliance and generate ill-feeling towards the authorities enforcing testing. Once again, a testing regime requires infrastructure and personnel which may be expensive and complex to organise. Finally, the status of incoming animals is only relevant if the herd is otherwise closed and other routes for camels to contract MERS-CoV are blocked.

Vaccination of livestock is one of the most useful strategies for elimination of endemic disease. There is currently no licensed vaccine against MERS-CoV available for any species, so an immunisation drive would be reliant on its development. Nonetheless the infrastructure needed for surveillance, as well as information collected, would probably aid effective roll-out of such a vaccine.

To put these measures into place, the expansion of the Animal Resources department in the Ministry of Agriculture would need to take priority as it is a prerequisite for many of the controls needed to reduce MERS-CoV incidence in camels. This department would need to hire their own vets, or license private vets to act on their own behalf. Collaboration between universities in the Middle East and elsewhere was recommended recently[33], citing the example of the Royal Veterinary College (London, UK) and Jordan University of Science and Technology

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[31] Van Doremalen, N, T Bushmaker, and VJ Munster. "Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions." *Euro Surveill* 18.38 (2013): 20590.
[32] "Consultation Paper - Proposed relaxation of brucellosis pre ..." 2014. 23 Sep. 2015 <http://www.dardni.gov.uk/consultation-paper-brucellosis-pmt.pdf>
[33] Holloway, P et al. "Building capacity to reduce biological threats in the Middle East." *Veterinary Record* 177.13 (2015): 337-338.

(JUST). The authors of this paper concluded that such twinning would aid in the training of high quality clinicians with better capacity to, amongst other things, contain biological threats. Importing veterinary talent may hasten effective development of the Animal Resources Department, as well as strengthen the prospects of future Arab vets.

***Action**: Offer a state herd health scheme for camels that tiers risk of MERS-CoV infection*

***Action**: Establish strictly controlled state herds to provide clean restocking supply for herds that would usually import animals, or are depopulated through test and cull regimes.*

***Action**: Expansion of the Animal Resources Department in the Ministry of Agriculture to launch a control strategy which may include: a national identification scheme; surveillance; domestic voluntary herd eradication scheme; vaccination drives.*

GLOBAL MOVEMENT OF CAMELS AND OPPORTUNITIES FOR CONTROL OF MERS-COV

Camels from countries which are exporting to KSA (Somalia, Ethiopia, Sudan, Kenya and Djibouti) also have a high seroprevalence of MERS-CoV. These strains of the virus have comparable ability to infect ex vivo cultures of human bronchial tissue[34] and therefore pose a zoonotic risk. Any attempts to control MERS-CoV on the Arabian peninsula must then take into account the regional flow of livestock and attempt to stem infection between countries as well as within countries.

Testing and rejection of affected imported livestock, or trade restrictions on certain countries, could form part of a MERS control strategy. It would be quite simple to enforce as the major exporters are separated by sea and come through ports.

However movement of camels across Gulf countries is widespread and would be harder to regulate. In addition, the reliance on imported camels from the Horn of Africa and the high seroprevalence of these animals may mean Saudis are forced to accept high-risk animals. An official ban may be met with black market solutions, which would be much harder to regulate. Such a ban would not be unprecedented however, as KSA had a nine year embargo on Somali livestock (introduced as a measure to control Rift Valley Fever) that ended in 2009[35]. The reliance on foreign livestock may be ameliorated by development of high health status domestic supply (as described above).

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[34] Chu, Daniel KW et al. "MERS coronaviruses in dromedary camels, Egypt." *Emerg Infect Dis* 20.6 (2014): 1049-53.

[35] "Export of camels from Horn of Africa threatened." 2015. 23 Sep. 2015 <http://country.eiu.com/article.aspx?articleid=882023472&Country=Djibouti&topic=Economy&subtopic=Forecast&subsubtopic=External+sector>

The potential for unintended economic and social consequences in the exporter region, which includes three out of the four 'Very High Alert' states in the Fragile State Index[36], must also be considered in analysis of this measure.

