
Irrational use of antibiotics and the risk of diabetes in Ghana

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SUMMARY

Epidemiological studies show clearly that Caesarean birth, perinatal or neonatal irrational antibiotic use is strongly associated with increased risk of obesity and diabetes in later life. Irrational use of antibiotics is a great global public health concern especially in developing economies like Ghana due to poor regulation on medicines. Unfortunately, this concern has been reduced to the fear of development of resistant organisms and the destruction of the world's limited range of antibiotics therapy at the expense of other insidious risks including the development of metabolic and atopic diseases. These risks however appear to have greater implications on public health systems of developing economies. Here, we review the ignored role of antibiotics in the global obesity pandemic and project the risk that it poses to the health system of a developing economy like Ghana.

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INTRODUCTION

The biggest challenge of health systems of many developing economies is the management of communicable diseases. Malaria still accounts for more than 40% of out-patients attendances in Ghana¹ and takes a greater part of the health budgetary resources. Although communicable diseases remain the main threat to health of developing countries, non-communicable diseases kill more people in the developing world.² In addition, it has been shown that rising incomes in these developing countries will stimulate rises in non-communicable diseases due to increased caloric intake, sedentary lifestyle, rapid nutrition transition and migration from rural to urban areas.

Nutrition transition, the shift from traditional diet to Western diets consisting more of processed foods, fat, and fructose, is fuelled by commercialization of the food trade^{3,4} and many previously deprived regions of the world now have high accessibility to western diets. To these regions, commercialization of the food trade promotes food security but this may enhance the development of non-communicable diseases. Furthermore the deliberate introduction of high amounts of fructose into the diet is a potential source of concern as fructose unlike glucose is preferentially metabolized more into fat

in the liver, leading to increased insulin resistance and visceral adipose tissue^{5,6} which are harbingers for diabetes and other metabolic syndromes.

Western lifestyle associated with increased alcohol and tobacco consumption^{7,8,9} partly due to aggressive marketing is a risk in the development of diabetes and other metabolic diseases. Subsequently, by the year 2030, non-communicable diseases will overtake communicable in many developing economies. Diabetes alone will increase by 150% in developing countries within that period.¹⁰

While the trends in diabetes in developing economies share some resemblance to trends seen earlier in the developed world, the projected absolute numbers of people to develop diabetes and other metabolic syndromes will overwhelm the health systems of these countries. Characteristically, diabetes and other metabolic diseases in developing economies affect people mostly in their productive years compared to much older people in the developed world.^{11,12}

Furthermore, low incomes, severe limitations of health resources and illiteracy will confound strategies that have worked in the developed world.

In view of the anticipated economic burden of therapeutic management of non-communicable diseases, there is the urgent need to use preventive strategies such as lifestyle changes and other public health interventions.

The precipitous rise in the prevalence of diabetes and other metabolic syndromes in the developing world, particularly in Southeast Asia, presuppose that perhaps the idea of high caloric diet (Western diet) consumption and sedentary lifestyle as the only cause may be too simplistic and insufficient to completely explain the trends. To support these assertions, several hypotheses have been proposed. Earlier suggestions had focused on racial and genetic susceptibility,¹³ typically initiated by the propounding of “Thrifting gene” hypothesis by Neel¹⁴ and other subsequent modifications.

However, other evidence suggests that common therapeutic agents like antibiotics may pre-dispose individuals to obesity and metabolic syndrome and may account partly for the rise in obesity-related diseases including cardiovascular and cerebrovascular accidents. Epidemiological studies show clearly that irrational antibiotic use is associated with increased risk of obesity, diabetes and asthma in later life.¹⁵ It appears that the average clinician may not be conscious of how a seemingly harmless action of inappropriate antibiotic usage can contribute to the global obesity pandemic and increased incidences of metabolic diseases. This review focuses on the apparent insidious role chronic and irrational antibiotic use may play in the increased obesity in the Ghanaian society using data from countries that are already suffocating under the stress of increased metabolic disorders.

