Chapter 12

Surveillance and Control of Asymptomatic Carriers of Drug-Resistant Bacteria

Euzebiusz Jamrozik and Michael J. Selgelid

Abstract Drug-resistant bacterial infections constitute a major threat to global public health. Several key bacteria that are becoming increasingly resistant are among those that are ubiquitously carried by human beings and usually cause no symptoms (i.e. individuals are asymptomatic carriers) until a precipitating event leads to symptomatic infection (and thus disease). Carriers of drug-resistant bacteria can also transmit resistant pathogens to others, thus putting the latter at risk of infections that may be difficult or impossible to treat with currently available antibiotics. Accumulating evidence suggests that such transmission occurs not only in hospital settings but also in the general community, although much more data are needed to assess the extent of this problem. Asymptomatic carriage of drug-resistant bacteria raises important ethical questions regarding the appropriate public health response, including the degree to which it would be justified to impose burdens and costs on asymptomatic carriers (and others) in order to prevent transmission. In this paper, we (i) summarize current evidence regarding the carriage of key drug-resistant bacteria, noting important knowledge gaps and (ii) explore the implications of existing public health ethics frameworks for decision- and policy-making regarding asymptomatic carriers. *Inter alia*, we argue that the relative burdens imposed by public health measures on healthy carriers (as opposed to sick individuals) warrant careful consideration and should be proportionate to the expected public health benefits in terms of risks averted. We conclude that more surveillance and research regarding community transmission (and the effectiveness of available interventions) will be needed in order to clarify relevant risks and design proportionate policies, although extensive community surveillance itself would also require careful ethical consideration.

E. Jamrozik (✉)

Monash Bioethics Centre, Monash University, Clayton, VIC, Australia

Royal Melbourne Hospital Department of Medicine, University of Melbourne,
Parkville, VIC, Australia

Wellcome Centre for Ethics and the Humanities and The Ethox Centre, Nuffield Department
of Population Health, University of Oxford, Oxford, UK

e-mail: zeb.jamrozik@gmail.com

M. J. Selgelid

Monash Bioethics Centre, Monash University, Melbourne, VIC, Australia

Keywords Antimicrobial resistance · Drug resistance · Asymptomatic infection · Drug-resistant infection · Ethics · Public health ethics

12.1 Introduction

The human body contains more bacterial cells than human cells. We all, thus, “carry” bacteria--especially in our digestive, respiratory, and urogenital tracts – and on our skin (Sender et al. 2016). Bacteria travel with and between human beings, following the daily flux of commuters in cities and crossing the world with international travellers. These ‘fellow travellers’ are often unsuspected since most of these bacteria cause no overt symptoms (i.e. the human carriers are mostly ‘asymptomatic’), and some even have symbiotic benefits for humans.¹ Yet, under certain circumstances (e.g., skin breakdown, bowel surgery, or the use of immunosuppression), some ubiquitous species of bacteria cause ‘invasive’ disease that may require antibiotic treatment and be life threatening if such treatments are ineffective or unavailable. With increasing use (and overuse) of antibiotics in recent decades, such ubiquitously carried bacteria have in many cases become increasingly resistant to first line (and, in some cases, second line and/or ‘reserve’) treatments (See Table 12.1). Some have become effectively untreatable with standard antibiotics, and those who develop invasive disease are at high risk of death and/or permanent morbidity (Klein et al. 2007; Tischendorf et al. 2016).

Asymptomatic carriers of resistant ubiquitous bacteria vastly outnumber symptomatic cases (Tischendorf et al. 2016; Smith et al. 2004; Safdar and Bradley 2008) and may carry them unknowingly for months or years (Smith et al. 2004; Carlet 2012; Zimmerman et al. 2013; Marchaim et al. 2007; Kennedy and Collignon 2010), creating risks of disease for carriers as well as risks of transmission to others

Table 12.1 Pathogens frequently carried by healthy individuals

Pathogen	Examples of resistant form(s) of public health importance ^b	Site of carriage
<i>Enterobacteriaceae</i> ^a	CRE (carbapenem resistant enterobacteriaceae)	Digestive tract
<i>Enterococcus faecium</i>	VRE (vancomycin-resistant enterococci)	Digestive tract
<i>Clostridium difficile</i>	Vancomycin resistant strains	Digestive tract
<i>Staphylococcus aureus</i>	MRSA (methicillin-resistant <i>S. aureus</i>)	Skin, nose
<i>Streptococcus pneumonia</i>	Penicillin resistant strains	Respiratory tract
<i>Haemophilus influenzae</i>	Penicillin / macrolide resistant strains	Respiratory tract

^aEnterobacteriaceae include: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter spp.*, *Serratia spp.*, *Proteus spp.*, and *Providencia spp.* *Morganella spp.* ^bAdapted from WHO List of Priority Resistant Pathogens

¹ Others can lead to indirect benefits because their presence in the ecological niche of asymptomatic carriage excludes and/or inhibits other more harmful organisms.

(Klein et al. 2007; Tischendorf et al. 2016; Safdar and Bradley 2008; Carlet 2012; Giske et al. 2008). In light of the potential transmission of resistant bacteria from asymptomatic carriers to others, asymptomatic carriage (otherwise referred to as asymptomatic infection, colonization, commensalism, persistence, the carrier state, etc. (Casadevall 2000)) has underexplored ethical implications for public health programs aimed at controlling the spread of drug resistant bacteria.

Though infection control policies often focus on symptomatic cases, in some cases they also apply to apparently healthy individuals (for example, quarantine involves those suspected, but not known, to be infected (Morgan et al. 2017; Kass 2001; Selgelid 2009; Millar 2009)). As more knowledge is gained regarding *community* (as opposed to in-hospital) transmission of drug-resistant bacteria, policy-makers will need to determine appropriate responses to this relatively new set of public health problems in the general community. Policy options could include screening and other kinds of interference with the lives of apparently healthy individuals. When potentially transmissible (resistant) asymptomatic carriage is diagnosed, there may sometimes be an ethical rationale for public health interventions to prevent transmission, and these measures (as well as screening itself) may entail significant burdens² for carriers (and others) as well as public health benefits. Beyond screening, interventions could include reporting the diagnosis of asymptomatic carriage to authorities, notification of third parties, monitoring of carriers, restrictions on freedom of movement (e.g. quarantine, isolation, travel bans), exclusion of carriers from working in certain occupations, and/or possibly even requirements for treatment of carriers in certain circumstances (See Table 12.1). Where the rate of carriage of highly resistant (i.e. effectively untreatable) bacteria is increasing and/or where community transmission poses significant risks, such public health interventions could have wide-ranging effects on social norms and the everyday lives of healthy individuals (as was the case for tuberculosis and HIV prior to the availability of effective treatments (Fitzgerald 2007)) resulting in stigma and/or social exclusion, in addition to the direct burdens of complying with public health interventions.