***Action**: Expansion of the Animal Resources department of the Ministry of Agriculture to introduce testing of imported camels with possible sanctions in response to high incoming MERS-CoV challenge.*

STAKEHOLDERS, FUNDING, AND COLLABORATION.

Any policy used to tackle MERS is likely to incur significant cost for the Saudi government. These costs may arise from the employment of skilled professionals, development and purchase of clinical products, compensation for culled animals, and administration of health schemes, to name a few. It is clear then that any sector with a stake in controlling MERS should contribute towards the strategy. The Kingdom of Saudi Arabia is recognised as the strongest Arab economy in recent years and is the leader of the Organisation of Oil-Producing Countries (OPEC), but falling oil prices and increased military spending in 2015 have led to the forecast of a budget deficit[37].

Public Health Sector

The Saudi Ministry of Health has a clear responsibility to protect its citizens from disease. MERS, being acute, deadly, and contagious, should be no exception.

In addition controlling MERS in KSA (and the Arab Peninsula more generally) should greatly lessen the risk of spread to other parts of the world. Therefore the global health community, including organisations such as the World Health Organisation (WHO), have an obligation to contribute towards the containment of MERS.

Veterinary Sector

State veterinary services in KSA come under the remit of the Ministry of Agriculture, specifically the Department of Animal Resources which was established in 1976. Disease in livestock has been identified as major limiting factor in production. A 1998 report[38] mentioned 'further development' of veterinary services in Saudi being planned, but it is unclear how much of this planning has materialised into national campaigns

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[36] "The Fragile States Index 2015 | The Fund for Peace." 2015. 23 Sep. 2015 <http://fsi.fundforpeace.org/rankings-2015>

[37] "OPEC leader Saudi Arabia is having to borrow money - Aug ..." 2015. 22 Sep. 2015 <http://money.cnn.com/2015/08/06/news/economy/saudi-arabia-oil-deficit/>

[38] Haenlein, GFW. "Global agenda for livestock research." *Small Ruminant Research* 2.27 (1998): 183.

Camel Meat, Milk and Racing Sector

The impact of MERS-CoV on camels themselves is overshadowed by the syndrome caused in humans. Multiple reports cite contact with sick camels predating development of the syndrome in humans. Experimental infection with cell culture-adapted human isolate of MERS-CoV induces a mild respiratory infection in camels[39]. In contrast, reports from the field of camel calves[40] and adult camels at abattoirs[41] suggest that camels shedding virus do not show overt clinical signs. It is not known whether subclinical infection has a negative effect on productivity or performance, although evidence from other respiratory infections in other livestock suggest it could do[42].

Tourism Sector

KSA is a popular destination for tourists; it welcomed 10.85 million in 2010[43]. Many of these travel as part of the Hajj, an annual pilgrimage to Mecca in the west of the country that all capable Muslims are obliged to make at least once in their lifetime. There are an estimated 1.6bn Muslims worldwide[44], and the 2014 Hajj was worth approximately $8.5bn to the Saudi economy.

This source of income may be reduced if pilgrims voluntarily forgo trips, or if they are restricted at the behest of their own national governments.

FURTHER RESEARCH

A great number of topics are unclear and this undermines the effectiveness of any proposed control measure. These include the exact transmission routes of MERS-CoV between humans, camels, and any other reservoir species; the effects of infection on camel health and productivity; the likelihood of an effective vaccine being developed; the MERS-CoV status of imported camels; and how endemic disease may be controlled in a nomadic, fragmented setting.

Given the breadth of unknowns and the urgency demanded, international organisations such as WHO, OIE and FAO should take responsibility as well as the Animal Resources