Global changes in human body stature-Impact on health and the role of environmental chemicals

The physical condition of the human stature has been changing. Humans are now taller and bigger than they used to be two decades ago. In February 2014, the people’s liberation army of China reported average increase in height and weight of Chinese soldiers over that of two decades ago. The US population has consistently grown taller from 1964. Epidemiological studies propose some health benefits for increased heights of a population, which include improved cardiovascular function¹⁶. However, this benefit will be nullified by the increased body weight. On the other hand, increased population height is associated with increased Ischemic Heart Diseases.¹⁷ Other data even suggest that shortness is associated with longevity and reduced risk of some

cancers.^{17,18} Interestingly, some historic and current clinical data show that antibiotics may be influencing our bodies significantly which may be predisposing humans to diabetes, ischaemic heart diseases and cancers.

Antibiotics and weight gain - a case for use in agriculture

Antibiotics form a backbone of the multimillion global poultry industry. First demonstrated by Jukes,¹⁹ antibiotics promote growth of vertebrates by enhancing the efficiency of conversion of feed to meat. Several other scientists corroborated Jukes results and subsequently antibiotics were introduced into agriculture as growth promoters.²⁰ Compared to human health, agriculture consumes more than 80% of all antibiotics produced.^{21,22,23,24} Antibiotic treated animals have altered gut anatomy and physiology including reduced intestinal weight and length,^{25,26} thinner intestinal epithelium, high efficiency in nutrient absorption and reduced metabolic demands of the gastrointestinal system.²¹

It had been previously thought that the effect of antibiotics were due to the ability of sub-therapeutic doses to control subclinical infections. This was plausible because poultry raised in germ-free environments do not respond to the growth promoting effects of antibiotics but grow faster and more efficiently and exhibit feed efficiencies approaching those of antibiotic-treated poultry.^{27,28} However, it has been established that the enhanced growth, although independent on the kind of antibiotic used; was more pronounced in antibiotics that were rarely absorbed from the intestines. Consequently, conventional antibiotic mechanisms such as inhibition in specific microbial cellular or organelle functions have not been implicated but rather the effects of antibiotics in killing or inhibiting gut microflora growth.

Consistent in both humans and animals are the alterations in gut microflora of treated subjects. The current general consensus is that gut microflora; commonly referred to as the microbiome, were involved in programming the metabolism and the immunity of the individual^{29,30} and early perturbations may affect size and immunity which may be very beneficial in agriculture but detrimental in human health.

Antibiotics and the obesity pandemic

It has been noted that babies born by caesarian section are more likely to be prone to obesity in later life than those born by natural means.³¹ The main explanation to this observation is that the acquisition of microorganisms from the birth canal of mothers appears to regulate the metabolism of the neonate.³²

Similarly, exposure to antibiotics during the first 6 months of life is associated with increase in body mass from 10 to 38 months²⁸ and an increased risk of being overweight in children before age 7.³³ Several experiments, many unpublished because of ethical reasons, show that exposing children to antibiotics caused increases in weight.

Kalliomäki *et al.*³⁴ has shown that 40% of overweight children had received antibiotics in infancy against 13% in the normal-weight group by the age of 6 months. Although there is no available data on antibiotic consumption amongst Ghanaian children, it is known that at least in the US children are prescribed on average about one course of antibiotics every year, often for ear and chest infections.³⁵ Similar trends are likely to be seen amongst urban and affluent Ghanaian children. Interestingly, more than half of antibiotics prescribed to children are deemed irrational and unnecessary.