A key ethical question concerns whether or not, or the extent to which, public health decision makers should be especially reluctant to impose public health measures that infringe upon the lives of those who are healthy (as opposed to those who are sick). In this chapter, we summarize current knowledge regarding asymptomatic carriage and community transmission, and argue that (i) beliefs that only those with symptoms pose risks to others (and related views, such as ‘microbial determinism’ – i.e. the idea that all those who acquire a pathogen will develop symptoms) should be discarded, (ii) policymakers should consider the risks posed by asymptomatic carriers of resistant organisms, and (iii) policy formation should be guided public health ethics frameworks such that the burdens imposed on carriers (and others) are minimized (and/or offset) and proportionate to the public health benefits in terms of risks averted; and (iv) designing proportionate interventions will require, *inter alia*, careful assessments of the risks related to asymptomatic carriage, including through expanded, ethically designed, public health surveillance programs.

²In this chapter we use the term ‘burden’ to refer to compromises of people’s (especially carriers’) liberties and/or wellbeing.

12.1.1 History

In the late nineteenth and early twentieth centuries, pioneering microbiologists such as Robert Koch significantly improved scientific understanding of the microbial agents of infectious disease. In 1890, Koch laid out criteria for inferring causal links between pathogens and disease states, including a requirement that every person with the microbe must show signs of the relevant disease. Only 3 years later Koch realized that this was an error since many people carry pathogenic microbes and can transmit them to others, without themselves showing signs of disease. This insight went against common wisdom at the time and was illustrated in famous cases such as that of ‘Typhoid Mary’ in New York in 1907: despite being asymptomatic, Mary Mallon transmitted typhoid to many other people through her work as a cook, resulting in several deaths (Soper [1939](#)).

12.1.2 Against Microbial Determinism

Despite this, people might be tempted to think that such cases (of asymptomatic carriage) are exceptions and that the acquisition of potentially pathogenic microbes by a human being (or other animal) will always (or almost always) lead to symptomatic infection (i.e. disease). In some ways, the false view that one’s infectious disease status is determined by the pathogens in one’s body (which we call ‘microbial determinism’) is akin to an erroneous view in genetics (‘genetic determinism’), according to which phenotype is determined by genotype (de Melo-Martín [2005](#)). Just as particular genetic polymorphisms do not always give rise to particular phenotypes (because many environmental factors as well as cellular and other causal processes are required), acquiring particular pathogens does not always lead to the relevant infectious diseases. Upon acquisition of a pathogen, a complex set of host-pathogen interactions (involving immunological and other causal processes) can lead to a variety of outcomes – e.g. the microbe being eliminated without symptoms, short- or long-term asymptomatic carriage, or symptomatic infection/disease (with rapid or delayed onset)(Casadevall [2000](#)).

12.1.3 Key Drug-Resistant Pathogens

This chapter focuses on the ethical implications associated with a subset of WHO Priority Resistant Pathogens (World Health Organisation [2017a](#)): among those with resistance profiles of public health concern, we concentrate on pathogens that are ubiquitous organisms in the bacterial flora of the human body in healthy individuals (Table [12.1](#)) where – in the majority of carriers, whether the bacteria are resistant or

not – they usually cause no symptoms³ until a precipitating event leads to invasive disease (Tischendorf et al. 2016; Safdar and Bradley 2008; Carlet 2012). Such invasive disease can occur in otherwise completely healthy carriers, although it is more common in those with comorbidities, especially those associated with reduced immune function (e.g. diabetes, HIV etc.). We are also particularly concerned with community as opposed to in-hospital transmission, as the latter has received more analysis elsewhere (Millar 2012), including in this volume.

Many of our arguments may be relevant to other increasingly resistant bacteria, including (i) gastro-intestinal and sexually transmitted pathogens that are associated with a high rate of symptomatic infection when a person is first exposed (e.g. *Campylobacter*, *Salmonella* (including typhoid), *Shigella*, and *Gonorrhea*) following which only some people will become chronic asymptomatic carriers, and (ii) *Helicobacter pylori*, a less ubiquitous pathogen for which carrier status is associated with a range of clinical severity from no symptoms to mild indigestion to overt peptic ulcer disease and/or stomach cancer.

12.2 The Public Health Problem

With widespread use (and overuse) of antibiotics, the number of asymptomatic carriers of resistant bacteria (henceforth ‘asymptomatic carriers’) is increasing. It is difficult to characterize the overall carriage rates of the many different types of clinically significant resistant organisms, since the rate of carriage (and the rate of invasive infection) of each varies considerably between populations, and quoted rates will depend on the quality and extent of public health surveillance in different settings (Laxminarayan et al. 2016; Bryce et al. 2016; Bernabé et al. 2017; Nordmann et al. 2011; Schwaber and Carmeli 2013). In any case, *symptomatic* resistant bacterial infections already cause hundreds of thousands of deaths globally per year (although few estimates of the total burden are available) (Laxminarayan et al. 2016; O’Neill 2015) and increase healthcare costs by billions of dollars (Klein et al. 2007; Giske et al. 2008; O’Neill 2015). The true population prevalence of *asymptomatic* carriage of resistant bacteria is often unknown, because not enough community surveillance data are available. Most data come from hospital settings and are biased by the inclusion of a disproportionate number of symptomatic cases and a focus on patients who have contact with healthcare institution(s) as opposed to the wider community (World Health Organization 2014).