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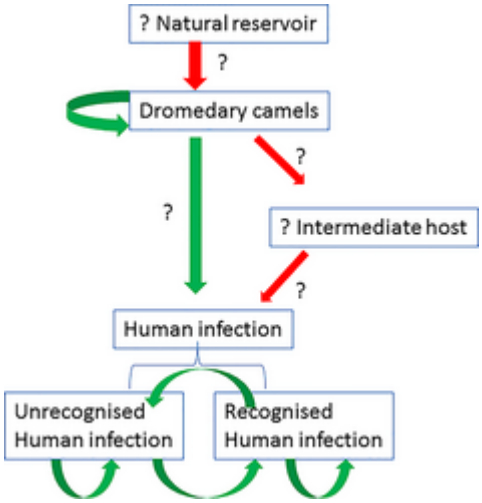
[39] Adney, Danielle R et al. "Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels." *Emerging infectious diseases* 20.12 (2014): 1999.
[40] Meyer, Benjamin et al. "Antibodies against MERS coronavirus in dromedaries, United Arab Emirates, 2003 and 2013." *Emerging infectious diseases* 20.4 (2014): 552-559.
[41] Chu, Daniel KW et al. "MERS coronaviruses in dromedary camels, Egypt." *Emerg Infect Dis* 20.6 (2014): 1049-53.
[42] Goodwin, KA et al. "Pneumonic lesions in lambs in New Zealand: patterns of prevalence and effects on production." *New Zealand veterinary journal* 52.4 (2004): 175-179.
[43] "International tourism - number of arrivals in Saudi Arabia." 2010. 23 Sep. 2015 <http://www.tradingeconomics.com/saudi-arabia/international-tourism-number-of-arrivals-wb-data.html>
[44] "The Future of the Global Muslim Population | Pew Research Center." 2013. 23 Sep. 2015 <http://www.pewforum.org/2011/01/27/the-future-of-the-global-muslim-population/>

department in the Saudi Ministry of Agriculture. Some strides have already been made - neutralising antibodies to a spike protein have been produced in camels[45] - but details on the nature of MERS-CoV and how best to control it remain elusive.



* Hemida et al (2015)

Green arrows represent confirmed transmission pathways. Red arrows represent potential transmission pathways, which may be confirmed in a few instances (for example, camel-to-human transmission in specific case reports) but not confirmed as main transmission pathways as yet.

[45] Muthumani, K. "A synthetic consensus anti–spike protein DNA vaccine ..." 2015. <http://stm.sciencemag.org/content/7/301/301ra132>

In conclusion, MERS-CoV is an urgent public health issue and there are a number of steps that should be taken to eliminate infection---.

A. Saudi Ministry of Health

1) Identify key opinion leaders and use them as channels for dialogue with the camel-keeping community.
2) Survey availability of hygiene products amongst camel keepers and take measures to remedy deficit if identified.

B. Saudi Ministry of Agriculture

1) Deliver media, also through KOLs, on the public and animal health benefits of delayed weaning in camels. (Possible collaboration on Ministry of Health)
2) Develop the Animal Resources Department into an authority with the capability to launch a national identification scheme; active animal disease surveillance; domestic voluntary herd eradication scheme; vaccination drives.
3) Establish strictly controlled state herds to enable clean restocking of affected herds.

C. International health and agriculture organisations (WHO, OIE, FAO)

1) Provide assistance in surveillance while the shortfall is met by a developing Animal Resources Department.
2) Contribute funding and expertise towards research aimed at vital future research.

D. Saudi Camel and Tourism Industry

1) Take an active role in dialogue with authorities, via KOLs.
2) Maintain pressure on authorities to act on MERS-CoV.

ANNEX 1 - Camels in the Arab World

There are two species of camels, both of which have been domesticated. The species which is found on the Arab Peninsula is the dromedary (*Camelus dromedarius*), with the Bactrian camel found mainly in Central Asia. Dromedaries are by far the more common, totalling about 95% of the global population.

Globally, the population of dromedaries rose from 12.9m to over 27m between 1963 and 2013, while approximately 265,000 were present in KSA in 2013[46]. While they are outnumbered by most other large livestock in KSA, camels are found in a great range of farming systems[47] - sedentary and nomadic, rural and urban - and occupies a cultural niche separate to cattle and small ruminants in the region. Bedouins valued their camels highly, and camel racing has seen a resurgence in recent years. There are multiple and ancient independent roots of camel husbandry in the Arab world, and today urban Arabs may keep camels mainly for the social benefits[48].

