## ANTIBIOTICS USE AMONGST SMALLHOLDER POULTRY FARMERS IN OWERRI, IMO STATE,

#### **NIGERIA**

# V.C. Anyanwu<sup>1\*</sup>, L. C. Ikpamezie<sup>1</sup>, V. U. Odoemelam<sup>1</sup>, I. H. Kubkomawa<sup>2</sup> and N. J. Okeudo<sup>1</sup>

<sup>1</sup>Department of Animal Science and Technology, Federal University of Technology, Owerri, Imo State, Nigeria <sup>2</sup>Department of Animal Health and Production Technology, Federal Polytechnic, Mubi, Adamawa State, Nigeria \*Corresponding author: <a href="mailto:anyanwuvivian982@gmail.com">anyanwuvivian982@gmail.com</a>; Tel: +2348060137545

### **Abstract**

This study aimed to survey antibiotic usage among smallholder poultry farmers in Owerri metropolis, Imo State, Nigeria. The study used a structured questionnaire given to 100 chicken farmers who were chosen at random from Owerri metropolis. Data collected included socio-cultural profile, antibiotic usage pattern, type and form of antibiotics, herbal products, knowledge and practices of antibiotic use among poultry farmers in the study area. Data collected were analyzed using descriptive statistics. The survey showed that most poultry farmers were females (60%) aged 30 and above (50%) and reared broiler chickens (99%). Antibiotics were mostly used for prophylaxis (98%) and to a lesser extent (20%) for therapeutic purposes. Most poultry farmers had secondary school education (58%), kept records of antibiotics used (99%) and purchased antibiotics from veterinary shops (99%). Tetracycline (42%) and sulphonamides (23%) were the most commonly used antibiotics. Most farmers (96%) used dosage as recommended by the manufacturer. Fortyfour (44%) of poultry farmers used herbal products as an alternative to antibiotics, while 55% solely used antibiotics. Results indicated that 99% of poultry farmers observed a withdrawal period, 90% were aware of the presence of antibiotic residues in poultry products, 86% were aware of the adverse effects of indiscriminate use of antibiotics on human health, and 77% were aware of rules and regulations concerning antibiotics residues in animal products. In conclusion, this survey revealed that poultry farmers are using antibiotics on their poultry birds inappropriately, despite being aware of the risks to human health.

**Keywords:** Antibiotic residues, Sulphonamides, Tetracycline, Withdrawal period

# Introduction

The use of antibiotics in the poultry sector is mainly for treatment, prophylaxis and growth promotion (Boamah et al., 2016; Oluwasile et al., 2014). This is in agreement with Mathew, Liamthong and Lin (2009) who stated that the primary purposes for administering antibiotics in livestock are to prevent infections, treat existing infections, enhance growth, and boost production in farm animals. This trend is likely to continue given the growing demand for protein of

animal origin. When antibiotics are used for growth promotion, a small amount is often administered as compared to therapeutic use. Therefore, this may cause bacteria to develop resistance to antibiotics (World Health Organization, 2015). The emergence and spread of antibiotic resistance compromise the nutritional and economic potential of poultry and other food-producing animals.

Poultry is one of the most widespread food industries worldwide. Chicken is the most commonly farmed species, with over 90 billion tons of meat produced each year (Food and Agriculture Organization, 2017). A large diversity of antimicrobials is used to raise poultry in most countries (Landers et al., 2012; Agyare, et al., 2018) and many antimicrobials are of importance in human medicine. Their uncontrolled use in livestock production often accelerates the onset of antimicrobial resistance in microorganisms and commensal organisms (Guetiya et al., 2016). This would result in treatment failures, economic losses and could act as a source of gene pool for transmission to humans. In addition, there are also human health concerns about the presence of antimicrobial residues in meat (Mirlohi et al., 2013; Darwish et al., 2013), eggs (Goetting et al., 2017) and products from livestock.

Susceptible bacterial strains in an environment are eliminated with the introduction of antibiotics leaving those that have the characteristics to withstand it behind. Resistant bacteria progressively flourish and dominate the community by horizontally and vertically disseminating the genes conferring antibiotic resistance to other bacteria (Madigan et al., 2014; Laxminarayan et al., 2013). Resistant bacteria can be transferred from poultry products to humans through consuming or handling meat contaminated with pathogens. Once these pathogens are in the human system, they could colonize the intestines and the resistant genes could be shared or transferred to the endogenous intestinal flora, jeopardizing future treatments of infections caused by such organisms (Marshall & Levy, 2011).