Globally, the rate of carriage and/or disease from resistant organisms tracks disadvantage, with higher rates in many low- and middle-income countries (LMICs) (Bernabé et al. 2017). For example, a recent study in a Malaysian hospital found that around 50% of patients screened on arrival to hospital were carrying

³Emerging microbiome research programs are, however, seeking links between strains of colonization and a wide range of ‘subclinical’ physical and mental health outcomes.

carbapenem resistant *Enterobacteriaceae* (CRE)⁴ in their digestive tract (Zaidah et al. 2017) – of whom perhaps up to 1 in 6 can be expected to develop invasive disease, with overall mortality among carriers reportedly around 10% (Tischendorf et al. 2016). In general, there is a much higher rate of mortality from resistant infections in poor communities, including among infants – some of whom acquire resistant infections from mothers and/or family members (and/or, for infants admitted to hospital, from staff or other patients) who are asymptomatic carriers (Chan et al. 2013). One 2016 estimate suggested that of the 680,000 annual neonatal deaths due to bacterial infection, the vast majority of which occur in LMICs, around 31% (214,500) were due to resistant infections (Laxminarayan et al. 2016).

Yet the problem is by no means confined to developing regions. A 2016 systematic review of *E. coli*⁵ urinary infections among children (with the usual source of such infections being asymptomatic carriage of *E. coli* in the child's digestive tract) found that the highest rates of resistance to first-line penicillin antibiotics occurred in (lower income) non-OECD countries (79.8%), but rates in (higher income) OECD countries were still relatively high (53.4%) (Bryce et al. 2016).

More epidemiological research is urgently needed to quantify the rates of carriage of key pathogens in different populations, as well as the rates of disease among carriers and the rates of transmission from (symptomatic and asymptomatic) carriers to others in different contexts. Novel, less expensive, genomic screening techniques are expected to facilitate such investigations (Kwong et al. 2017).

12.2.1 Antibiotic Use and Drug Resistance

The use of antibiotics that kill sensitive bacteria in the human microbiome inevitably leads to the evolutionary selection of drug resistant bacteria. Despite concerns regarding underuse, the vast majority of drug resistant bacteria in humans arise due to antibiotic overuse and 'appropriate' use (Llewelyn et al. 2017).⁶ Importantly, when antibiotics are prescribed/taken to treat one type of (suspected or confirmed) infection, many other bacteria carried in the body are exposed to the same antibiotics, which select for resistant strains by killing sensitive ones. It is mainly these 'off-target' effects that lead to asymptomatic carriage of resistant forms of ubiquitous bacteria (Llewelyn et al. 2017). This means that whether a given prescription for antibiotics is 'appropriate' (e.g. because the patient actually has a symptomatic infection with the pathogen for which she is being treated) or not, each additional dose of antibiotics potentially adds to the burden of resistant bacteria carried in the

⁴i.e. highly resistant bacteria predominantly found in the digestive tract, a group considered "critical" (i.e. of highest importance) on the WHO Priority list.

⁵*E. coli* is an important species in the family of *Enterobacteriaceae*, carried primarily in the digestive tract (see Table 12.1 and footnote above).

⁶In this paper we focus on human use, although animal and agricultural use is an important contributor to drug-resistant human infection.

body (Carlet 2012). Furthermore, at the population level, it is otherwise relatively healthy occasional users of antibiotics (taken together) who contribute the most to the prevalence of (asymptomatic carriage of) drug-resistant bacteria, rather than the relatively few, relatively sick individuals whose antibiotic use is more frequent and/or intensive (Olesen et al. 2018). In any case, although reducing the use of antibiotics is one important policy to reduce carriage of drug-resistant bacteria, this chapter focuses on other potential community interventions that have received less ethical analysis in this context (Bryce et al. 2016; Barbosa and Levy 2000; Bronzwaer et al. 2002).

12.2.2 *Transmission*

Even those who never use antibiotics can acquire resistant pathogens through (direct or indirect) contact with carriers (Zimmerman et al. 2013; Schwaber and Carmeli 2013; Waters et al. 2004; Paterson 2006). Living in close contact with carriers (Eveillard et al. 2004; Granoff and Daum 1980), hospitalization (Eveillard et al. 2004; Cronin et al. 2017), working in healthcare (Eveillard et al. 2004; Albrich and Harbarth 2008), and travel to countries with high rates of resistant organisms (Kennedy and Collignon 2010) are all risk factors for the acquisition of resistant pathogens via transmission. Increasingly, outbreak investigations have demonstrated transmission networks that connect symptomatic and asymptomatic individuals both within hospitals and in the wider community (Smith et al. 2004; Kwong et al. 2017). Community transmission of some pathogens is relatively well understood; for example, colonization with methicillin resistant *S. aureus* (MRSA) is associated with transmission within families (Eveillard et al. 2004; Fritz et al. 2014; Manian 2003), while the transmission of many other resistant pathogens has been primarily studied in the hospital setting (if at all).

12.2.3 *Duration of Carriage*

Once an individual becomes a carrier of resistant bacteria, the duration of carriage depends on complex local factors at the site of carriage including competition from other strains or other species of bacteria, as well as the carrier's immune response, and whether (more) antibiotics are used (Andersson and Hughes 2010). Few studies have estimated the average duration of carriage of key resistant bacteria in the general population; studies in returned travellers have suggested a decrease in carriage over months, with most individuals carrying detectable levels of resistant strains for a few months and a minority (around 10%) developing long-term carriage of 6 months or more (Kennedy and Collignon 2010).

12.3 Potential Public Health Responses

Strategies for preventing the transmission of drug-resistant bacteria from asymptomatic carriers include a wide range of potential interventions (Table 12.2). Each of these interventions could involve burdens for carriers (and others, for example family members) – to a greater or lesser degree, depending on the chosen policy and its implementation. Such burdens may include reduced well-being, infringements on privacy,⁷ restrictions of other freedoms (including freedom of movement and freedom to decide on the medical interventions to which one will be subjected (Table 12.2)⁸) (Inness 1996), and significant financial costs.⁹ Interventions can be more or less coercive ranging from being offered, recommended, or self-enforced to strictly coerced and/or backed by legal sanctions including fines and/or prison terms.