Camels are seasonal breeders, with the rut occurring in the late autumn. Gestation is twelve to thirteen months long. Calves may be weaned from four months onwards, although are frequently left for a year or more[49]. The main calving period is between winter and early spring.

There are currently no health status schemes in Saudi Arabia for camels. However unmonitored and unregulated movement within and into KSA is a prominent feature of camel farming; a 2012 survey[50] found just 25 out of 218 camel herds (about 11%) in KSA were static. This sort of fluidity in livestock populations would diminish the effectiveness of universal routine and pre-sale testing.

From an international standpoint, KSA is a net importer of camels - in 2013 around 70% of camels slaughtered in KSA were imported[51].

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[46] "FAOSTAT." 2004. 17 Sep. 2015 <http://faostat.fao.org/>

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[51] "VDU's blog: Are MERS cases in Saudi Arabia and the UAE ..." 2014. 23 Sep. 2015 <http://virologydownunder.blogspot.com/2014/06/are-mers-cases-in-saudi-arabia-and-uae.html>

Antibiotic Resistant Tuberculosis: local and global solutions

Luke Smith

Introduction

Tuberculosis: A Global Emergency

Two decades ago, the World Health Organisation (WHO) declared tuberculosis (TB) a global emergency. An estimated 2 billion people are infected with *Mycobacterium tuberculosis*[1], the bacterium responsible for TB. It is primarily transmitted via aerosol expelled by pulmonary-TB sufferers through coughing and sneezing[2]. The majority of infections are "latent"[52]; however, the average risk of reactivation of infection is 5-10% over a patient's lifetime, making latent cases a considerable source of potential infection[2]. Annually, 8.6 million people globally develop active TB, with 1.3 million people dying of active infection. The burden of disease has far-reaching effects, not only through premature deaths but also through workforce losses, pressure on healthcare resources, impacts on families and caregivers. Without effective management, the number of active cases will rise, as infection rates currently outstrip death rates by 7.3 million people per year. The global epidemiology of the TB epidemic presents a barrier to control, being primarily a disease of poverty, with the majority of active cases occurring in poor and marginalised populations within low and middle-income countries.

A concerted international effort and implementation of the DOTS[53] programme proved effective in the fight against TB[3]. Despite this success, TB remains a leading cause of death by infectious disease worldwide[1,4,5], potentially explained by waning political interest in TB programmes and rising antimicrobial resistance among TB strains (for which treatment by DOTS protocol is inadequate[6]). With globalisation and increased population mobility, the escalation of the HIV pandemic creating vulnerable, immunosuppressed populations, and the rise in drug resistance[1,4], TB remains a global problem and threat even in countries where it has largely been eliminated. The rise in resistant TB strains has renewed interest in tackling this disease associated with crippling societal and healthcare burdens. This paper seeks to inform policy to combat the rise of TB, including drug resistance, using a One Health approach, which recognises the interdisciplinary and intersectoral importance for this disease. A focus on the semiautonomous region of Karakalpakstan in the Republic of Uzbekistan highlights the need for strong political will and an integrated One Health approach to produce effective interventions to combat antimicrobial resistant TB.

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[52] Latent TB cases are those where a person is infected with *M. Tuberculosis* but there is no active infection present and patients are neither symptomatic nor infectious.

[53] DOTS (directly observed treatment, short-course) is a protocol whereby a medical professional observes administration of all drugs in the routine: requiring a patient to travel to a clinic to access treatment.

Antimicrobial Resistant Tuberculosis: A Global Problem

Definitions and Prevalence:

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive[7]. AMR majorly limits the arsenal of drugs available to treat microbial infection. Emergence of AMR tuberculosis (AMR-TB) strains is particularly concerning because these are associated with greater mortality and morbidity compared to susceptible strains[8]. There are two widely accepted AMR-TB classifications as laid out in Table 1:

Table 1: Classification of Antimicrobial Resistance

AMR Classification	Definition	Prevalence
Multi Drug-Resistant (MDR)	Resistance to the most potent first line drugs (rifampicin & isoniazid)[4,9].	2012 WHO report estimated prevalence at 630,000 (5% of estimated TB cases)[10].
Extensively Drug-Resistant (XDR)	Resistance to the drugs defined by MDR in addition to fluoroquinolone resistance and resistance to at least one second-line injectable[9,11].	In 2011 84 countries had reported at least one case of XDR-TB[4]. WHO reported XDR prevalence at 9% of the MDR-TB population[10].
Totally Drug-Resistant (TDR)*	Resistance to all first and second-line drugs.	Four cases were reported in Mumbai, India in December 2012[4]

*NB: Whilst the term TDR-TB has not been clearly defined, the sheer diversity of resistance in these strains presents a serious and formidable challenge to treatment.

In 2012, a WHO report estimated 3.7% of new TB cases and 20% of previously treated TB cases were MDR[10]. Worryingly, identification of new TB cases as MDR suggests transmission of MDR-TB, whilst the latter figure may imply that treatment is ineffective or even driving resistance. Emergence of XDR-TB could herald the arrival of virtually untreatable TB without the arrival of new anti-tubercular drugs. AMR has major repercussions for healthcare systems as standard treatments become ineffective, causing infection to persist and spread. Without proper diagnostics and treatments for drug resistant strains AMR-TB is a barrier to proper infection control.

We recommend collaboration between local general practitioners, pharmaceutical companies, relevant political figures and WHO alongside TB specialists to coordinate development of new drugs and produce guidelines to ensure effective usage of new pharmaceutical agents.

The Issue of Resistance – the Case for Karakalpakstan:

Local resistance figures for eastern Europe and Asia, where 9-32% of new cases and over 50% of previously treated TB were found to be MDR[4], are much higher than global statistics. Uzbekistan has notably high levels of AMR *M. tuberculosis,* especially in Karakalpakstan, a semiautonomous region of west Uzbekistan[11]. In a 2001-2002 survey, 13% of new cases and 40% of previously treated cases were found to be MDR[11]. Data from 2009 exposed that Karakalpakstan has considerably higher levels of MDR-TB compared to the rest of Uzbekistan[12]. An international, collaborative, multi-sectorial approach is needed to stop the issue spiralling out of control further. Bacteria do not respect borders - globalisation now enhances the chance for global spread of resistant strains; even if the receiving countries have effective means to treat affected patients, some regions, like Karakalpakstan, will continue to act as reservoirs of AMR-TB.

We also recommend, inclusion of other relevant stakeholders in the control efforts. The tourism and travel industries should be involved through educated border control; screening for TB to help reduce its movement between countries could range from simple checks at borders for symptoms to more stringent tests required as part of visas for those from high risk countries. Fostering collaboration between important stakeholders in TB control will help funding through a centralised pool contributed to by some/all of these parties. These efforts should be headed by an advisory board, which issues recommendations to the necessary parties for implementation.

Drivers of Resistance

A Paradoxical Product of Treatment

AMR is an inevitable consequence of antimicrobial use due to natural selection, but overuse and misuse of drugs have hastened its development.[7].

Drivers of Resistance	Definition
Inappropriate monotherapy	Treatment with a single pharmaceutical agent, a cocktail of drugs is used to treat TB unless otherwise indicated.
Intermittent treatment	Where not all the prescribed antimicrobials are taken. Due to the patient missing a dose or appointment
Functional monotherapy	Resistance to all first and second-line drugs.

The main causes of AMR are inappropriate monotherapy and intermittent treatment[4], which select in favour of strains with resistance characteristics. It is also important to take note of functional monotherapy as it highlights the need for resistance diagnostics. This resistance can be

amplified with further inappropriate treatment or propagated via transmission of resistant strains to other people[12].