In Nigeria especially in Owerri, Imo State, the use of antibiotics in animal feedstocks has also exacerbated the spread of resistance. Especially egregious is their use for non-curative reasons such as prophylaxis, metaphylaxis, and growth promotion which by one estimate accounted

for 25–50% of all antibiotic consumption in the early 20s (Kamini et al., 2016). Antibiotic use for growth promotion has been banned in the European Union (EU) since 2003 then in 2012, the Federal Drug Administration in America banned the use of antibiotics in livestock without a veterinary prescription (FDA, 2011). There are still many countries where this practice remains unlegislated.

Antibiotic resistance (AR) which is the ability of an organism resist effects of an antibiotic to which it was normally susceptible (Madigan et al., 2014) has become an issue of global interest (WHO, 2015). Microbial resistance is not a new phenomenon since all microorganisms have an inert ability to resist some antibiotics (Agyare et al., 2018). However, the rapid surge in the development and spread of AR is the main cause for concern (Agyare, et al., 2018). In recent years, enough evidence highlighting a link between excessive use of antimicrobial agents and antimicrobial resistance from animals as a contributing factor to the overall burden of AR has emerged (Marshall & Levy, 2011; Lawal et al., 2015; Adebowale et al., 2016; Mamza et al., 2017). However, to effectively curb these challenges, the identification of knowledge and practices regarding antibiotic use among poultry farmers will enable veterinary extension agents to design and disseminate appropriate educational messages with the view of assisting them to engage in best antibiotic use practices thereby slowing the development of antibiotic-resistant bacteria as well as provision of safe poultry products to the public. Thus, this study was conducted to ascertain the baseline knowledge and practices regarding antibiotic use among small-scale poultry farmers in Owerri Metropolis, Imo State, Nigeria.

# Materials and Methods Description of the study area

This study was carried out in Owerri, Imo State, located within the Southeastern vegetation belt of Nigeria. Imo state lies between 4 °4 ′ and 6° 3 ′N and Longitude 6° 15′ and 8 °15′ E (Ministry of Lands and Survey, Imo State, 1984). Meteorology Department, Ministry of Lands and Survey of Imo State (2004) stated that Owerri stands at an altitude of 90m, with mean annual rainfall, temperature and relative humidity of 2500mm, 26.5-27.5 °C and 70-80%, respectively.

#### Method of data collection

Data collection was done using structured questionnaires. Multi-stage purposive random sampling was carried out with 100 Questionnaires.

## Data analysis

Data obtained from the study were analyzed using an SPSS data package for descriptive statistics (Frequency and Percentages).

### **Results and Discussion**

Table 1, shows the socio-economic characteristics of the farmers, females constituted the majority (60.6%) of the farmers than males (39.4%). Over 50% of the farmers were above 30 years of age while 44.4% were between the ages of 15 and 30. It was observed that most of the farmers (57.6%) had secondary education and (42.4%) had university education. It was gathered that 99% of the farmers were into broilers and 1% were into layers production, this could probably be a result of the yuletide period as it is easier and cheaper to rear and sell broilers than layers.

The result of antibiotics usage in poultry production by farmers in Table 2, showed that 100% of farmers used antibiotics in rearing their poultry. It was also observed that 90% of farmers used antibiotics as recommended by veterinary drug vendors, 5.1% used antibiotics as instructed by veterinarians, 3% used antibiotics by themselves without any prescription whereas, 1% used antibiotics as instructed by fellow farmers. Also, it was observed that 100% of the farmers purchase antibiotics from veterinary drug sellers and 100% keep records of antibiotics used on their birds.

The result on the type of antibiotics used by farmers indicated tetracyclines to be (42%), followed by sulphonamides (23%), aminoglycoside (16%), penicillins (15%) and combination of antibiotics (3%) were commonly used antibiotics amongst farmers in the study area (Table 3).

Table 4 shows farmers' responses when asked if they used other substances (ethnoveterinary method) besides antibiotics in poultry production. Responses showed 44% of farmers used different types of substances while 55% used only antibiotics in rearing their poultry.