Thus, the design and implementation of infection control policy will inevitably involve ethical tradeoffs (Millar 2009; Millar 2012). The focus of most drug-resistant infection policy regarding asymptomatic carriers has been on healthcare contexts (primarily hospitals), yet – with few exceptions (Millar 2009; Millar 2012) – there has been little explicitly ethical analysis of such policies. There has

Table 12.2 Infection control interventions and potential burdens

Public health interventions that could lead to reduced well-being, privacy infringements, and reductions in other freedoms (e.g. freedom of movement, freedom to decide on medical interventions)	
Intervention Types	Description/examples
Screening	Testing apparently healthy individuals for carriage
Informing carriers of their status	Communicating and explaining the diagnosis of a carrier state
Notifying public health authorities	Requirements for health workers to report the diagnosis of carrier status
Monitoring	Serial (re)testing to assess carrier status
Treatment or decolonization	Skin/nasal decolonization of MRSA; faecal transplant for CRE
Limitations on freedom of movement	Isolation, quarantine, travel bans
Limitations on social practices	Change of occupation, altered norms of social interaction

⁷We consider privacy to be a freedom; see, for example, Inness (1996).

⁸This paper focuses on burdensome interventions for carriers; there are of course a range of other interventions including nudging or minimally-burdensome behavioral interventions (we thank an anonymous reviewer for pointing this out) and interventions to change healthcare worker behaviors such as antibiotic prescribing (which have received some discussion elsewhere).

⁹Costs arise both for the individuals directly affected and, where public health measures are financed through taxation, for the whole community.

been even less ethical analysis of public health infection control interventions to prevent the transmission of drug resistant bacteria in the general community (i.e. outside healthcare settings).

12.3.1 Surveillance, Notification, and Monitoring

Screening is routinely used to detect asymptomatic carriage of resistant bacteria among hospital patients (Morgan et al. 2017; Perencevich et al. 2004; Cooper et al. 2004). In many jurisdictions, hospitals are required to notify or report the diagnosis of asymptomatic carriage to local infectious diseases departments and/or central agencies, resulting in exceptions to the usual right to privacy over one's own health information (Morgan et al. 2017; Inness 1996; World Health Organisation 2017b). In order to form a more accurate estimate of the reservoir of asymptomatic infection in the community, and accurately assess the transmissibility and invasiveness (i.e. propensity to cause symptomatic disease) of a given pathogen, surveillance would ideally go beyond (hospital) patients and include members of the general community such as (but not necessarily limited to) the close contacts of those known to be carriers. Yet this raises questions regarding how policy should address potential scenarios in which large numbers of asymptomatic carriers of highly resistant pathogens are identified. Furthermore, the accuracy of tests used in surveillance has ethical implications especially where, for example, a false positive test result leads to significant burdens for someone who is not actually a carrier of resistant microbes (or where a false negative result provides false reassurance).

12.3.2 Restrictions of Freedom of Movement (Isolation, Quarantine, Travel Bans)

Although isolation and quarantine of asymptomatic carriers and/or their contacts have sometimes been successful in hospitals, whether such measures would be feasible and/or successful in the general community (e.g. where community members are identified as carriers by public health surveillance) remains uncertain. Restricting the freedom of movement of healthy carriers (or those suspected to be carriers) in the general community would plausibly involve significant infringements on individual liberty, and such restrictions might often lead to greater burdens for healthy carriers than for those suffering with the symptoms of the relevant disease (or, for example, confined to hospital for other reasons), as discussed below (See Sect. 12.4.2).

12.3.3 Treatment and Decolonization

Many asymptomatic bacterial infections in certain populations – for example, asymptomatic bacteriuria in most females – do not require treatment because they lead to a low rate of disease in the carrier (Nicolle et al. 2005). In other cases, either because of risks to the carrier or to others, treatment may lead to a net benefit (although not necessarily to the carrier herself). Treatment of asymptomatic *resistant* bacteria is often more difficult and sometimes referred to as decolonization. Decolonization strategies have been used for MRSA, primarily carried on the skin and in the nose – which allows for topical (i.e. non-invasive) bactericidal treatment¹⁰ (Coates et al. 2009). Although decolonization has primarily been used in carriers with recurrent symptomatic infection in order to benefit the carrier herself, they have also been used in family members (and pets) of at-risk patients and healthcare workers in order to prevent harm to others (Albrich and Harbarth 2008; Guardabassi et al. 2004).

Decolonization for organisms carried in the digestive tract is sometimes more invasive than decolonization of the skin. For example, an effective, last-line treatment for resistant *C. difficile*¹¹ is faecal transplantation (i.e. decolonization (Morgan et al. 2015)), whereby the bowel microbiome of the patient is replaced by feces from a healthy donor (Van Nood et al. 2013). There have been recent reports of the successful use of fecal transplantation to clear (symptomatic or asymptomatic) carriage of ubiquitous bowel organisms that have become highly resistant (e.g. CRE), Freedman and Eppes 2014; Manges et al. 2016; Crum-Cianflone et al. 2015). At present, the use of such procedures has been largely confined to unwell patients, including in intensive care units (Carlet 2012). Yet if such strategies prove to be safe, effective and reliable, they could be more widely implemented to address the carriage and transmission of resistant bowel organisms.

12.4 Ethical Issues

Asymptomatic infection raises a number of important ethical issues. In this chapter we focus on ethical considerations related to policy responses to the problem of asymptomatic carriage of resistant strains of ubiquitous bacteria because, as described earlier (i) asymptomatic carriers of such pathogens vastly outnumber symptomatic cases, (ii) carriers are at risk of severe and difficult to treat invasive disease, (iii) carriage of resistant pathogens places others in the community at risk,

¹⁰One limitation of *S. aureus* decolonization is that it uses bactericidal products (albeit with different formulations to other relevant antibiotics) to which the organism can also become resistant.

¹¹*C. difficile*: a species of bacteria that is commonly (but not ubiquitously) carried asymptomatically in the bowel and most frequently causes disease in individuals already treated with antibiotics for other conditions.

and (iv) public health interventions to prevent the transmission of resistant bacteria are potentially associated with significant burdens for carriers (and others). Determining the appropriate responses will thus require scientific data regarding the risks involved (e.g. for a given pathogen or resistance mechanism in a given population) as well as moral judgments about the degree to which burdensome interventions to prevent these risks would be justified. An initial question relates to the extent to which the ethical permissibility of a burdensome infection control measure depends on whether contagious carriers are symptomatic as opposed to asymptomatic (i.e. 'healthy'). We begin by arguing for a useful way of applying existing public health ethics frameworks to policy questions, and then give an account of how the principles in such frameworks should be used to inform policy related to asymptomatic carriers.