Trends in antibiotic usage show increases and correlates very well with economic status of the population. It has been reported that the emerging economies of Brazil, Russia, India, China, and South Africa (BRICS) alone account for more the 70% for these rising trends in the past decade.³⁶ This makes it difficult to exclusively evaluate the effects of antibiotics on human weight without high caloric diet, in particular fructose and sedentary lifestyles which are confounding factors. Although many of these studies have been in children, limited data from adults show similar patterns. In an unpublished experiment involving US Naval recruits, it was established that supplementation with antibiotics resulted in increased body mass. Thuny *et al.*, (2010)³⁷ reported that treating adults with vancomycin and gentamicin combination, two antibiotics that are poorly absorbed from the intestines, for endocarditis was significantly linked to development of obesity within a year.

To understand the interaction between high caloric diet and antibiotic therapy, Cho *et al.*³⁸ simulated experiments in mice where animals received a high caloric diet alone or in combination with antibiotics. Antibiotic-treated mice gained twice the weight of untreated mice. Interestingly, the effects were greater amongst female animals than male. After antibiotic use, changes in the expression of gut microbial genes involved in metabolism of carbohydrates into short-chain fatty acids were observed with enhanced expression in genes involved in storing unused calories as lipids.

The diabetes epidemic in China

Type 2 diabetes has reached epidemic proportions in the general adult population in China.³⁹ The National Dia-

betes Research Group of China says that, just over two decades ago Type 2 was so rare in China that less than 1% of the population had the disease.

Today diabetes has reached alarming rates with more than 11% of the population having diabetes and approximately 500 million people having pre-diabetes; abnormally high hyperglycaemia but not high enough for a diagnosis. Interestingly, in China as in other Asian countries, obesity does not correspond so well with the development of diabetes; as diagnosis occurs at a much lower BMI of 23.7 kg/m² compared to 27 kg/m² in other populations.^{41,42} Researchers believe that there is a tendency among East Asians to accumulate belly fat (higher visceral adipose fat) which is a predisposing factor to the development of Type 2 diabetes.⁴² Genetic predisposition as well as high caloric diet and increasing sedentary lifestyle have been proposed to be the causes of the increases in diabetes.¹³ So far, no diabetic gene exclusive to Chinese or Asians has been reported. Although Western food consumption is growing rapidly amongst Chinese it still has not reached a huge proportion of the population to be solely responsible for these increases. Other East Asian countries that share similar genetic makeup and consuming high caloric diets as some Chinese are also experiencing increases in the incidence of diabetes but have not reached endemic rates. Moreover, globally there are countries that consume more calories and are less active than Chinese and yet diabetes has not reached such alarming rates. It is known that people living in cities and urban areas, tend to be less physically active partly because of mechanization of transport and white collar jobs and have high risk of obesity and diabetes. A Chinese study showed that diabetes prevalence differed in regions with economic status; however the prevalence of diabetes was similar between urban residents and rural residents in economically developed regions implying that there may be more to it than the presumed sedentary lifestyles.⁴¹

China's abnormal antibiotic consumption

Data on antibiotic consumption in China is unprecedented in the world. China has become the world's leading antibiotics consuming country, with an average consumption of 138 grams per person per year. Literally, the average Chinese now consumes ten times the antibiotic of an average American. Over 50% of outpatient's prescriptions from Chinese hospitals contain at least one antibiotic.^{51,52} This is in contrast to the US where only 15% of prescriptions have an antibiotic.⁵³ According to data from the World Health Organization, up to 80% of all hospital admissions in China receive some type of antibiotic and broad-spectrum antibiotics and multiple antibiotic courses account for 58%.⁵⁴ This figure is much higher than the international level of 30%.

China along with four other countries currently account for more than 76% of the increase in global antibiotic consumption between 2000 and 2010.³⁶

Data from animal studies have shown that there is an association between antibiotic consumption and accumulation of visceral adipose fat. Visceral adipose fat is a risk in the development of diabetes. Some Chinese patients at diagnoses for diabetes have normal BMI but high visceral adipose fat.