Successful administration of drugs is vital to ensure that patients are cured and that resistance is not promoted. This requires social, economic and political stability[1]. An inadequate socio-political infrastructure compounds the effects of irrational prescription (especially monotherapy), posing significant barriers to patient adherence and effective treatment[1], and therefore increasing the risk of AMR-TB emergence. The epidemiology of TB clearly demonstrates this association, with the majority of cases occurring in poor and marginalised groups of low to middle-income countries[1]. Economic stability is a key factor when considering AMR-TB control, for treatment of AMR-TB is a resource burden. For example, in South Africa where the incidence of resistance TB strains is less than 3%, treatment consumes approximated 35% of the TB budget[1]. This disparity suggests that sustainable MDR-TB control programmes require economic stability and appropriate strategies to mitigate the risk of economic downturn, such as ring-fenced budgets. It may therefore be possible that recent economic crises have had a negative impact on TB control[5] if not through reductions in healthcare budgets as a whole then internally via changes to resource allocation away from TB.

We recommend that TB programmes be allocated set budgets, which are protected in times of economic downturn. This should include the investment in any necessary infrastructure (e.g. laboratories for accurate diagnostics) and be based on previous strategies that have been shown to work: such as the DOTS programme.

The Aral Sea Basin – Environmental Impacts on Health

The Aral Sea basin is situated in central Asia, partly in northern Uzbekistan. It was formerly one of the world's largest lakes, its tributaries a vital source of water for irrigation. However, the basin has steadily shrunk to 10% of its original size due to the diversion of its tributaries by Soviet irrigation projects in the 1960s. This severe environmental degradation has had important socio-economic impacts[13]. The Aral Sea region once had a flourishing fishing industry, but shrinkage of the Aral Sea caused an increase in dry, unusable areas and concomitantly decreased the fishing zone. In 20 years (1960-1980) commercial fishing catches became non-existent, decimating the local economy, thus having major public health implications. Moreover, desertification has led to the increased occurrence of dust storms laced with salts and toxic chemicals that are a likely a significant contributor to the high incidence of respiratory diseases in the region[14]. Environmental degradation in the region exacerbated poverty, thus negatively impacting public health. It is likely that addressing these environmental and socio-economic issues will have positive impacts on the problem of TB, a disease of poverty.

We recommend research be conducted in collaboration of a number of ministries within the Uzbek Government (including the Ministry of Health) to explore solutions to the environmental degradation in the region, to acknowledge the impact of the environment on public health, and to highlight the benefits of a One Health approach.

Stigma Associated with disease – the role for social scientists and community work

The social stigma associated with TB in Karakalpakstan often discourages people from seeking treatment, such as through the DOTS programme[15]. First and second-line drugs are more discreetly available for private sale in Karakalpakstan[11], resulting in many patients using these in an unregulated manner instead of entering the DOTS programme, which carries the risk of their TB-status becoming public knowledge[15]. This trend promotes monotherapy and intermittent therapy worsening patient prognoses, as they are more at risk of resistant infections, whilst driving the AMR epidemic and hampering infection control.

We recommend that governments set about to educate people on TB, its symptoms, what to do and the negative impacts of not seeking treatment. Moreover, de-stigmatisation of the DOTS programme or improving its discretion should be key goals. Anti-tubercular drugs should be made privately inaccessible without prescription.

DOTS-Plus: A Step in the Right Direction

DOTS-plus is an extension of the DOTS protocol to incorporate treatment of MDR-TB and was implemented in Karakalpakstan with the Ministry of Health in cooperation with Médecins Sans Frontières (MSF)[12]. Psychosocial support was offered to try to reduce the risk of default; this included monthly food packages for discharged patients and financial support for transport to outpatient facilities along with counselling to stress the importance of adherence to treatment[11]. Despite these measures, rates of default were high and increased further when the programme was scaled up in 2007[12].

We recommend a thorough investigation of the reasons behind default by patients and why the rates of default have increased, in order to overcome these barriers to treatment, both in Karakalpakstan and other regions in future.