The result of antibiotics withdrawal, awareness of antibiotics residues, rules and regulations in Table 5, showed that 99% of farmers observe a withdrawal period when they give antibiotics to their poultry and this lasts for one week. Awareness of antibiotics residues in poultry products, over 90% of farmers were aware while 5% were not aware of antibiotics residues in poultry products. It was observed that the majority (86%) of farmers were aware of the effects of antibiotic residues on humans while 13% of farmers were not aware. Moreover, 77% of farmers knew about rules and regulations against antibiotic residues in poultry products while 22% did not know about the rules and regulations.

Table 1: Distribution of respondents according to their socioeconomic characteristics

	Frequency	Percent	Valid Percent	Cumulative Percent
	Sex			
Female	6	0 60.6	60.6	60.6
Male	3	9 39.4	39.4	100.0
Total(N=100)	9	9 100.0	100.0	
, ,	Age			
15-30 yrs.	4	4 44.4	44.4	100.0
30-above	5.	5 55.6	55.6	55.6
Total(N=100)	9	9 100.0	100.0	
, ,	Level of education			
SSCE	5	7 57.6	57.6	57.6
Degree	4.	2 42.4	42.4	100.0
Total(N=100)	9	9 100.0	100.0	
,	Breed			
Layers		1.0	1.0	1.0
Broilers	9	8 99.0	99.0	100.0
Total(N=100)	9		100.0	

Table 2: Responses on antibiotics use in poultry production

	Frequency	Percent	Valid Percent	<b>Cumulative Percent</b>		
Do you use antibiotics?						
Yes	99	100.0	100.0	100.0		
No	00	00.0	00.0	00.0		
Total(N=100)	99	100.0	100.0			
<b>'</b>	Why use antibiotics					
Prevention	97	98.0	98.0	98.0		
Treatment	2	2.0	2.0	100.0		
Total(N=100)	99	100.0	100.0			
W	ho recommends and	ibiotics to use				
Self	3	3.0	3.0	3.0		
Drug vendor	90	90.9	90.9	93.9		
Veterinarian	5	5.1	5.1	99.0		
Fellow farmers	1	1.0	1.0	100.0		
Total(N=100)	99	100.0	100.0			
PI	ace of purchase					
<b>Local vendor</b>	. 00	00.0	00.0	0.00		
Pharmacy	00	00.0	00.0	0.00		
Drug sellers	99	100.0	100.0	100.0		
Total(N=100)	99	100.0	100.0	100.0		
· · · · · · · · · · · · · · · · · · ·	Record keeping					
Yes	99	100.0	100.0	100.0		
No	00	00.0	00.0	0.00		
Total(N=100)	99	100.0	100.0	100.0		

Table 3: Responses on type and form of antibiotics used

	Frequency	Percent	Valid Percent	<b>Cumulative Percent</b>			
Commonly used antibiotics							
Aminoglycoside	16	16.2	16.2	16.2			
Tetracycline	42	42.4	42.4	58.6			
Sulphonamides	23	23.2	23.2	81.8			
Penicillin	15	15.2	15.2	97.0			
Combinations	3	3.0	3.0	100.0			
<b>Total(N=100)</b>	99	100.0	100.0				
Form of	Form of administration						
Infeed	00	0.00	0.00	00.0			
In water	43	43.4	43.4	43.4			
Both	56	56.6	56.6	100.0			
<b>Total(N=100)</b>	99	100.0	100.0				
Dosage gi	ven						
Leaflet	95	96.0	96.0	96.0			
Veterinarian	1	1.0	1.0	97.0			
Drug vendor	3	3.0	3.0	100.0			
Total(N=100)	99	100.0	100.0				
When last	When last were antibiotics given						
A week before study	98	99.0	99.0	99.0			
2 weeks before	1	1.0	1.0	100.0			
Total(N=100)	99	100.0	100.0				

Table 4: Responses on the use of other substances

	Frequency	Percent	Valid Percent	<b>Cumulative Percent</b>
Do you use	other substances?			
Yes	44	44.4	44.4	100.0
No	55	55.6	55.6	55.6
Total(N=100)	99	100.0	100.0	
Name of	substance used			
Bitter leaf	55	55.6	55.6	55.6
Moringa	20	20.2	20.2	80.8
Opete (Costus afer)	12	12.1	12.1	96.0
Scent leaf	3	3.0	3.0	99.0
Total(N=100)	99	100.0	100.0	