Diabetes in Ghana

The earliest available post-independence data shows that prevalence was 0.2% of the population in 1964⁴³ and this has increased steadily over the years. A Ghana Diabetes Association study showed that between 1990 and 2000 prevalence increased from 2-3% to 6.4%.⁴⁴ Most of the increases occurred in urban centers with over 10.7% of the population having impaired glucose tolerance. The number of people with diabetes in Ghana is expected to double by 2030.^{45,46} Additionally, it is reported that in Ghana due to some sociocultural practices and beliefs as well as rapid urbanization, there are indications that diabetes incidence in the Kumasi Metropolis, for example, amongst the adult population alone may be higher than many urban areas of Sub-Saharan Africa.^{47,48} Further projections by Mbanya *et al.*⁴⁹ indicate that diabetes-related morbidity and mortality in Ghana will increase dramatically in the coming years. The cost of managing diabetes in Ghana has increased steadily from \$180 – \$420 in 2000 to \$106 – \$638 in 2007 per year.⁵⁰ These figures exclude other cost in managing comorbidities such as dialysis in renal failure and hypertension. It is plausible that explosion in diabetes incidence in Ghana as pertains in South-East Asia may excessively increase the health budget, threaten the national insurance system and overwhelm Ghana's fragile economy. However, since approximately 90% of reported diabetes cases in Ghana are type 2, intensive public health education and appropriate interventions could salvage and reverse the current trend.

Ghana's antibiotic consumption

Due to poor drug regulation, data on antibiotic consumption patterns in Ghana is limited although antibiotics remain readily available in health facilities across the country and can easily be obtained without authorization from a qualified prescriber. Indeed the incidences of antimicrobial resistance and treatment failures give clear indications of irrational use of antibiotics. A report by Donkor *et al.*⁵⁵ indicates that about 30% of tertiary students in Accra take an antibiotic within a month. In the same study 70% of respondents had self-medicated without a prescription. A study in the Cape Coast metropolis showed that over 70% of respondents obtained antibiotic without prescription.⁵⁶ Consistently, amoxicil-

lin, a broad spectrum antibiotic, accounts for more than 50% of antibiotics obtained without prescription in Ghana.

Respiratory conditions such as colds and coughs account for a chunk of the diseases for which antibiotics are used in Ghana.^{55,56}

Furthermore, with the recent introduction of pre-school in Ghana, and more mothers taking up jobs, baby respiratory infections are also expected to increase, which most invariably are managed with aggressive antibiotic therapy, even though many of these infections such as common cold are of viral origin and do not require antibiotic therapy. In line with this reasoning, infant antibiotic exposure may be underestimated.

The Thrifty genotype explained with antibiotics

Neel in 1962 attempted to explain why some people or populations were more susceptible to the development of diabetes through genetics and natural selection¹⁴. He proposed that early in the evolution of man when famine, as selective pressure, was predominant, inheritance of diabetes predisposing genes called “THRIFTY GENES” were beneficial in enhancing efficiency of conversion of food into fat for storage in anticipation of harder times. However these genes became a disadvantage in the modern world where famine is rare and food is readily available.

This hypothesis has been widely used to explain why some populations have high rates of diabetes. Unfortunately, years of research have not been able to identify the so called “THRIFTY GENES”⁵⁷ and this has led to modifications and/or abandoning of the hypothesis. However, factoring in the role of antibiotics, whose use gained more grounds in health around the time the hypothesis was postulated, the hypothesis becomes more compelling. The evidence presented here so far shows that antibiotics enhance the efficiency of conversion of food to fat for storage which in the hypothesis is due to “THRIFTY GENES”. Exposures to antibiotics promote expression of several genes involved in carbohydrate metabolism. It may be suggested that Neel's “THRIFTY GENES” are not more than genetic modification that occurs due to antibiotic exposure that promotes food utilization.

Chinese and Ghanaian Health systems parallelism

The Chinese health system is failing in its effort to control diabetes. It is said that for every new diagnoses of diabetes in China, two other people (70%) remain undiagnosed.^{58,59} Ghana's health system cannot be said to be a miniature of the Chinese, however, there are some structural and policy driven features that resembles the Chinese system.