12.4.1 *Applying Public Health Ethics Frameworks*

Existing public health ethics frameworks are applicable to the problem of the carriage and community transmission of resistant bacteria by asymptomatic carriers. The principles in different frameworks overlap considerably; Table 12.3 provides a list of relevant principles and examples of how they might be interpreted (based on previous work (Selgelid 2009)). These principles are usually framed as necessary conditions for determining when a given intervention would be justifiable. However, were this to be so, it might seem that certain principles would be difficult to satisfy

Table 12.3 Principles from public health ethics Frameworks

Public Health Ethics Principle	Interpretation/Example
Need for evidence	Evidence of efficacy is needed to justify imposition of potentially burdensome public health interventions.
Least restrictive alternative	Where two interventions are expected to be equally effective, the intervention that involves the least restrictions of liberty should be selected.
Proportionality	The burdens involved in an intervention should be outweighed by public health benefits achieved.
Equity	The intervention should be implemented (and burdens imposed) in an equitable, non-discriminatory manner.
Least harmful alternative	Where two interventions are expected to be equally effective, the intervention that involves the least harms should be selected.
Reciprocity	Those who benefit from public health policies/interventions have a reciprocal duty to assist and/or compensate those on whom burdens are imposed.
Due legal process	Appropriate legal procedures should be followed and individuals should have the right of appeal.
Transparency	Policymaking should be transparent and democratic.

(as necessary conditions) in the context of asymptomatic carriage of drug-resistant bacteria (and/or in many other public health contexts). If the existence of evidence of an intervention's effectiveness is conceived as a necessary condition, for example, then some might think that the current lack of evidence (e.g. of the risks of community transmission of resistant bacteria) precludes the implementation of relevant public health interventions. Such an approach would likely reduce the scope of legitimate public health interventions to a very narrow set (for example, those for which we have very substantial evidence regarding the effectiveness of relevant interventions, and where the attendant burdens are well characterized, etc.). For this and other reasons it is arguably more useful to conceive of such principles as pointing to ethically relevant desiderata that are achieved to a greater or lesser degree (i.e. on a scale) rather than as necessary conditions that are either satisfied or unsatisfied depending on whether some threshold has been crossed (Selgelid 2016).¹² For example, there can be more or less (reliable) evidence regarding the expected public health benefits associated with a given intervention—and a relative lack of evidence (such as the current gaps regarding our knowledge of community transmission of drug-resistant pathogens) might suggest that an intervention should first be instituted as (public health) research (rather than suggesting that it would be ethically unacceptable to implement it at all), and re-evaluated as more evidence comes to light. Furthermore, since there is not likely to be widespread agreement among public health practitioners on any threshold that could be used to characterize a sufficient amount of evidence to justify the implementation of a given intervention (in public health practice, rather than in research), policymakers should consider both evidence and ethical acceptability as matters of degree existing on a scale—the idea being that the more (reliable) evidence one has that an intervention is likely to create a net public health benefit, the more ethically acceptable it would be to implement it in policy, other things being equal.

Likewise the harms of potential interventions should be considered to exist on a spectrum from least to most harmful, liberty infringements on a spectrum from least (e.g., minor and/or short-term) to most restrictive (e.g. major and/or longer duration),¹³ and transparency of policy making on a spectrum from least to most

¹²For illustration of how such an approach might work in the context of public health policy regarding gain-of-function research see Selgelid (2016).

¹³Although the Least Restrictive Alternative and Least Harmful Alternative principles are usually framed as necessary conditions, there are often cases where policymakers will be uncertain whether one intervention is more effective and/or less restrictive or harmful than another. In such cases of uncertainty, a scalar framing of the principles might run as follows: “The more confidence policymakers have that two interventions are associated with similar expected public health benefits and significantly different restrictions, the more moral considerations would support selecting the less restrictive alternative, other things being equal. The more confidence policymakers have that two interventions are associated with similar expected public health benefits and significantly different burdens, the more moral considerations would support selecting the less harmful/burden-some alternative, other things being equal.” However, in a restricted set of cases where policymakers are very certain that one intervention is equally (or more) effective and less restrictive or harmful, interpreting the principles as necessary conditions will yield similar guidance, other

transparent, and so on—the idea being that the ethical acceptability of interventions will be a matter of degree, and a function of the extent to which they are harmful, restrictive, transparent, etc., other things being equal (Allen and Selgelid 2017). There might often be reasonable disagreement about exactly how the estimated degrees of evidence, harmfulness, restrictiveness, transparency, etc. can/should determine what ultimately ought to be done; but, as a starting point, policymakers should consider how well, or poorly, each available intervention fares with respect to the values/concerns highlighted by each principle before making *judgements* regarding what policies/interventions should be implemented. We consider this to be a practical approach to ethically sensitive public health policymaking; in the next section we illustrate such an approach in the context of asymptomatic carriage of drug resistance.

12.4.2 *Public Health Intervention for Healthy Carriers*

One might think that public health agencies should be more reluctant to interfere with the lives of healthy asymptomatic carriers as opposed to sick individuals who carry, and/or are suffering from clinical infection due to, the same (resistant) pathogens. The proportionality principle may help to explain such intuitions. Firstly, one way in which it may make a difference, ethically speaking, whether a carrier is symptomatic or not when imposing potentially burdensome public health interventions is that asymptomatic carriers are more likely to be living active lives in general society; whereas the more symptomatic one is, the more likely it is that they will be bedbound and/or admitted to a healthcare facility. In the latter kind of case, one's liberty and well-being are in a sense already impaired by illness, and so some restrictions (to prevent transmission of drug-resistant bacteria) may impose few, if any, additional burdens.¹⁴ For example, public health measures limiting the freedom of movement of carriers (See Table 12.2) would be a more significant burden for healthy carriers whereas the isolation of sick individuals is a relatively minor additional burden, since such individuals are more likely to be restricted in their movement (e.g. confined to a healthcare facility) due to illness.¹⁵ Thus, if the risk of transmission from a healthy individual is similar to, or less than, the risk from a sick

things being equal. We thank an anonymous reviewer for pressing us on this point. For more on this kind of approach to public health ethics frameworks, see Allen and Selgelid (2017).