Table 5: Responses on antibiotics withdrawal, awareness of antibiotics residues, rules and regulations

-	Frequency	Percent	Valid Percent	<b>Cumulative Percent</b>			
Do you observe the withdrawal period?							
Yes	99	100.0	100.0	100.0			
No	00	00.0	0.00	00.0			
<b>Total(N=100)</b>	99	100.0	100.0				
How long is y	How long is your withdrawal period						
One week	99	100.0	100.0	100.0			
Two weeks	00	00.0	0.00	0.00			
Three weeks	00	00.0	0.00	0.00			
None	00	00.0	0.00	0.00			
Total(N=100)	99	100.0	100.0				
Are you aware of	Are you aware of antibiotic residues in poultry products?						
Yes	94	94.9	94.9	100.0			
No	5	5.1	5.1	5.1			
Total(N=100)	99	100.0	100.0				
Are you aware of t	Are you aware of the effects of antibiotic residues on humans?						
Yes	86	86.9	86.9	100.0			
No	13	13.1	13.1	13.1			
<b>Total(N=100)</b>	99	100.0	100.0				
Do you know about rules and regulations against residues in products?							
Yes	77	77.8	77.8	100.0			
No	22	22.2	22.2	22.2			
Total(N=100)	99	100.0	100.0				

The findings on the socio-economic characteristics of the farmers showed that most of the farmers were females constituting about 60.6%. This implies that more females than males were in charge, were ready to answer questions and due to the yuletide season, reared birds for sale during the festivities to generate income to meet their household needs. This agrees with Moreki et al. (2010); Alabi et al. (2020) and Bamidele et al. (2022) stating that women play a dominant role in smallholder poultry production. However, this is in disagreement with the findings of a study on antimicrobial usage in livestock management in North-Eastern Nigeria: A survey of livestock farmers by Mamza et al. (2017), in which they reported 54% of farmers as males and 46% as females. Also, a high percentage (55.6%) of farmers were above 30 years of age and had some level of education at least to secondary school level (57.6). This concurs with the findings of Mamza et al. (2017) where 80.5% of farmers were reported to be above 30 years of age and Adebowale et al. (2016), in a study carried out on commercial poultry layer farmers in Southwest Nigeria, in which they reported that 83.5% of the farmers attended tertiary education. However, experience rather than age and level of education is considered more important in livestock management. It was observed in this study that a higher percentage (99%) of the farmers reared broilers than layers. This is probably due to factors like the farmer's economic

status, the cost of bird and feed, the festive season, early maturity and ease of management.

This study reports showed 100% of farmers used antibiotics while rearing their birds and 98% administered antibiotics on probably healthy birds for prophylaxis and growth promotion while 2% administered them on sick animals for treatment. Similar observations were made in the country by Mamza et al. (2017); Adebowale et al. (2016); Oluwasile et al. (2014), in Ghana by Boamah et al. (2016) and in Cameroon by Kamini et al. (2016). Although, the administration of antibiotics to birds either for treatment, prophylaxis or as growth promoter improves feed efficiency and live weight gain, its inappropriate use has been associated with the emergence of antimicrobial-resistant bacteria which are transferred to humans when they consume such animal products (Guetiya et al., 2016).

Tetracyclines (42%), followed by sulphonamides (23%), aminoglycoside (16%), penicillins (15%) and combination of antibiotics (3%) are commonly used antibiotics by the farmers. It aligns with Mamza et al. (2017), Adebowale et al. (2016) and Oluwasile et al. (2014) who noted similar findings in their study in Nigeria. Results on the form of antibiotics administration showed that most farmers give antibiotics to their birds (56%) in water and feed while (43%) give them only in water. This is in line with the observations of Mamza et al. (2017), Adebowale et al. (2016), and Lawal et al. (2015) that most antibiotics

used in poultry production in Nigeria are given to them through their feed or water prophylactically. Response on the dosage given to birds by the farmers showed that 96% of farmers used dosage as recommended on the leaflets of the antibiotics used, 3% used dosage as recommended by the drug vendors and 1% used dosage as recommended by the veterinarian. Question on when they gave the birds antibiotics before the study showed that 99% of farmers gave antibiotics to birds a week before the study while 1% administered antibiotics two weeks before.