Most health facilities in China are owned and operated by the government. In order to enhance accessibility and affordability without compromising quality, the government (central, city, provincial) publishes the prices of services just like the National Health Insurance Authorities in Ghana. Hospitals in China are unable to meet their budgetary requirements and rely heavily on drug sales to meet their needs.

The Chinese government has reduced subventions to public hospitals and it is estimated that only 20% of hospitals income comes from the government.^{60,61,62} To stay afloat, facilities guided by profitability under provide, split or over-provide certain services to increase their revenue.^{63,64} Prescribers on their part are pressurized to prescribe medicines irrationally to meet the budget deficits and over half of hospital spending by patients is on pharmaceuticals.⁶⁵ Like China, some pharmaceutical companies in Ghana also induce prescribers to prescribe their products to boost the sale of their products.⁶⁶ National data show that 60% of hospitals' revenue is generated by selling drugs and 30–40% of drug consumption represented inappropriate utilization in China.⁶⁷ In Ghana, government subventions are inadequate and insurance claims are delayed for a considerable period in the fiscal year. Hospitals are forced to rely on internally generated funds which may include increased drug sales.

Retail pharmacy practice is poorly developed in China and the practice of prescribing and dispensing is not distinct and clearly separated. Similarly in Ghana, The National Health Insurance Scheme does not decouple prescribing practices from dispensing practices. This breeds conflict of interest and promotes irrational antibiotic prescribing and usage. The National Health Insurance of Ghana like the Chinese government also does not pay dispensing fee as pertains in many countries⁶⁷, but rather retail pharmacists and dispensers earn their income from the difference between the wholesale and retail prices. This does not motivate pharmacists to monitor irrational use of antibiotics since they stand to benefit from such practices.

The psyche of Chinese patients is such that they are likely to request for antibiotics from their General Physician even when in the opinion of the practitioner antibiotic use may be unnecessary. In Ghana, one of the objectives of the Ghana National Drug Programme (GNDP) is to promote the rational use of medicines. In spite of the efforts made by the programme, antibiotics are easily obtained from pharmacies without prescription.⁶⁸ Drug regulation especially Class A and B drugs is a problem and several unlicensed and unaccredited persons dispense antibiotics to the general public. The

Food and Drugs Authority (FDA) in Ghana and the Ghana Pharmacy Council are under resourced to regulate the rational use of medicines. There are efforts by several non-governmental organizations to promote rational drug use. For example, the Antibiotic Drug Use, Monitoring and Evaluation of Resistance in Ghana (ADMER), a Ghana-Denmark initiative aims at building research capacity to help combat irrational antibiotic use. The efforts of government agencies including the FDA, GNDP and non-governmental organizations towards the rational use of antibiotics should be stepped up if Ghana is to avert the explosion of diabetes in the near future.

CONCLUSION

Ghana's economic growth has improved over the current decade. Rapid economic growth is associated with increased antibiotic consumption as well as increased metabolic and cardiovascular diseases. In view of the overwhelming evidence implicating antibiotic consumption to increased obesity and other metabolic related diseases, there is the urgent need to strictly enforce the regulations on the use of antibiotics in Ghana. With current trends, irrational antibiotic use in Ghana can only be expected to increase in the coming years. Therefore diabetes and other related metabolic diseases are expected to increase. The solution as has been emphasized elsewhere is lifestyle modification with active education for the promotion of rational antibiotic use. In practical terms, rational use of antibiotics will require that patients receive appropriate antibiotics, preferably narrow spectrum that meet their specific clinical needs, in the right doses for the appropriate duration at a reasonable cost. The long-term effects of irrational antibiotic use may be a price too costly for our fragile health system to bear. A multifaceted approach including education of clinicians, doctors, pharmacists, nurses and patients and adherence to rational prescribing and dispensing in Ghana as well as monitoring should provide the framework for the quest to reverse these trends.

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