¹⁴Those who are ill may also be more likely to understand and comply with burdensome restrictions because they can more easily perceive that they are infected and a risk to others; in some such cases restrictive measures may even be unnecessary since voluntary measures suffice. We thank an anonymous reviewer for suggesting this point.

¹⁵Some might worry that the systematic imposition of additional burdens on those who are already (in one sense) badly off due to illness would be inequitable; arguably, this would be particularly worrisome if these burdens were disproportionate (see following discussion of proportionality) to the risks averted which is less likely in cases where (i) the additional burden is small and/or (b) the risk of transmission from sick individual carriers is at least as high as, or higher than, the risk from healthy carriers (i.e. most cases).

individual, the burdens would be higher when imposing a given intervention on healthy carriers. Secondly, there may be cases in which healthy carriers and sick carriers impose different risks of transmission to others. Sick carriers may impose higher risks of transmission because (i) in at least some cases, the degree of symptoms (e.g. related to the resistant bacterial infection in question) is correlated with the risk of transmission¹⁶ (Lerner et al. 2015) or because (ii) hospitalisation for illness places one in (direct or indirect) contact with other patients who are at particularly high risk of acquiring and suffering from (resistant) infection due to medical comorbidities and/or contamination of the shared hospital environment. In cases where such conditions hold, not only would the burdens of certain interventions be lower among sick carriers (as discussed above), but the risks (to others) averted would be greater, meaning that imposing similarly restrictive interventions on healthy carriers would be comparatively less proportionate (because more significant burdens would be imposed to avert lower risks). On the other hand, there might be cases in which healthy carriers impose higher risks on others. For example, healthcare workers or food handlers who carry resistant pathogens might impose increased risks on others because of the nature of their work. In such cases, it may be more justifiable to impose burdensome restrictions on such individuals, because these would be more proportionate to the risks involved (c.f. vaccination of healthcare workers (van Delden et al. 2008)).

12.4.3 *Burdens of Interventions and Support for Carriers*

As noted previously, public health interventions to control the spread of resistant bacteria in the general community could potentially burden carriers to a greater or lesser degree. They may also involve burdens for family members and contacts of known carriers, as well as direct financial costs for those involved and funding costs of relevant public health policy options (which are borne by the wider community and/or lead to forgoing other opportunities to improve public health)¹⁷. While the threat of drug-resistant infections as an urgent public health problem might prompt some to consider or propose particularly far-reaching and/or coercive interventions, several other public health ethics principles (in addition to the proportionality principle) can provide useful guidance regarding the ethical reasons to ensure that the burdens (and costs) of an intervention are not only proportionate to the public health benefits but also as low as possible (i.e. without unduly compromising the goals of a policy to reduce risks and thereby lead to public health benefits).

¹⁶for example, urinary frequency and incontinence related to urinary tract infection (e.g. with *E. coli*), diarrhea (e.g. from resistant *Clostridium difficile*), etc. potentially increase the risk of transmission to others.

¹⁷We thank anonymous reviewers for emphasizing the implications for family members and for pointing out the opportunity cost of public health policies.

First, the least harmful alternative principle holds that interventions must be no more harmful to carriers than necessary (i.e. minimally harmful) – because compromising individuals’ well-being requires justification. If two alternative policies/interventions are expected to be equally beneficial in terms of public health protection, then the alternative that is less harmful to carriers should be preferred, other things being equal – See Table 12.3. Second, the reciprocity principle entails that policymakers should consider obligations to assist and support carriers as part of policy implementation so as to reduce or offset the ‘net burdens’ for those affected. This could include preferential/non-discriminatory access to healthcare, psychological support, assistance with finances or finding other employment, etc.

More broadly, public health agencies should aim to reduce burdens related to stigma through public education campaigns and through informing carriers about important aspects of carriage (for example, that carriage of resistant organisms is frequently not permanent) at the time of diagnosis. Overly burdensome interventions may also lead to perverse incentives for (potential) carriers to avoid diagnosis and/or contact with health authorities, which could lead to greater risks for the carrier and others, undermining the purported public health benefits of a given policy (meaning that the need for evidence includes evidence regarding how well a policy actually works in practice).¹⁸

12.5 The Need for More Surveillance and Research

Practical ethical deliberations guided by the above principles should always be informed by the best available empirical data on the relevant risks related to carriage of a given pathogen and the expected benefits of an intervention. An initial challenge is that, for many infections transmitted by asymptomatic carriers, the risks are not yet well understood because few data are available. There is thus an ethical imperative for increased public health surveillance and research on such infections, including programs aimed at collecting and analyzing long-term data (i.e. involving monitoring) related to asymptomatic carriage in the general community. This again requires careful ethical consideration, since ethically appropriate surveillance also requires striking a balance between public health goals and individual interests; here, too, public health ethics principles and analysis should help to guide policy formation (World Health Organisation 2017b). Likewise, there is an urgent need for more research regarding the relative effectiveness of different potential public health interventions, as well as qualitative research aimed at better characterizing the burdens experienced by carriers. Being able to draw on such empirical data will only serve to improve public health ethics analysis and, ultimately, public health policy.

¹⁸ We thank the participants at the 2018 Brocher workshop “Invisible epidemics: ethics and interventions for asymptomatic carriers of infectious diseases.”, in particular Niels Nijssingh and Christian Munthe for helpful discussions of this point.

12.6 Conclusions

All human beings are asymptomatic carriers of bacteria, meaning that ‘microbial determinism’ is false. The increasing prevalence of carriage of *resistant* strains of ubiquitous bacteria is an urgent public health issue, and many apparently healthy individuals are at risk of resistant infections and risk transmitting such pathogens to others. Deliberations regarding the design and implementation of public health policy should be guided not only by empirical data regarding the health risks of a given resistant strain and the public health benefits of a given intervention (and much more data are needed to clarify these risks and benefits), but also by ethical analysis regarding the justification of burdens imposed on carriers. Principles of existing public health ethics frameworks should help policymakers identify important considerations that have particular implications for the design and implementation of infection control policies regarding asymptomatic carriers. The proportionality principle in particular provides reasons for being wary about imposing potentially burdensome interventions on otherwise healthy carriers of drug resistant pathogens—which is not to say that such interventions would never be ethically appropriate.