Diagnostics, Treatments and Therapies

Diagnostics

Rapid and accurate diagnosis of both TB and drug resistance is required to facilitate treatment and prevent transmission in order to combat the AMR-TB epidemic[16]. In a document aimed at educating clinicians on TB, the Centers for Disease Control (CDC) states that culture is the gold standard[17], however the current main diagnostic test employed in developing countries is sputum smear microscopy[5], a 125-year-old technique with high false positive rates[17]. Drug susceptibility

testing (DST) of infecting strains is a second key diagnostic tool in combatting AMR-TB. The current gold standard technique for DST can take up to 8 weeks for a finalised result[16] but molecular methods do exist for the rapid detection of resistance to first-line drugs[18]. However, for second-line drugs the accuracy of DST techniques employed are questionable, with limited data existing on mutations which confer resistance to second-line drugs[16,18]. Whether it is the result of or in spite of current diagnostics available, case detection rates for TB are generally low[16] and insufficient DST results in detection of fewer than 25% of estimated MDR-TB cases.[8].

We recommend that the necessary infrastructure be put in place to allow full and proper diagnosis of TB and drug resistance, DST notification of all TB cases and individualised treatment programmes. DST should continue during treatment to allow for changes to the 'drug cocktail' accounting for any changes in resistance.

Treatment

Bedaquiline, approved by the FDA in 2012, was the first new TB specific drug produced in forty years [19]. There is a severe gap in the production of drugs to treat TB; especially AMR-TB strains which are resistant to first-line drugs. The inattention of the market to TB-related pharmaceutical research is one which can be attributed to poverty. TB affects the poor and marginalised and with high costs of drug development new anti-tubercular agents are effectively market failures[1].

MDR-TB cases are resistant to the most potent, first line drugs. Second-line treatment, by comparison is substandard, being less efficacious, more expensive and associated with major side effects making it poorly tolerated[4,18]. The WHO recommends treatment to last at least 20 months with an intensive phase involving a second-line injectable lasting at least 8 months[10]. Despite these guidelines, it is estimated that only one in ten MDR-TB patients have access to effective treatment[2]. When this is all considered, it may be unsurprising to find that of MDR-TB cases identified, less than half are successfully treated. This reflects high rates of mortality and default[54] from treatment[1] with the latter something which must be addressed urgently. Prophylaxis is another area which needs to be addressed: echoing the production of new anti-tubercular pharmaceuticals, no new vaccines against TB have been produced in 90 years[5]. Worryingly, the current vaccine (so called 'BCG') doesn't seem to reduce transmission, its duration of protection is variable and there is no perceived benefit of 'booster' doses[20].

We recommend the prioritisation of research and development of new diagnostics, drugs and vaccines by the global health community through WHO in collaboration with local governments and public health authorities and the pharmaceutical industry. New drugs produced should have fewer side effects and shorter treatment periods and as a priority be made accessible to those

[54] Treatment default is the discontinuation of treatment. Studies may define the parameters differently, such as length required before a case is defined as defaulted from treatment.

with MDR-TB to help combat default. Preferential treatment (such as tax incentives) to pharmaceutical companies who undertake TB research and development could attract more investment into the sector.

Conclusion

Drug-resistant TB is a rapidly growing problem that cannot be ignored. Combatting it is possible, as exemplified by the Baltic States where strong political commitment, public health investment and changes to medical practice[5] have stopped high levels of AMR-TB from spiralling out of control. In light of this, we recommend the following changes to help combat the issues brought up in this paper:

1. *Collaboration between key stakeholders to coordinate development of new drugs and to produce guidelines to ensure effective usage of new pharmaceutical agents led by an advisory board.*
2. *Foster the sharing of skills between important stakeholders in TB control with a centralised pool contributed to by some/all of these parties.*
3. *Investment in TB programmes via protected budgets.*
4. *Research into the impact and improvement of environmental factors which negative affect respiratory health with monitoring to help inform residents to help reduce exposure.*
5. *We recommend that governments set about to educate people on TB, its symptoms, what to do and the negative impacts of not seeking treatment. Moreover, de-stigmatisation of the DOTS programme or improving its discretion should be key goals. Anti-tubercular drugs should be made privately inaccessible without prescription.*
6. *Investigation into the factors behind default in the DOTS programme in each instance of its conception in a new region.*
7. *Infrastructure for TB and DST diagnostics should be increased so it has the capacity to carry out DST on all TB cases, to inform treatment.*
8. *Incentivise investment and research into TB diagnostics, drugs and vaccines. Having these made accessible to those in need.*

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