Farmers indicated using different substances (ethnoveterinary method) with 55.6% of farmers admitting using bitter leaf, 20% indicated using moringa, 12% indicated using Opete (*Costus afer*) and 3% using scent leaf. This is in line with the findings of Bamidele et al. (2022) that smallholder farmers use ethnoveterinary medicine because they are easily accessible and affordable.

High knowledge of antibiotics withdrawal period, residues, rules and regulations among the farmers could probably be due to their being in the city and interaction with other farmers in the study area and enlightenment programs from different stakeholders.

#### Conclusion /Recommendation

In conclusion, the results of this study identified the knowledge and practices of antibiotic usage among poultry farmers in the study area. The study observed that misuse of antibiotics was due to its inappropriate administration in the form of prophylactic, therapeutic and growth promoters by farmers for economic gains, non-adherence to the withdrawal period and rules and regulations stipulated. However, due to the public health implications of antibiotic resistance, there is an imminent need for collaborative and cross-disciplinary research to curb the challenges of indiscriminate use of antibiotics in poultry production to enhance biosafety. There is also a need to respect the withdrawal periods of antibiotics to reduce the level of antibiotic residues in meat samples to the barest minimum, as well as provide safe poultry products to the public and reinforce controls through regular sampling/monitoring programs, analysis, prudent use of rules and regulations and educational campaigns to minimize further development of antibiotics resistance. The information obtained in this study therefore calls for increased surveillance measures and monitoring of antibiotic usage in human and animal production worldwide. Hence, appropriate policies and educational messages has to be circulated about the rational use of antibiotics in poultry production. There should be observation of the withdrawal period, and strict adherence to rules and regulations by the stakeholders concerned.

#### References

- Adebowale, O. O., Adeyemo, O. K., Awoyomi, O., Dada, R., & Adebowale, O. (2016). Antibiotic use and practices in commercial poultry laying hens in Ogun state, Nigeria. Revue d'Elevage Médecine Vétérinaire des Pays Tropicaux 69(1), 41 45. DOI: https://doi.org/10.19182/remvt.31170
- Agyare, C., Boamah, V. E., Zumbi, C. N., & Osei, F. B. (2018). Antibiotic use in poultry production and its effects on bacterial resistance. Antimicrobial resistance—A global threat, 33-51. DOI: 10.5772/intechopen.79371
- Alabi, O. O., Ajayi, F. O., Bamidele, O., Yakubu, A., Ogundu, U. E., Sonaiya, E. B., ... & Adebambo, O. A. (2020). Impact assessment of improved chicken genetics on livelihoods and food security of smallholder poultry farmers in Nigeria. Livestock Research for Rural Development. 32(5), 77-82. http://www.lrrd.org/lrrd32/5/alabi32077.htm 1
- Bamidele, O., Amole, T. A., Oyewale, O. A., Bamidele, O. O., Yakubu, A., Ogundu, U. E., ... & Hassan, W. A. (2022). Antimicrobial usage in smallholder poultry production in Nigeria. *Veterinary Medicine International*, 2022. https://doi.org/10.1155/2022/7746144
- Boamah, V. E., Agyare, C., Odoi, H., & Dalsgaard, A. (2016). Antibiotic practices and factors influencing the use of antibiotics in selected poultry farms in Ghana. *Journal of Antimicrobial Agents*. 2:120. http://dx.doi.org/10.4172/2472-1212.1000120
- Darwish, W. S., Eldaly, E. A., El-Abbasy, M. T., Ikenaka, Y., Nakayama, S., & Ishizuka, M. (2013). Antibiotic residues in food: The African scenario. *Japanese Journal of Veterinary Research*, 61(Supplement): S13-S22. DOI: 10.14943/jjvr.61.suppl.s13
- Food and Agricultural Organization (2017). FAO
  Publications Catalogue. United Nations:
  Retrieved from
  <a href="http://www.fao.org/3/bi6407e">http://www.fao.org/3/bi6407e</a>. pdf Antibiotic
  Use in Poultry Production and Its Effects on
  Bacterial Resistance
  <a href="http://dx.doi.org/10.5772/intechopen.79371">http://dx.doi.org/10.5772/intechopen.79371</a>
  43
- Food and Drug Administration. (2011). Summary report on antimicrobials sold or distributed for use in food-producing animals. Washington DC: Department of Health and Human Services. Available at: http://www.fda.gov/downloads/ForIndustry/

- UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf.
- Guetiya Wadoum, R. E., Zambou, N. F., Anyangwe, F. F., Njimou, J. R., Coman, M. M., Verdenelli, M. C., ... & Colizzi, V. (2016). Abusive use of antibiotics in poultry farming in Cameroon and the public health implications. *British Poultry Science*, *57*(4), 483-493. https://doi.org/10.1080/00071668.2016.1180
  - https://doi.org/10.1080/00071668.2016.1180
- Kamini, M. G., Keutchatang, F. T., Mafo, H. Y., Kansci, G., & Nama, G. M. (2016). Antimicrobial usage in chicken farming in Yaoundé, Cameroon: a cross-sectional study. *International Journal of Food Contamination*, 3(1), 1-6. DOI 10.1186/s40550-016-0034-6
- Landers, T. F., Cohen, B., Wittum, T. E., & Larson, E. L. (2012). A review of antibiotic use in food animals: Perspective, policy, and potential. *Public Health Reports*, 127(1), 4–22. <a href="https://doi.org/10.1177/00333549121270010">https://doi.org/10.1177/00333549121270010</a>
- Lawal, J. R., Jajere, S. M., Geidam, Y. A., Bello, A. M., Wakil, Y., & Mustapha, M. (2015). Antibiotic residues in edible poultry tissues and products in Nigeria: A potential public health hazard. *International Journal of Animal and Veterinary Advances*, 7(3), 55-61.
- Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., ... & Cars, O. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases*, *13*(12), 1057-1098. DOI: 10.1016/S1473-3099(13)70318-9
- Marshall, B. M., & Levy, S. B. (2011). Food animals and antimicrobials: Impacts on human health. *Clinical Microbiology Reviews* 24(4),718–733. Doi: 10.1128/CMR.00002-11.
- Meteorology Department, Ministry of Lands and Survey (2004). Annual Report Abstract, Ministry of lands and survey, Imo State. Pp.16-18.
- Mirlohi, M., Aalipour, F., & Jalali, M. (2013).

  Prevalence of antibiotic residues in commercial milk and its variation by season and thermal processing methods.

  International Journal of Environmental Health Engineering; 2:41. DOI: 10.4103/2277-9183.122429
- Madigan, M. T., Martinko, J. M., Bender, K. S., Buckley, F. H., & Stahl, D. A. (2014). Brock Biology of Microorganisms. 14th ed. Illinois: Pearson International; p.1006.

- Mamza, S. A., Geidam, Y. A., Mshelia, G. D., & Egwu, G. O. (2017). Antimicrobial Usage in Livestock Management in North-Eastern Nigeria: A survey of livestock farmers. *International Journal of Science and Research Methodology*, 8(2), 149-172.
- Mathew, A. G., Liamthong, S., & Lin, J. (2009): Evidence of Int 1 transfer between Escherichia coli and Salmonella typhi. Food Biology. 6(8), 959-964. https://doi.org/10.1089/fpd.2009.0263
- Moreki, J. C., Poroga, B., Dikeme, R., & Seabo, D. (2010). Ethnoveterinary medicine and health management in poultry in Southern and Western Districts, Botswana. Livestock Research for Rural Development. 22(6), 107-112
- http://www.lrrd.org/lrrd22/6/more22107.htm Oluwasile, B. B., Agbaje, M., Ojo, O. E., & Dipeolu, M. A. (2014). Antibiotic usage pattern in selected poultry farms in Ogun state. *Sokoto Journal of Veterinary Science*, 12(1), 45 50. http://dx.doi.org/10.4314/sokjvs.v12i1.7
- W. H. O. (2020). W.H.O "Antimicrobial resistance"; https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance, (2020).
- W. H. O. (2015). Antibiotic resistance: multi-country public awareness survey; 2015. Available from http://apps.who.int/iris/bitstream/10665/194 460/1/9789241509817 eng.pdf?ua=1