Acknowledgement Reprinted with permission of John Wiley and Sons (Licence 4890151079850); original citation: Jamrozik, E., & Selgelid, M. J. (2019). Surveillance and control of asymptomatic carriers of drug-resistant bacteria. *Bioethics*, 33(7), 766–775.

References

- Albrich, W.C., and S. Harbarth. 2008. Health-care workers: Source, vector, or victim of MRSA? *The Lancet Infectious Diseases* 8 (5): 289–301.
- Allen, T., and M.J. Selgelid. 2017. Necessity and least infringement conditions in public health ethics. *Medicine, Health Care and Philosophy* 20 (4): 525–535.
- Andersson, D.I., and D. Hughes. 2010. Antibiotic resistance and its cost: Is it possible to reverse resistance? *Nature Reviews Microbiology* 8 (4): 260–271.
- Barbosa, T.M., and S.B. Levy. 2000. The impact of antibiotic use on resistance development and persistence. *Drug Resistance Updates* 3 (5): 303–311.
- Bernabé, K.J., C. Langendorf, N. Ford, J.-B. Ronat, and R.A. Murphy. 2017. Antimicrobial resistance in West Africa: A systematic review and meta-analysis. *International Journal of Antimicrobial Agents*.
- Bronzwaer, S.L.A.M., O. Cars, U. Buchholz, et al. 2002. The relationship between antimicrobial use and antimicrobial resistance in Europe. *Emerging Infectious Diseases* 8 (3): 278.
- Bryce, A., A.D. Hay, I.F. Lane, H.V. Thornton, M. Wootton, and C. Costelloe. 2016. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ* 352: i939.
- Carlet, J. 2012. The gut is the epicentre of antibiotic resistance. *Antimicrobial Resistance and Infection Control* 1 (1): 39.
- Casadevall, A. 2000. Pirofski L-a. Host-pathogen interactions: Basic concepts of microbial commensalism, colonization, infection, and disease. *Infection and Immunity* 68 (12): 6511–6518.

- Chan, G.J., A.C.C. Lee, A.H. Baqui, J. Tan, and R.E. Black. 2013. Risk of early-onset neonatal infection with maternal infection or colonization: A global systematic review and meta-analysis. *PLoS Medicine* 10 (8): e1001502.
- Coates, T., R. Bax, and A. Coates. 2009. Nasal decolonization of *Staphylococcus aureus* with mupirocin: Strengths, weaknesses and future prospects. *Journal of Antimicrobial Chemotherapy* 64 (1): 9–15.
- Cooper, B.S., S.P. Stone, C.C. Kibbler, et al. 2004. Isolation measures in the hospital management of methicillin resistant *Staphylococcus aureus* (MRSA): Systematic review of the literature. *BMJ* 329 (7465): 533.
- Cronin, K.M., Y.S.P. Lorenzo, M.E. Olenksi, et al. 2017. Risk factors for KPC-producing Enterobacteriaceae acquisition and infection in a healthcare setting with possible local transmission: A case–control study. *Journal of Hospital Infection* 96 (2): 111–115.
- Crum-Cianflone, N.F., E. Sullivan, and G. Ballon-Landa. 2015. Fecal microbiota transplantation and successful resolution of multidrug-resistant-organism colonization. *Journal of Clinical Microbiology* 53 (6): 1986–1989.
- de Melo-Martín, I. 2005. Firing up the nature/nurture controversy: Bioethics and genetic determinism. *Journal of Medical Ethics* 31 (9): 526–530.
- Eveillard, M., Y. Martin, N. Hidri, Y. Boussougant, and M.-L. Joly-Guillou. 2004. Carriage of methicillin-resistant *Staphylococcus aureus* among hospital employees: Prevalence, duration, and transmission to households. *Infection Control & Hospital Epidemiology* 25 (2): 114–120.
- Fitzgerald, C. 2007. Kissing can be dangerous. The public health campaigns to prevent and control tuberculosis in Western Australia, 1900–1960. *Australian Journal of Social Issues Subscriptions* 42 (2): 273.
- Freedman, A., and S. Eppes. 2014. Use of stool transplant to clear Fecal Colonization with Carbapenem-Resistant Enterobacteriaceae (CRE): Proof of concept. *Open Forum Infectious Diseases* (1): S65. Oxford University Press.
- Fritz, S.A., P.G. Hogan, L.N. Singh, et al. 2014. Contamination of environmental surfaces with *Staphylococcus aureus* in households with children infected with methicillin-resistant *S. aureus*. *JAMA Pediatrics* 168 (11): 1030–1038.
- Giske, C.G., D.L. Monnet, O. Cars, and Y. Carmeli. 2008. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrobial Agents and Chemotherapy* 52 (3): 813–821.
- Granoff, D.M., and R.S. Daum. 1980. Spread of *Haemophilus influenzae* type b: Recent epidemiologic and therapeutic considerations. *The Journal of pediatrics* 97 (5): 854–860.
- Guardabassi, L., S. Schwarz, and D.H. Lloyd. 2004. Pet animals as reservoirs of antimicrobial-resistant bacteria Review. *Journal of Antimicrobial Chemotherapy* 54 (2): 321–332.
- Inness J.C. 1996. *Privacy, intimacy, and isolation*: Oxford University Press on Demand.
- Kass, N.E. 2001. An ethics framework for public health. *American Journal of Public Health* 91 (11): 1776–1782.
- Kennedy, K., and P. Collignon. 2010. Colonisation with *Escherichia coli* resistant to “critically important” antibiotics: A high risk for international travellers. *European Journal of Clinical Microbiology & Infectious Diseases* 29 (12): 1501–1506.
- Klein, E., D.L. Smith, and R. Laxminarayan. 2007. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerging Infectious Diseases* 13 (12): 1840.
- Kwong, J.C., C. Lane, F. Romanes, et al. 2017. *bioRxiv* 175950.
- Laxminarayan, R., P. Matsoso, S. Pant, et al. 2016. Access to effective antimicrobials: A worldwide challenge. *The Lancet* 387 (10014): 168–175.
- Lerner, A., A. Adler, J. Abu-Hanna, S.C. Percia, M.K. Matalon, and Y. Carmeli. 2015, 21. Spread of KPC-producing carbapenem-resistant Enterobacteriaceae: the importance of super-spreaders and rectal KPC concentration. *Clinical Microbiology and Infection* (5): 470. e1–70. e7.
- Llewelyn, M.J., J.M. Fitzpatrick, E. Darwin, et al. 2017. The antibiotic course has had its day. *BMJ* 358: j3418.

- Manges, A.R., T.S. Steiner, and A.J. Wright. 2016. Fecal microbiota transplantation for the intestinal decolonization of extensively antimicrobial-resistant opportunistic pathogens: A review. *Infectious Diseases* 48 (8): 587–592.
- Manian, F.A. 2003. Asymptomatic nasal carriage of mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) in a pet dog associated with MRSA infection in household contacts. *Clinical Infectious Diseases* 36 (2): e26–e28.
- Marchaim, D., S. Navon-Venezia, D. Schwartz, et al. 2007. Surveillance cultures and duration of carriage of multidrug-resistant *Acinetobacter baumannii*. *Journal of Clinical Microbiology* 45 (5): 1551–1555.
- Millar, M. 2009. Do we need an ethical framework for hospital infection control? *Journal of Hospital Infection* 73 (3): 232–238.
- . 2012. ‘Zero tolerance’ of avoidable infection in the English National Health Service: Avoiding the redistribution of burdens. *Public Health Ethics* 6 (1): 50–59.
- Morgan, D.J., S. Leekha, L. Croft, et al. 2015. The importance of colonization with *Clostridium difficile* on infection and transmission. *Current Infectious Disease Reports* 17 (9): 43.
- Morgan, D.J., R.P. Wenzel, and G. Bearman. 2017. Contact precautions for endemic MRSA and VRE: Time to retire legal mandates. *JAMA* 318 (4): 329–330.
- Nicolle, L.E., S. Bradley, R. Colgan, J.C. Rice, A. Schaeffer, and T.M. Hooton. 2005. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clinical Infectious Diseases*: 643–654.
- Nordmann, P., T. Naas, and L. Poirel. 2011. Global spread of carbapenemase-producing *Enterobacteriaceae*. *Emerging Infectious Diseases* 17 (10): 1791.
- Olesen, S.W., M.L. Barnett, D.R. MacFadden, et al. 2018. The distribution of antibiotic use and its association with antibiotic resistance. *bioRxiv* 473769.
- O’Neill, J. 2015. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance. Chaired by Jim O’Neill. December 2014.
- Paterson, D.L. 2006. The epidemiological profile of infections with multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. *Clinical Infectious Diseases* 43 (Supplement_2): S43–S48.
- Perencevich, E.N., D.N. Fisman, M. Lipsitch, A.D. Harris, J.G. Morris Jr., and D.L. Smith. 2004. Projected benefits of active surveillance for vancomycin-resistant enterococci in intensive care units. *Clinical Infectious Diseases* 38 (8): 1108–1115.
- Safdar, N., and E.A. Bradley. 2008. The risk of infection after nasal colonization with *Staphylococcus aureus*. *The American Journal of Medicine* 121 (4): 310–315.
- Schwaber, M.J., and Y. Carmeli. 2013. An ongoing national intervention to contain the spread of carbapenem-resistant *Enterobacteriaceae*. *Clinical Infectious Diseases* 58 (5): 697–703.
- Selgelid, M.J. 2009. A moderate pluralist approach to public health policy and ethics. *Public Health Ethics* 2 (2): 195–205.
- . 2016. Gain-of-function research: Ethical analysis. *Science and Engineering Ethics* 22 (4): 923–964.
- Sender, R., S. Fuchs, and R. Milo. 2016. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology* 14 (8): e1002533.
- Smith, D.L., J. Dushoff, E.N. Perencevich, A.D. Harris, and S.A. Levin. 2004. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem. *Proceedings of the National Academy of Sciences of the United States of America* 101 (10): 3709–3714.
- Soper, G.A. 1939. The curious career of Typhoid Mary. *Bulletin of the New York Academy of Medicine* 15 (10): 698.
- Tischendorf, J., R.A. de Avila, and N. Safdar. 2016. Risk of infection following colonization with carbapenem-resistant *Enterobacteriaceae*: A systematic review. *American Journal of Infection Control* 44 (5): 539–543.
- van Delden, J.J.M., R. Ashcroft, A. Dawson, G. Marckmann, R. Upshur, and M.F. Verweij. 2008. The ethics of mandatory vaccination against influenza for health care workers. *Vaccine* 26 (44): 5562–5566.

- Van Nood, E., A. Vrieze, M. Nieuwdorp, et al. 2013. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *New England Journal of Medicine* 368 (5): 407–415.
- Waters, V., E. Larson, F. Wu, et al. 2004. Molecular epidemiology of gram-negative bacilli from infected neonates and health care workers' hands in neonatal intensive care units. *Clinical Infectious Diseases* 38 (12): 1682–1687.
- World Health Organisation. 2017a. *WHO guidelines on use of medically important antimicrobials in food-producing animals*. Geneva: WHO.
- . 2017b. *WHO guidelines on ethical issues in public health surveillance*. Geneva.
- World Health Organization. 2014. *Antimicrobial resistance: global report on surveillance*: World Health Organization.
- Zaidah, A.R., N.I. Mohammad, S. Suraiya, and A. Harun. 2017. High burden of Carbapenem-resistant Enterobacteriaceae (CRE) fecal carriage at a teaching hospital: Cost-effectiveness of screening in low-resource setting. *Antimicrobial Resistance & Infection Control* 6 (1): 42.
- Zimmerman, F.S., M.V. Assous, T. Bdolah-Abram, T. Lachish, A.M. Yinnon, and Y. Wiener-Well. 2013. Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge. *American Journal of Infection Control* 41 (3): 190–194.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.